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Research Article

Practical Considerations in the Measurement of the Internal Relative Humidity of Pharmaceutical Packages with Data Loggers

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Abstract. The utility of temperature/humidity data loggers are evaluated as a low-cost approach to enrich practical understanding of the actual time dependent humidity that a pharmaceutical product is exposed to. While this approach is found to have significant utility in general, small systematic biases in the measurements due to the presence of the data logger are observed. Taking these biases into account enables more productive extrapolation of measured time/humidity profiles.

KEY WORDS: data logger; humidity; moisture; stability; water activity.

INTRODUCTION

It is well accepted that moisture plays a critical role in modifying the rates of chemical degradation and physical changes in pharmaceutical formulations. Pharmaceutical scientists control moisture effects mainly through the selection of primary packages with suitable moisture-barrier properties. However, in most cases, the moisture content of the packaged drug product is a moving target—the internal environment of the package rises slowly to equilibrium to the external storage environment at a rate determined by the characteristics of the package and its contents. The science surrounding the moisture ingress into packages is well established, and rigorous models are available to predict the performance of packaging configurations and extrapolate the effect of packaging changes (1–5). However, because these models are mathematically complicated and often require significant experimental calibration, they are generally used only in the later stages of product development, if at all. A simpler and more direct approach is to measure the relative humidity inside packages using small temperature/humidity data loggers. High-quality data loggers that fit easily into most bottle packages are commercially available, providing a simple low barrier-of-entry approach to increase insight into product-specific packaging performance. While these approaches are no substitute to more rigorous modeling approaches, their low cost and simplicity makes them a valuable complement to the direct measurement of product moisture or water activity in the course of stability studies, enabling broader and earlier implementation in development. We have critically evaluated the potential of data loggers to collect internal package relative humidity data to complement and enrich the interpretation of stability studies of pharmaceutical tablet formulations and report herein several caveats and limitations associated with their use as well as strategies to minimize the inherent limitations of this approach.

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EXPERIMENTAL

Temperature/humidity data loggers used in this study are MicroRHTemp data loggers manufactured by MadgeTech, Inc. (Contoocook, NH, USA). These data loggers have a nominal temperature accuracy of ±0.5°C and a nominal humidity accuracy of ±3% relative humidity (RH). All data loggers were packaged in 75-cc Blake HDPE bottles with induction sealable 33–400 mm Clic-loc® III caps obtained from O-I (formerly known as Owens-Illinois, Inc.; Perrysburg, OH, USA) together with 0–60 placebo tablets. Bottles were induction-sealed unless otherwise noted. A picture of the bottles and data loggers used in this study is shown in Fig. 1. The moisture permeation rates of these bottles when induction-sealed were 0.27 and 1.33 mg/day at 25°C/60%RH and 40°C/75%RH, respectively, using the desiccant approach described by Waterman *et al.*(5). Bottles were stored in calibrated ES2000 CDMD temperature and humidity environmental test chambers manufactured by Bahnson Environmental Specialties, LLC (Raleigh, NC), and the nominal RH values of the chambers were assumed to be the "correct" values for the purposes of assessing the accuracy of individual data logger measurements. The composition of the placebo tablets that provide the model drug product discussed in this work is shown in Table I below. Fits of the experimental data presented in Fig. 4 were produced using SigmaPlot for Windows, version 10.0. All fits are single, three-parameter exponential fits.

THEORETICAL BACKGROUND

The theoretical basis for modeling the moisture ingress into packaged drug products has been laid out by a number of authors, including a recent publication by the Product Quality

Fig. 1. Picture of 75-cc HDPE bottles and data loggers used in this study

Research Institute container-closure working group (6). As described in Eq. 1 below, the driving force for moisture ingress into a container is proportional to the difference in the vapor pressure of water (or analogously water activity or relative humidity) between the internal and external environments. The progression toward equilibrium of gas-phase moisture between these two environments is the root of product moisture changes with time, and packaging serves only to delay this equilibrium. The impact of packaging can be reduced to its water permeation rate (K), normalized with respect to water vapor pressure (6).

$$\frac{dn}{dt} = \frac{P}{l}A(p_{ext} - p) = K(p_{ext} - p) \quad (1)$$

n	Total mass of water in container
t	Time
P	Effective permeability coefficient
l	Effective thickness of packaging material
A	Effective surface area of package material for diffusion
$K=(P/l)A$	Partial pressure normalized total water permeation rate through packaging and seal
p_{ext}	Partial pressure of water outside the container
p	Partial pressure of water inside the container

Table I. Composition of Placebo Tablets Described in This Work

Component	Function	Quantity (% w/w)[a]
Silicified microcrystalline cellulose	Filler	20.8
Lactose, Fast Flo	Filler	75.7
Croscarmellose sodium	Disintegrant	3.00
Magnesium stearate	Lubricant	1.00

[a] Of a total tablet weight of 200 mg

Integration of Eq. 1 above gives Eq. 2, an equation for the total moisture of the system. This formula is conceptually quite simple and very powerful as a qualitative tool for understanding the relative performance of different packaging types. However, this simple mathematical treatment hides within it the fact that the partial pressure inside the package (p) is itself an empirically derived function of the total moisture content (n) and the moisture sorption properties of the container contents (3,4).

$$n = \int K(p_{ext} - p)dt = K\int (p_{ext} - p)dt \quad (2)$$

Equation 2 can be expressed in terms of relative humidity by incorporating the saturation vapor pressure of water (p_o) as shown in Eq. 3.

$$n = 100Kp_o\int\left(\frac{p_{ext}}{100p_o} - \frac{p}{100p_o}\right)dt$$
$$= 100Kp_o\int(\%RH_{ext} - \%RH)dt \quad (3)$$

The equation for %RH as a function of moisture (n) for a pharmaceutical formulation is often known as the moisture sorption isotherm and can be determined experimentally using a variety of commercially available dynamic vapor sorption instruments or manual gravimetric experiments to relate equilibrium headspace relative humidity at a given temperature to the mass of water absorbed. An example isotherm for a typical tablet formulation is shown in Fig. 2. The moisture/humidity relationships measured empirically in the moisture sorption isotherm experiment define the shape of the %RH/total moisture (n) relationship in Eq. 3 above. This relationship is valid as long as the ingress of moisture is gradual enough to allow constant equilibrium distribution of moisture in the system prior to the addition of additional moisture. In the moisture isotherm experiment, the product is exposed to a given relative humidity for several hours before measurement is taken to allow this equilibrium to be established. In pharmaceutical packages, the rates of moisture ingress are slow enough that quasi-equilibrium is constantly re-established as new moisture is added to the system (5). The nature of the moisture vapor transmission properties of the packaging in relation to the mass of formulation contained in the package determines how rapidly the internal contents of the package will retrace the path defined by the moisture sorption isotherm, but the path traveled is the same for a given product. In this respect, the moisture isotherm of the product defines the "moisture state function" of all package configurations for this product.

For a package with low internal %RH exposed to a high %RH external environment, the relative humidity increases inside packaged drug product over time as shown in Fig. 3. Examination of these %RH/time relationships provides great physical insight into moisture effects on the chemical and physical stability of formulations during long-term storage. When convoluted with an understanding of the stability performance of the product as a function of %RH, these relative humidity/time profiles allow the prediction of the stability performance of the product with time and rational selection of packaging that adequately provides moisture protection. The value of these %RH/time relationships is further enhanced by the ability to extend small amounts of

measured data to a range of packaging configurations. A rigorous approach for the calculation of RH/time profiles from measured moisture isotherms and package moisture transmission rates has been described by Chern *et al.* (3,4). However, this mathematical approach can be significantly simplified by the approximation that product moisture isotherms are most often fairly linear in the region of primary interest for pharmaceutical packaging applications from 10–60%RH (see for example Fig. 2 above) (7). With the introduction of the approximation that incremental changes in moisture will be proportional to water vapor pressure (*i.e.*, $n \propto cmp$, where m is the mass of the drug product formulation and c is a constant representing the slope of the n/p relationship per unit mass) across a limited range, Eq. 1 can be simplified to Eq. 4 and further rearranged to Eq. 5.

$$\frac{dn}{dt} \approx cm\frac{dp}{dt} = K(p_{ext} - p) \tag{4}$$

$$cm\frac{dp}{dt} + Kp = Kp_{ext} \tag{5}$$

Since Kp_{ext} is a constant, Eq. 5 is a first-order ordinary differential equation with constant coefficients. Its solution is of the form of Eq. 6. Dividing by the saturation water vapor pressure (p_o) to place this into relative humidity context gives Eq. 7.

$$p(t) = A + Be^{\frac{-Kt}{cm}} \tag{6}$$

$$\%RH = \frac{100p(t)}{p_o} = A' + B'e^{\frac{-Kt}{cm}} \text{ where } A' = \frac{100A}{p_o} \text{ and } B' = \frac{100B}{p_o} \tag{7}$$

A key insight that follows from Eq. 7 is seen in the relationship of the variables K, t, and c in the exponential term. Barry *et al.* (6) have previously proposed that the moisture protection performance of packaging configurations can be said to be equivalent if the moisture transmission rate per unit product remains constant. Put in terms of Eq. 7, the moisture transmission per unit product corresponds to the ratio of $\frac{K}{cm}$, since m will be proportional to the number of tablets per container. As the moisture transmission per unit product changes, Eq. 7 further predicts that timescale of the curve will change proportionately, without an overall change in the shape of the curve. For example, if the number of tablets per bottle was doubled (*i.e.*, $m'=2m$), this would be mathematically equivalent to dividing the time in half, and it would take twice as long to reach a given %RH. This provides a convenient shortcut to extrapolate a measured RH/time profile to a new packaging configuration as long as the relative effect of the change on the moisture transmission per unit product can be reasonably predicted. Most easily, this allows the extrapolation between different bottle fill counts as described below, but comparisons between different packages with known differences in moisture transmission rates (e.g., bottles of different wall thickness or between bottles and blisters).

This simplified view of the mathematical relationships underlying moisture ingress into pharmaceutical packages is enabled by the relatively crude assumption of a linear moisture/RH relationship for the drug product in question. While never completely accurate, this remains approximately correct in the most important region in the center of the RH range where a significant difference exists between the internal and external RH conditions and moisture/RH changes are most rapid. Deviations from linearity (and thus from the mathematical relationships assumed above) must be expected at very low and very high %RH. In case of high % RH, however, the impact of these deviations is muted by the exponential decrease in the driving force for moisture ingress as the internal and external RH conditions approach equilibrium. Despite the limitations of our assumptions, the empirical utility of the insights they produce is demonstrated in the following section. In practice, the same time axis scaling approaches may also be useful in cases where the linearity of the moisture/RH relationship is clearly invalid. In such cases,

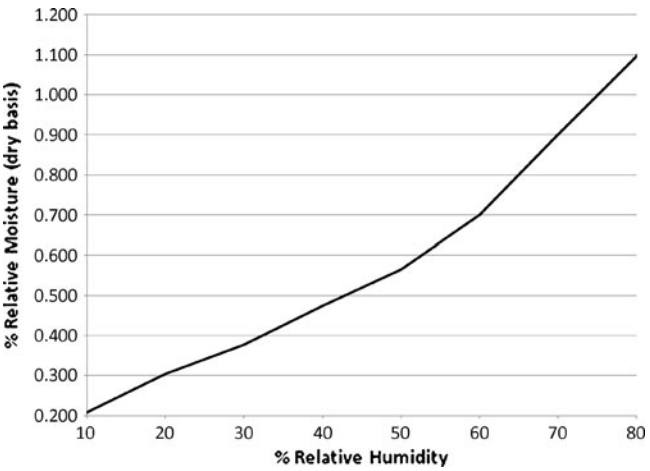

Fig. 2. Moisture sorption isotherm (40°C) for the placebo tablet formulation evaluated in this work. All moisture values are presented on a dry basis

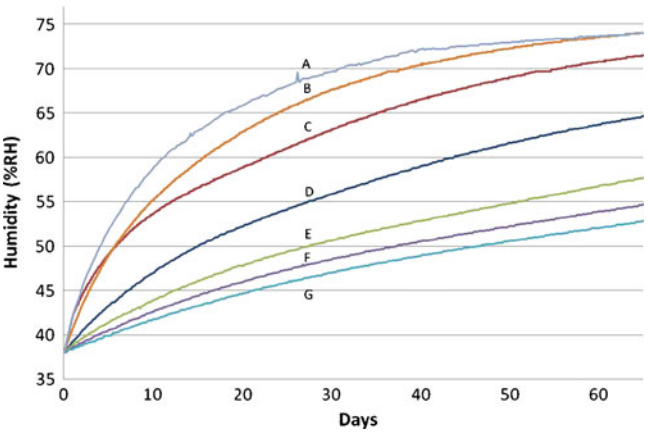

Fig. 3. Measured internal package humidity for representative placebo formulation in 75-cc HDPE bottles with **a** 0, **b** 1, **c** 5, **d** 15, **e** 30, **f** 45, or **g** 60 tablets stored at 40°C/75%RH

Table II. Comparison of the Measurement Performance of Five Data Loggers Stored in a Common Temperature/Humidity Environment

ICH storage condition	Mean temperature (°C)	%RSD	Mean %RH	%RSD
25°C/60%RH	25.7	0.6	61.1	1.6
30°C/65%RH	30.3	0.6	65.6	1.4
40°C/75%RH	39.8	0.4	76.3	1.1

ICH International Conference on Harmonization, *RH* relative humidity, *RSD* relative standard deviation

Table III. Fit Parameters Associated with Fig. 4 in the Form %RH= $A+Be^{-xt}$, where $x=k/cm$ as Described in Eq. 7

Tablets per bottle	*A*	*B*	*x*
15	40.9615	40.4224	39.9834
30	34.0385	34.5776	35.0166
45	0.0184	0.0108	8.46E−03
60	40.9615	40.4224	39.9834

The units of A and B are %RH, and the units of *t* are in days

the failure of the linearity assumption does not necessarily undermine the validity of decoupling the time axis from the shape of the RH profile, though the corresponding math will certainly be more complicated and less generalizable.

RESULTS AND DISCUSSION

Although temperature/humidity data loggers are relatively inexpensive instruments, they nevertheless perform their function with very acceptable accuracy and precision. For example, the averages and relative standard deviations (RSDs) of temperature and humidity are shown in Table II for five randomly selected data loggers stored in stability chambers under standard ICH storage conditions commonly used for pharmaceutical stability studies. In each case, the average temperature was within 1°C of the nominal chamber temperature and the RSD was ≤0.6%. Average humidity values were within 1.5%RH of the nominal chamber values with RSDs≤1.6%. These performance attributes are well within what is acceptable for variation in temperature and humidity of the stability chambers themselves, and on the surface, these data loggers appear to be very appropriate to the measurement of internal temperature and humidity conditions within drug product packages.

When these same data loggers are placed into induction-sealed HDPE bottles together with 0–60 tablets and allowed to measure the internal package conditions as these bottles are stored in a 40°C/75%RH stability chamber for several months, the time/humidity profiles shown in Fig. 3 are obtained. It can be seen from Fig. 3 that the empirical measurements of humidity/time profiles show some deviation from the simplified theory presented above. For example, although the profiles are offset in the expected approximate spacing with high tablet count packages having the slowest increases of humidity with time, the experimental profiles occasionally cross during the first few days of storage in ways that are not explained by the simple assumptions of the theoretical model, especially when the bottles contain zero to five tablets. Likewise, simple exponential fits of the curves to Eq. 7 generally tend to provide good fits in the later gradually rising portions of the profiles, with more marked deviations in the early regions when the humidity is rising rapidly and provide poor replication of the time=0 intercept (Fig. 4, Table III).

The predictions of Eq. 7 about the possibility of extrapolating conditions measured for one packaging configuration to that of other configurations by merely shifting the time axis by a predictable factor do appear to be borne out by the experimental results, as shown in Fig. 5. Yet, within this successful replication of the theoretical predictions, there is also a significant mismatch between the theoretical time factor to extrapolate between packaging conditions (*i.e.*, proportional to tablet counts) and what is observed in

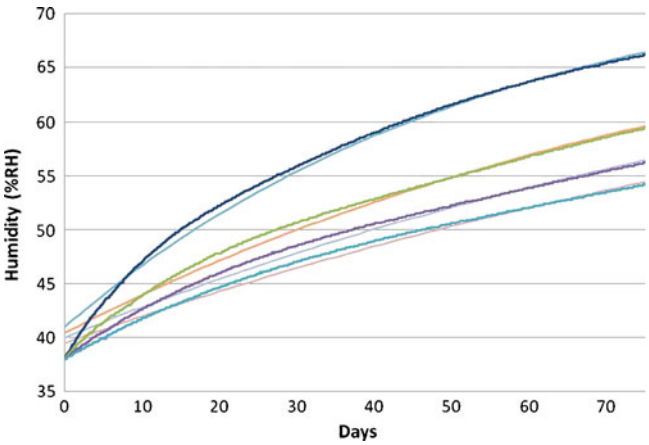

Fig. 4. Measured internal package humidity for representative placebo formulation in 75-cc HDPE bottles with **a** 15, **b** 30, **c** 45, or **d** 60 tablets stored at 40°C/75%RH. Each profile is overlaid with its best fit exponential curve of the form of Eq. 7

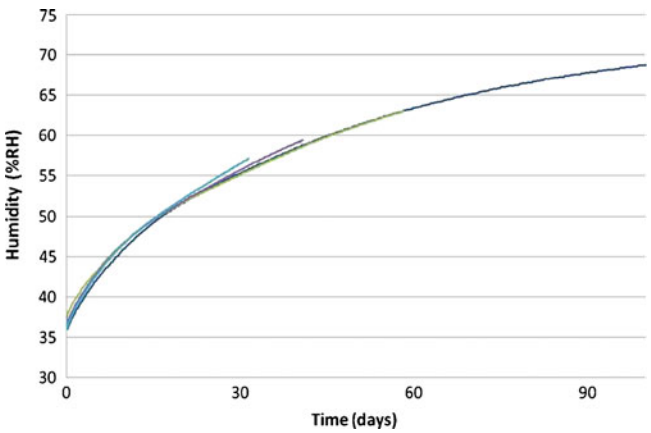

Fig. 5. Overlaid humidity/time profiles for 15, 30, 45, and 60 count bottles from Figure 3 graphed *versus* time divided by empirically determined factors 1.0, 1.735, 2.47, and 3.205, respectively, to achieve optimal overlap

Table IV. Evaluation of the Systematic Bias Necessary to Produce the Empirical Observations of Fig. 4

Actual number of tablets in bottle	Ratio of bottle contents to 15 count bottles	Empirical time factor	Tablets per bottle+systematic bias=5 tablets	Adjusted ratio (comparable to empirical time factor)
15	1.0	1.000	20	1.000
30	2.0	1.735	35	1.750
45	3.0	2.470	50	2.500
60	4.0	3.205	65	3.250

practice. Empirical adjustment of the time axes reveals that the most successful overlaying of the time/humidity profiles is achieved if the packages are assumed to contain further moisture-absorbing contents approximately equivalent to five of the placebo tablets used in this study. In other words, the profiles measured for bottles containing 30 and 60 tablets can be inter-converted most successfully if the bottles are instead assumed to contain 35 and 65 tablets, respectively (Table III). Some small amount of the extra moisture sorption properties of the package contents can be attributed to gas-phase moisture content within the package that was neglected from consideration in the theoretical assumptions (6). However, a quick comparison of the moisture isotherm in Fig. 2 with the saturation vapor pressure of water at 40°C reveals that only a small fraction of this unexpected moisture capacity of the package contents can be explained in this way (5). Instead, the remaining contents of the package, and the data logger itself, must have non-negligible moisture sorption properties under these conditions. This can be demonstrated in practice by comparing the time/humidity profiles for bottles containing multiple data loggers to those containing a small number of tablets (Table IV). As shown in Fig. 6, the rise of humidity with time for bottles containing two data loggers are slowed by an amount almost intermediate between two bottles containing zero and five tablets.

CONCLUSIONS

The promise of miniature data loggers such as those evaluated in this study for the *in situ* measurement of internal package relative humidity is somewhat challenged by the subtle bias of the data loggers themselves on the quantity to be measured, as we report above. However, if the origin and magnitude of this systematic bias are understood, the measured data can be extrapolated to simulate unperturbed %RH/time profiles. The nature of the experimental bias is most pronounced when the package contains few tablets/capsules, but becomes decreasingly important as the number of tablets/capsules increases. The accuracy of the measurement was found to be reasonably good and more accurate than the reproducibility of the packaging material examined in this study. The simplicity and affordability of this approach remain highly attractive and hold promise as a valuable complement to other measurement approaches.

The present work focuses on only the most direct and convenient implementation of extrapolation between package configurations as a function of the moisture ingress/tablet ratio. It is immediately clear how this ratio will change when the number of tablets per bottle is varied, and this simple relationship is powerful out of proportion to its simplicity. However, the concepts of this extrapolation are equally valid when applied to changes that affect the base moisture ingress rate of the package, rather than the number of tablets in the package. Changes between bottle types or even between bottle and blister types can be supported by this same rational. The relative moisture permeation rates of the most common pharmaceutical packages are easily measureable and are reported in the scientific literature (5). Of course, when broader extrapolation approaches are used, the inherent variability between different embodiments of the same or similar packaging configurations should be taken into account as an additional source of variability. For example, a range of moisture ingress rates can be expected from the same blister packaging material depending on blister cavity size and shape. It may be expected that these uncertainties will be more significant than those reported in this work, and pragmatic error bars should be applied to the %RH/time profiles obtained by such extrapolation. Nevertheless, there is often great value in even %RH/time profiles with wide error bars in helping to provide a clear scientific basis for packaging selection. Together with understanding of the %RH/stability relationships obtained by stability studies under constant % RH conditions, this semi-quantitative understanding of moisture protection of various packaging configurations can help to quickly narrow the list of appropriate packaging configurations without the need for further stability studies on all possible packaging configurations.

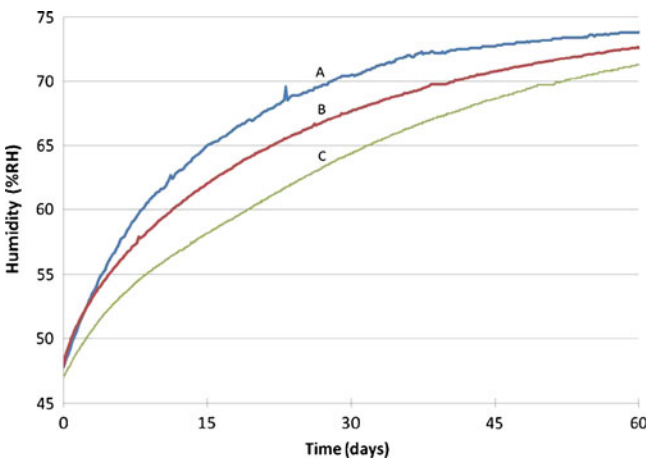

Fig. 6. Overlaid humidity/time profiles for HDPE bottles containing one data logger **a**, two loggers **b**, or one data logger and five tablets **c**

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