Model for Moisture Transport into Inhalation Aerosols

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INTRODUCTION

Moisture content is an important variable to control in many pharmaceutical formulations and manufacturing processes. It is well known that moisture has deleterious effects on solid dosage forms resulting in changes in hardness, disintegration, dissolution and crushing strength. Moisture also mediates unwanted phase transitions for solids where amorphous regions re-crystallize to form structured crystalline material. Particle aggregation in nonaqueous suspensions, represented by metered dose inhalers (MDIs), is also attributed to water. Whereas the effects of moisture on oral solid dosage forms are well-documented (1), its behavior in pharmaceutical nonaqueous suspensions is unreported save for a single reference by Miller (2). Byron (3) has noted the paucity of published experimental evidence concerning the effects of moisture in MDIs.

The diagram in Figure 1 describes the MDI physical system. Modeling the ingress of moisture may be a critical step toward evaluating the impact of water on aerosol formulation stability. Inasmuch as Miller (2) has previously offered a qualitative discussion of moisture ingress, the objective of this work is to formulate the time dependence of water permeation, through the elastomeric components or gaskets of the metered valve, into the MDI. Specifically, the mass balance describing steady-state diffusion through thin membranes (4, 5) is applied to the MDI. In addition, suggestions aimed toward predicting the physical stability of moisture-sensitive suspension aerosols are discussed.

THEORY

The pseudo-steady state rate of moisture (subscript w) permeation from region I to IV (see Fig. 1) is described by the following mass (m) balance (4, 5):

$$\frac{dM}{dt} = \frac{P_w}{m_f}(a^I - a^{IV}) \quad (1)$$

M is the ratio of the mass (m) of water (subscript w) to the mass of the formulation (subscript f),

$$M = \frac{m_w}{m_f} \quad (2)$$

The mass of water is normalized to the total mass of the formulation because the raw moisture content data is typically reported in de-dimensional form as parts per million (ppm) in the formulation. The permeability coefficient replaces the product of constants

$$P_w = \frac{18.01 D_w H_w A p^o_w}{\delta RT} \quad (3)$$

where

D = diffusion coefficient
A = surface area through which mass transfer occurs
H = partition coefficient
δ = elastomer thickness
p° = vapor pressure of water
T = absolute temperature
R = gas constant

Equation 1 describes the proportionality between the total moisture transferred per unit time into the canister, dM/dt, and the difference in the activity of water, a, outside and inside the canister. The proportionality constant, P_w, is parametrically dependent on gasket material and thickness, valve configuration, and temperature. The permeation coefficient of water through the elastomer, P_w, has the units of mass per time.

Equation 1 assumes that the partitioning of moisture between the vapor and condensed phases, which occurs inside the canister, is instantaneous compared to the transfer of moisture through the elastomeric components of the metered valve. In other words, $a^{III} = a^{IV}$ at all times during the ingress of moisture. The differential mass balance can be integrated by recognizing that the moles of water and surfactant are negligible compared to the moles of propellant. The time-dependent profile of moisture content (M(t)) in an MDI is:

$$M(t) = M_\infty - (M_\infty - M_o)\exp\left(-\frac{P_w a_I}{m_f M_\infty} t\right) \quad (4)$$

where the subscripts, 0 and ∞, refer to the initial and equilibrium moisture contents.

MATERIALS AND METHODS

The formulation consisted of Freon 11, Freon 12, Span 85, and an undisclosed drug. The sampling frequency and moisture analysis results were reported by Miller (2), and are reproduced with permission. Moisture levels in the canisters were evaluated using Karl Fischer coulometric titration (6). The samples were introduced into the apparatus by a proprietary method intended to ensure that all of the water in the sample would be measured. Canisters were removed from the stress condition (37°C) and allowed to equilibrate to room temperature (25°C) prior to testing. A minimum of two canisters was sampled at each time point.

Curve fitting was accomplished using a SAS® non-linear procedure. The asymptotic regression provided estimates for the parameter M_∞ and the ratio P_w/m_f. Correlation coefficients, R^2, for evaluating the goodness of the fit, were also obtained from the non-linear regression.

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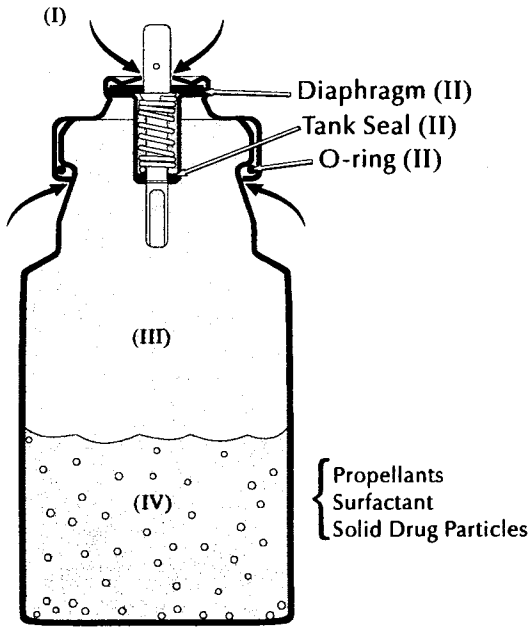

Fig. 1. Schematic of a metered dose inhaler showing three different gaskets (diaphragm, tank seal, and O-ring) and entry points for moisture ingress (curved solid arrows). The regions depicted are as follows: (I) environmental humidity chamber, (II) valve gasket, (III) vapor phase, (IV) condensed phase.

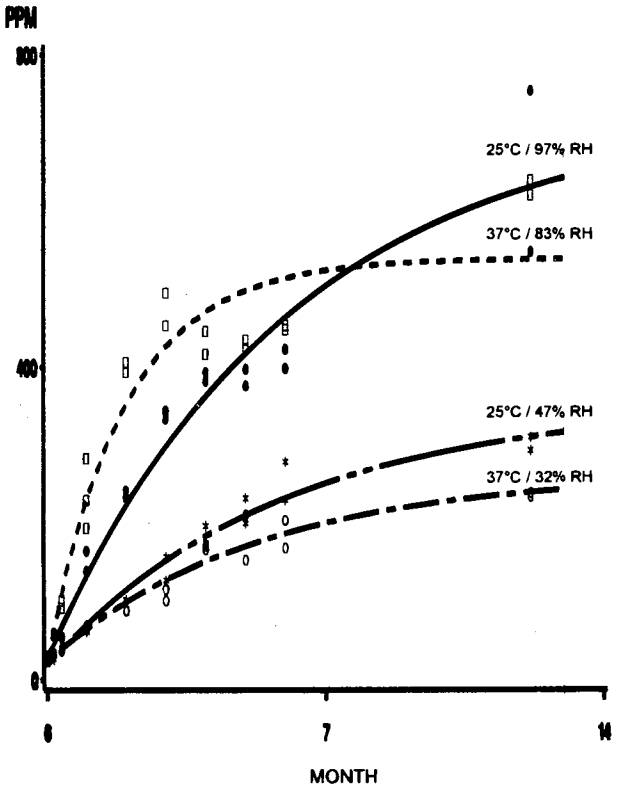

Fig. 2. Water content of MDIs at various storage conditions. Experimental data are from reference (2). Curves represent the fit of Equation 4 to the data.

RESULTS AND DISCUSSION

Moisture ingress profiles were dependent on temperature and relative humidity (Figure 2). That is, the estimated final moisture level and the rate of moisture uptake (listed in Table I) were influenced by the evironmental conditions.

For example, the predicted moisture contents, at a specified temperature, exhibited the same rank order as the water activity. Also, for the room temperature results, the ratio of water activity was equal to the ratio of equilibrium moisture contents. The inequality of these ratioes at the elevated temperature was probably due to room temperature equilibration prior to moisture determination. Thermal re-equilibration affects the partitioning of moisture between the liquid (IV), vapor (III), and elastomer (II). Although, there may be other possible explanations, changing the temperature of the canister effectively changes the activity and partitioning of water in the MDI.

Similar statements can also be made regarding the permeability coefficients. Whereas the moisture permeation increased as the temperature was raised, only the room temperature samples had equal values at the same temperature. Again, a possible cause for this inequivalence was the thermal re-equilibration.

Also, the model (Eq. 4) suggests that changing gasket material, which is equivalent to changing P_w, can influence the time dependent profile of moisture ingress. This has important implications related to accelerated product stability studies. Current recommendations for stressing products are 40°C / 85% RH for 3 months (8) or 40°C / 75% RH for 6 months (9). Provided that equilibrium is not attained during the accelerated stress study, smaller values of P_w suggest that 40°C / 75% RH for 6 months is more stressful (more water into the canister over the length of the study) than 40°C / 85% RH for 3 months. Using a different gasket elastomer effectively changes the permeability and may yield higher moisture readings at 40°C/ 85% RH for 3 months if the water permeability has increased substantially due to the new elastomer.

Although the correlation coefficients (Table I) indicated that a substantial portion of the variation is described by the model, the plot (Figure 2) demonstrated that up to 12 months of data must be collected to reasonably estimate the equilibrium moisture content of this formulation by fitting the data to the model. This time commitment could be reduced, however, by separately determining the permeability coefficient of the elastomer and equilibrium moisture content of the formulation.

It has previously been noted that the differential form of the mass balance, Equation 1, describes the proportionality between the permeation rate and the difference in water activity. This provides the basis for expeditiously determining the mass transfer coefficient. Plotting the initial slope, determined by

Table I. Results of the Non-Linear Regression of Miller's Experimental Data to Equation 4

Temp [°C]/ %RH	R^2	M_∞ [ppm]	P_w/m_f [$\times 10^6$ month^{-1}]
25/47	0.967	356 (61)	122 (44)
25/97	0.942	721 (154)	123 (55)
37/32	0.950	264 (45)	154 (60.)
37/83	0.909	538 (62)	328 (123)

Note: Values in parentheses are 95% confidence intervals.

linear regression, as a function of the difference in water activity will yield the permeability coefficient.

A second set of experiments, probing the vapor-liquid-equilibrium and effectively removing the barrier to diffusion, would substantially reduce the time necessary to estimate the final moisture level. Equilibrium between gaseous and liquid phases is categorized into specific cases depending on whether the phases are ideal or non-ideal solutions. The fact that water and propellants are only partially miscible (10) implies that the condensed phase is non-ideal. The water present in the vapor phase mixture of hydrocarbons, at pressures greater than the vapor pressure of the propellants, has been shown, however, to approximate ideality (11). Therefore, a suspension MDI involves an ideal gas phase in contact with a non-ideal liquid.

Technically the condensed phase is a suspension; however, the effects of drug and surfactant were not explicitly considered. Obviously, their presence has important effects upon interpreting the equilibrium content and physical properties of water in the MDI. Consider, for example, that while neither propellant has an inherent capacity for water greater than ~100 ppm (10) the formulations which contain solid and surfactant were shown to have much greater water contents (see data at 25°C/97% RH). Plausible explanations are that the water was incorporated into reverse micelles and/or sorbed onto particle surfaces. The presence of inverted micelles is often extrapolated from studies using model solvents (12) to the higher vapor pressure propellants, but to date studies in the actual propellants are lacking. As Elworthy (13) has demonstrated the applicability of vapor-liquid-equilibrium experiments to micellar solutions of lecithin in benzene, it is reasonable to suggest that similar experiments involving propellants, propellant solutions containing surfactants, and MDI formulations would also be insightful.

CONCLUSIONS

A model has been developed which describes the transfer of moisture into an MDI. Included in the expression for moisture ingress (Eq. 4) are a lumped kinetic parameter (permeability coefficient) and two thermodynamic quantities (initial and equilibrium moisture contents). Further, the implications of the model for predicting moisture content profiles have been discussed. The permeability coefficient could be determined from the initial rates and the difference in water activity, while phase equilibrium could establish moisture content specifications and assess the physical stability of moisture sensitive inhalation aerosols.

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