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Prediction of the changes in drug dissolution from an immediate-release tablet containing two active pharmaceutical ingredients using an accelerated stability assessment program (ASAP*prime*®)

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Abstract

The computer program ASAP*prime*® has been used successfully for some time to predict the stability of active pharmaceutical ingredients (APIs) in solid-dosage forms. In this study, we have demonstrated that the ASAP*prime*® program can also be used to predict the slow-down in dissolution of two APIs in an immediate release tablet. The tablets were pre-equilibrated at 25 °C at different relative humidities (30–75 %), sealed in aluminum pouches and stored at temperatures ranging from 50–60 °C for 3, 7 or 14 days. The storage times were selected to encompass the time needed to produce a slowdown in dissolution such that the amount of the two APIs fell below the acceptance criteria of no less than 80 % dissolved in 20 min. Up to 6 months of stability data from a 40 °C/75%RH open dish study were also included in the modeling. The effects of temperature (T in °K) and relative humidity (RH) were then shown to be related to the isoconversion (IC) time by an empirical, modified Arrhenius equations, where IC is the time for the amount dissolved to equal 80 % of the label claim. These studies showed that while the slowdown in dissolution of API 2 was influenced more by the relative humidity than API 1, the overall slowdown in dissolution was more sensitive to changes in temperature than changes in relative humidity. In addition to showing that ASAP*prime*® could be used to model the effects of temperature and relative humidity on dissolution, the software was also used to demonstrate that no special precautions were necessary to protect the tablets from moisture and they could be stored in Aclar blisters®. It was also shown that the water content of the tablet was not a critical quality attribute and need not be included in the drug product specification.

Keywords: Accelerated stability, Accelerated stability assessment program (ASAP*prime*®), Arrhenius relationship, Dissolution, Stability prediction, Temperature effects, Moisture effects

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Background

The use of accelerated stability studies is a well-established technique that has been widely used for more than 60 years to predict the shelf life and storage conditions of drugs and drug products (Baertschi 2007; Huynh-Ba 2008; Karstensen 1990; Waterman & Carella 2007). Whereas the experimental approaches may vary between studies, the general principles are the same and are based on the extrapolation of the rate of degradation at two or more temperatures above the intended condition, using the Arrhenius Relationship (Eq. 1).

$$\ln k = \ln A - \frac{E_a}{RT} \quad (1)$$

where k is the rate constant for the reaction, T is the temperature, A is the collision frequency factor, E_a is the activation energy and R is the gas constant. Equation 1 is actually a variation of the empirical relationship developed by van't Hoff in 1887 to describe the effect of temperature on chemical equilibria and used later by Arrhenius who found that the logarithm of the rate (or rate constant) for various reactions was proportional to the reciprocal of the absolute temperature. Predictions of stability based on the Arrhenius relationship (Eq. 1) work well for well-controlled homogenous systems (such as solutions) over relatively small temperature ranges (e.g. 50 °C). However, the Arrhenius relationship is less reliable over larger temperature ranges when the dependency of A and E_a on T described by Eyring (Stella, 2000) results in non-linear relationships between ln k and 1/T. Another important source of error arises from extrapolation of the data because the confidence interval of the predicted value increases as the difference between the measured and predicted values increases.

Deviations from ideal behavior (Eq. 1) in more complex, heterogenous systems, make the prediction of stability in solid dosage forms (SDF) more difficult. However, Waterman and co-workers (Waterman & Swanson 2014; MacDonald 2010; Colgan & Hofer 2015; Stella 2000; Timmerman 2003; Waterman 2011) have shown that the predominant factor that determines the rate of degradation in solid dosage forms, in addition to temperature, is the presence of water. That group has shown the rate of degradation of active pharmaceutical ingredients in tablets and other SDFs may be predicted using a modified Arrhenius equation (Eq. 2), which takes into account the water content as well as the temperature:

$$\ln k = \ln A - \frac{E_a}{RT} + B(RH) \quad (2)$$

where B is the humidity sensitivity factor and RH is the relative humidity. Having demonstrated the applicability of various statistical approaches for the evaluation of data (Eq. 2) to predict the shelf life of SDFs, Waterman and co-workers (Waterman & Swanson 2014; MacDonald 2010; Colgan & Hofer 2015; Stella 2000; Timmerman 2003; Waterman 2011) have developed computer software (ASAP*prime*®) to facilitate the calculations. This approach relies on the measurement of the rates of degradation at

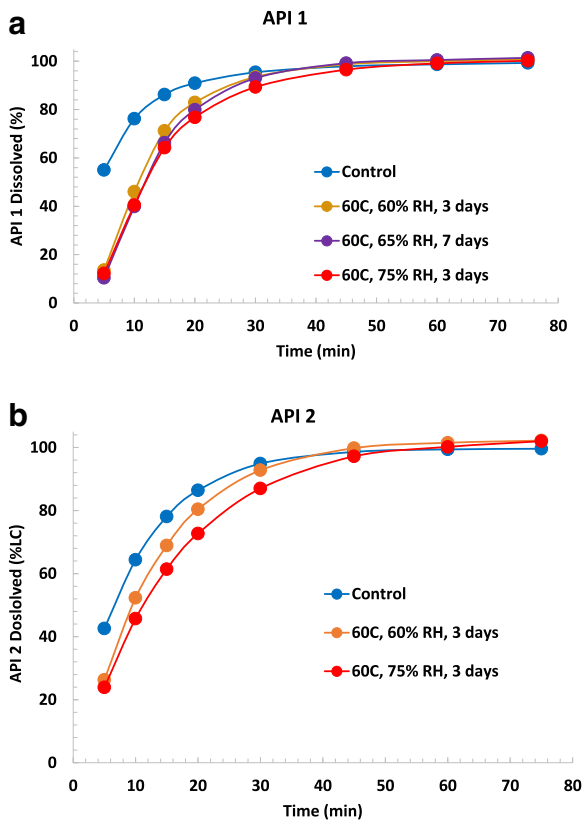

Fig. 1 **a** Dissolution Profiles of API 1 under Different Storage Conditions, in pH 1.5 Media. **b** Dissolution Profiles of API 2 under Different Storage Conditions, in pH 6.8 Media

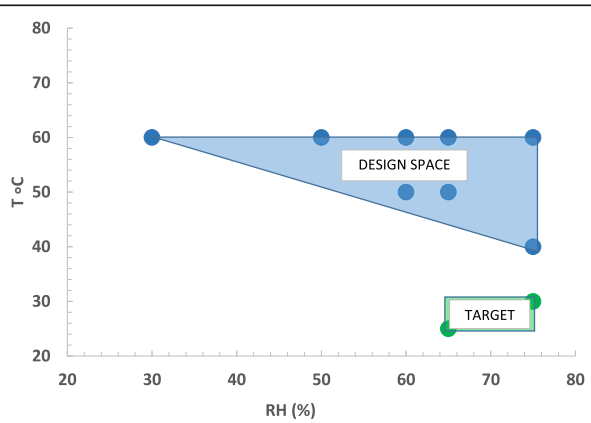

Fig. 2 Design Space showing the Conditions Studied (*blue*) and the Conditions for the Predictions (*green*)

Table 1 [a] Temperature (T) and relative humidity (RH) conditions used in ASAP modeling

Experiment	T (°C)	RH (%)	Sampling Points (days)
1	60	30	0, 7, 14
2	60	50	0, 3, 7
3	60	60	0, 3
4	60	65	0, 3, 7
5	60	75	0, 3
6	50	60	0, 7, 14
7	50	65	0, 7, 14
8[b]	40	75	0, 3, 6[c] months

[a]Additional stability data at 40 °C/60%RH for API 1 from a separate, unrelated study were also included in the modeling for API 1. The inclusion of the data does not change the overall conclusion for API 1. Data for API 2 at 40 °C/60%RH were not available
[b]Open Dish Study
[c]Only API 1 was tested at 6 months

various temperatures and relative humidities. Equation 2 contains two independent variables (T and RH); therefore, at least three combinations (a 3-point protocol) of T and RH are necessary to obtain values of A, E_a and B by regression analysis or other curve fitting techniques. The greater the number of points in the protocol the greater the reliability of the estimates of the regression coefficients, and the predicted shelf life.

If the stability of the drug product is significantly affected by the presence of moisture, sealing in a water-impermeable package (such as aluminum foil or blister) may be required to reduce the rate of degradation by eliminating any further ingress of water toward the product. Packaging in a semi-permeable container or blister may slow down the degradation by reducing the moisture vapor transmission rate (MTVR). However, if the product is particularly sensitive to the presence of water, packaging with a desiccant may be necessary. Accelerated stability studies of SDFs are frequently conducted in so called "open dish" studies in which the test article is exposed to the atmosphere and equilibrates with the ambient humidity. An alternative approach to understanding the effects of humidity on the rate of degradation is to first pre-equilibrate the SDF with an atmosphere of known RH and then seal it in a water-impermeable pouch made of aluminum foil. In addition to predicting the effects of temperature and relative humidity, ASAP*prime*® has the added advantage of allowing the effects of packaging in water-impermeable or partially impermeable containers or blisters on stability to be predicted.

Although the intended application of (ASAP*prime*®) is the prediction of the rates of chemical degradation in SDFs there is no reason that this approach cannot be applied to physical instability, because Eq. 2 is empirical and simply a way of correlating the rate of change of any measurable parameter of product performance as a function of time, temperature and relative humidity. Accordingly, the objective of this study was to test the hypothesis that ASAP*prime*® software can be used to predict the dissolution rate of change of the active ingredients in tablets at the intended storage condition, based on data obtained at elevated temperature and relative humidity. This approach is reasonable because the majority of changes in dissolution rate of SDFs can be attributed to changes in water content (Waterman & Swanson 2014; MacDonald 2010; Colgan & Hofer 2015; Stella 2000; Timmerman 2003; Waterman 2011). The SDF used to test the hypothesis was an investigational immediate release tablet containing two active pharmaceutical ingredients (API 1 and API 2) that had previously shown slowed dissolution at 40 °C/75 % RH in an open dish study and enabled better understanding of the risk to dissolution changes at room-temperature storage.

Results and discussion

Slowdown in dissolution of both APIs was observed for tablets stored at highly elevated temperature and relative humidity conditions, likely due to physical changes of the SDF, no chemical degradation of either API was observed under these conditions. Representative dissolution profiles are shown in Fig. 1a, which demonstrates that the dissolution of API 1 at 20 min decreased from an initial value of 90.9 to 82.9 % after three days storage in an open dish at 60 °C/60 % RH. The dissolution of API 1 decreased to 79.9 % after storage in an open dish for 7 days at 60 °C/65 % RH and 76.8 % after 3 days at 60 °C/75 % RH. A similar slowdown in the dissolution of API 2 was also observed (Fig. 1b).

The impact of temperature and RH (30–75 %) (T/RH) on dissolution at long term storage conditions was evaluated through a number of stressed and open dish studies. The dissolution changes at 20 min for both APIs over long term storage are of particular interest,

Table 2 Stability studies/conditions used for external model validation

Study	T (°C)	RH (%)	Time Points for Validation	Packaging Configurations	Initial Tablet Water Content
1	25	60	12 months	Aclar Blisters	2.1 %
	30	65	12 months		
	40	75	6, 12 months		
2	25	60	6, 12 months	Open Dish	4.1 %

Table 3 Regression coefficients for data fitted to the modified Arrhenius equation (Eqs. 2 and 3) and the Dimensionless equation (Eq. 4) for the two active ingredients

API	ln A (SD)	E_a (kcal/mol) (SD)	C (x 10^{-4}) (SD x 10^{-4})	B (x 10^{-2}) (SD x 10^{-2})	R^2
1	73.8 (5.7)	50.0 (3.9)	2.52 (0.02)	5.3 (0.8)	0.937
2	71.4 (9.7)	51.0 (6.6)	2.58 (0.03)	10.4 (1.9)	0.954

as typical dissolution specifications for immediate release tablets are Q = 80 % at 20 min. (The quantity, Q, as defined per USP <711>, is the amount of dissolved active ingredient, in percent label claim). The data were analyzed by ASAP*prime*® to develop a model describing the effect of moisture and temperature on dissolution over the product shelf life at target storage conditions. The T/RH design space and target are shown in Fig. 2. Detailed experimental design and durations are shown in Table 1.[1] The predicated data from ASAP*prime*® modeling were compared against real-time stability data to validate the approach (Table 2). The experimental data used to construct the model relating the percent dissolved to values of T and RH were generated by pre-equilibrating the tablets at 25 °C and various values of RH (30–75 %) (Fig. 2). The mean values for the amounts of each API dissolved (n = 3) after 20 min are provided in Appendix 1. The data were fitted to Eq. 2 and the value for the regression coefficients

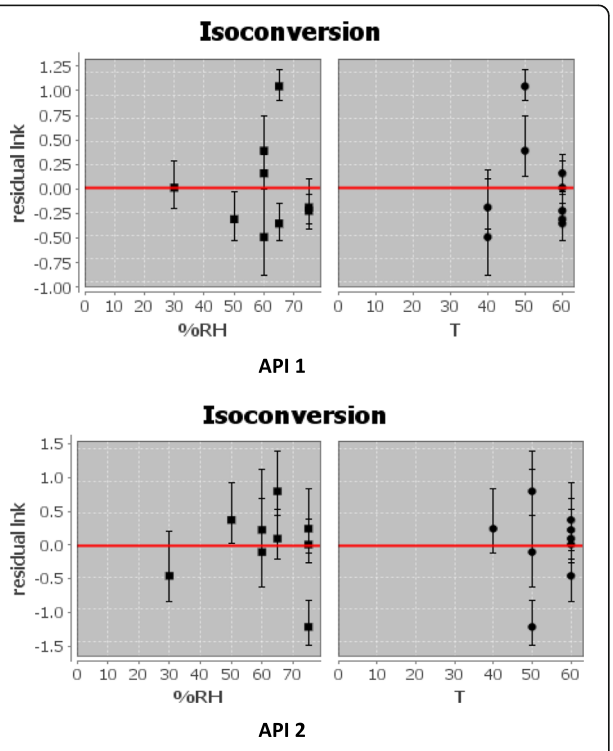

Fig. 3 Residuals for the Predicted Isoconversion Values for the Two Active Pharmaceutical Ingredients

(A, E_a, B and R^2) are shown in Table 3. The values of 0.937 and 0.954 for R^2 mean that 6.3 % (API 1) and 4.6 % (API 2) of the variance in the data for the two APIs are not explained by the model. Figure 3 shows the residuals obtained from the predicted values and those obtained by experiment were randomly distributed, indicating that there was no systematic error in the predictions.

Effects of temperature and relative humidity on dissolution

The computer software (ASAP*prime*®) uses the isoconversion method (Waterman (2011)), rather than regression analysis to calculate the values of A, E_a, B, where the isoconversion time, IC is the time to reach the predetermined value for the acceptance criteria (not less 80 % dissolved after 20 min). Replacement of the rate constant, k with the reciprocal of IC gives:

$$\ln\frac{1}{IC} = \ln A - \frac{E_a}{RT} + B(RH) \tag{3}$$

Equation 3 can be re-written in dimensionless terms by substitution of $\frac{E_a}{R}$ by C,

$$\ln\frac{1}{IC} = \ln A - \frac{C}{T} + B(RH) \tag{4}$$

where C is the temperature sensitivity factor. Equation 4 allows the effects of changing T and RH to be assessed independently of each other. The effect of changing the atmospheric moisture from a value of RH_1 to RH_2 at a fixed value of T (ΔRH) may be determined as follows:

$$\ln\frac{IC_{RH2}}{IC_{RH1}} = B(RH_1 - RH_2) \tag{5}$$

Equation 5 can be re-written in non-logarithmic terms to give:

$$\frac{IC_{RH2}}{IC_{RH1}} = F_{\Delta RH} = e^{B(RH_1 - RH_2)} \tag{6}$$

where $F_{\Delta RH}$ is the factor by which the isoconversion time (the time to reach Q = 80 %) changes for a given change in RH (ΔRH). Equation 6 predicts that the value of $F_{\Delta RH}$ is independent of the intital and final values of RH and depends only on the difference. Therefore, the values of $F_{\Delta RH}$, for 10 % change in absolute RH (ΔRH = 10 % RH) are 1.70 and 2.83 for API 1 and API 2, respectively. This means that the change in isoconversion time for the two APIs for a 10 % change in absolute RH is approximately 70 % for API 1 and approximately 183 % for API 2 at a fixed temperature.

The effect of changing T at a fixed value of RH (ΔT) is slightly more complicated because the value of $F_{\Delta T}$, depends on the initial, (T_1) and the final temperature (T_2), as follows:

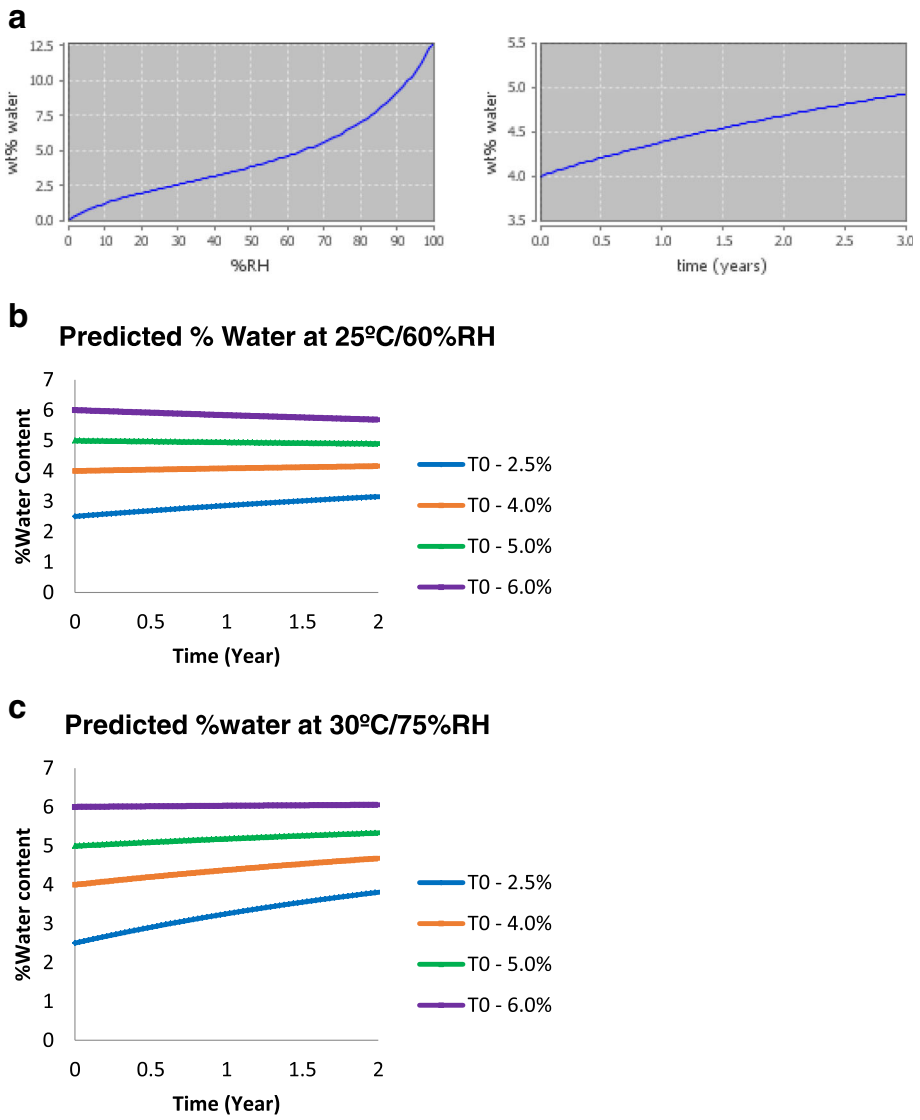

Fig. 4 a Predicted Water Isotherm (*left*) and the Predicted Water Content in the Tablets after Open-Dish Storage at 25 °C/60%RH (initial water content 4.0 %). **b** Predicted Water Contents in Tablets Packaged in Aclar Blisters Over 2 Years at 25 °C/60%RH with Different Initial Water Contents. **c** Predicted Water Contents in Tablets Packaged in Aclar Blisters Over 2 Years at 30 °C/75%RH with Different Initial Water Contents

$$\ln\frac{IC_{T2}}{IC_{T1}} = C\left(\frac{1}{T_2} - \frac{1}{T_1}\right) \tag{7}$$

or

$$\ln\frac{IC_{T2}}{IC_{T1}} = C\left(\frac{T_1 - T_2}{T_1 T_2}\right) \tag{8}$$

and

$$\frac{IC_{T2}}{IC_{T1}} = F_{\Delta T} = e^{C\left(\frac{T_1 - T_2}{T_1 T_2}\right)} \tag{9}$$

That being said, the error in using a constant value of the product T_1T_2 is less than 10 % over relatively small temperature ranges (20 – 60 °C), in which case Eq. 9 simplifies to:

$$\frac{IC_{T2}}{IC_{T1}} = F_{\Delta T} = e^{C\Delta T \times 10^{-4}} \tag{10}$$

Therefore, the values of $F_{\Delta T}$, for 10 °C change in temperature are 12.4 and 11.0 for API 1 and API 2, respectively. This means that the change in isoconversion time for a 10 °C change in temperature for API 1 and API 2 are approximately 1250 % and 1100 %, respectively, at a fixed value of RH.

It can be shown that the combined effect changing both T and RH ($F_{\Delta T,\Delta RH}$) can be estimated by:

$$F_{\Delta T,RH} = e^{(B\Delta RH + C\Delta T \times 10^{-4})} \quad (11)$$

or

$$F_{\Delta T,RH} = F_{\Delta T} \times F_{\Delta RH} = \left(e^{B\Delta RH}\right) \times e^{(C\Delta T \times 10^{-4})} \quad (12)$$

Therefore, the combined effect of changing the storage conditions from the accelerated conditions 40 °C/75 % RH to the intended storage condition of 25 °C/60 % RH (ΔT = 15 °C ΔRH = 15 % RH) predicted by the model ($F_{\Delta T} \times F_{RH}$) is 96.5 and 181.3, for API 1 and API 2, respectively. The individual contributions from temperature and relative humidity are as follows

API 1

$$F_{\Delta T} = 43.6 \quad (13)$$

$$F_{RH} = 2.21 \quad (14)$$

API 2

$$F_{\Delta T} = 38.9 \quad (15)$$

$$F_{RH} = 4.66 \quad (16)$$

It is clear from Eqs. 13–16 that the contribution to a reduction in dissolution at 20 min for both drugs from elevating the temperature is significantly greater than the contribution from increasing the relative humidity and that the effects of temperature on the dissolution of both drugs is about the same. Interestingly, although the effects of humidity change were relatively small, the effect of RH on the dissolution of API 1 (F_{RH} = 2.21) was much less than the effect on API 2 (F_{RH} = 4.66). The reason for the difference in the effect of water on the dissolution of the two APIs is not clear; however, it does have important implications for the stability of the tablets at room temperature, which are discussed in the next sections.

Effects of initial water content

The weak dependency of drug dissolution on RH (Eq. 4) was investigated further to determine if it was necessary to control the water content of the tablets in the drug-product specification. The amount of water taken up by the tablets at specific values of RH was entered into ASAP*prime*® to determine the water sorption isotherm over the entire range of RH (Fig. 4a).[2] Fig. 4a shows a sigmoidal relationship between the water content of the tablets in which the water content increases slowly up to 50 % RH to a value of 4 % and then increases exponentially to approximately 13 % at 100 % RH. Tablet water content change on stability can also be predicted based on the GAB parameters and given packaging configurations. Figure 4b and c are examples of predicted tablet water contents under 25 °C/60%RH and 30 °C/75%RH storage conditions over 2 years at different initial values. The software uses this information to predict the effect of the water content on the dissolution of the tablets. Figure 5 shows the anticipated effect that the amount of drug dissolved at 20 mins after two years' storage decreases and the effect is more pronounced for API 1 than for API 2, which is expected from the previous discussions described above. Although the effect of humidity is much less for API 1 than API 2, the dissolution rate drop for both APIs are primarily driven by effect of temperature, which is more significant for API 1 than API 2; therefore, more changes are observed in API 1 than API 2 at the end of the two-year storage and the differences are more pronounced at 30 °C than at 25 °C. Despite the differences in the effects of initial moisture on the dissolution of the two APIs, ASAP*prime*® predicts that the dissolution of both drugs will remain within specification after storage (Q = 80 %) for two years at either 25 °C/60 % RH, or 30 °C/75 % RH independent of the initial water content up to 6.3 % water, which is the equilibrium water content of the tablets at 75 % RH. The equilibrium water content at 60 % RH was found to be 4.1 %.

Stability in Aclar® blisters

Although the ASAP*prime*® analysis predicted some differences in the sensitivity of the dissolution of the two APIs to moisture, the results also indicated the effect of RH was insufficient to warrant the need for special packaging. This is supported by the results of two studies summarized in Table 4, which show very little, if any, increase in moisture content of the tablets packaged in Aclar® blisters for three to six months at various storage conditions. Table 4 also shows very good agreement between the observed values of water content and the

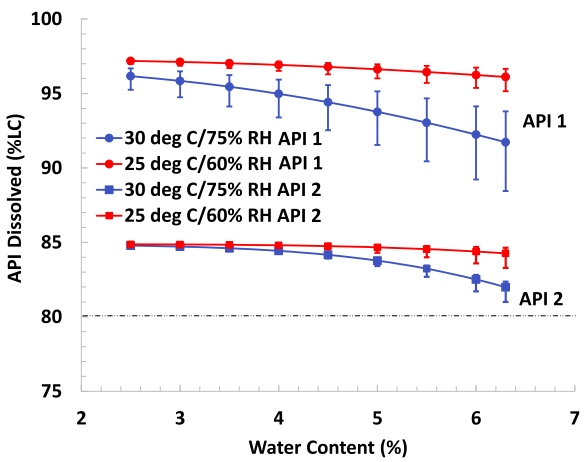

Fig. 5 Relationship between the Predicted Percent Dissolved at 20 min of Both Active Pharmaceutical Ingredients after Two Years and the Initial Water Content at 25 °C/60%RH and 30 °C/75%RH

Table 4 Predicted and observed water content of tablets packaged in Aclar® foil blisters at different storage conditions (Temperature (T) and Relative Humidity (RH))

Study	Storage Conditions			Water Content (% w/w)		
	T (°C)	RH (%)	Time (months)	Initial	Predicted	Observed
1	30	75	6	2.1	2.4	2.2
	40	75	6		2.8	2.7
	25	60	6		2.3	2.0
2	25	60	3	2.4	2.5	2.4
	30	65	3		2.5	2.3
	40	75	3		2.8	2.7

values predicted by ASAP*prime*®. Finally, Table 5 shows no difference in the amounts of the two APIs dissolved from tablets, packaged in Aclar® blisters, following storage for 12 months at 25 °C/60 % RH, 30 °C/65 % RH and 40 °C/75 % RH. Similar results were observed on a different batch of tablets stored at the same conditions in an open dish (Table 5). Notably, the ASAP*prime*® software predicted very accurately that the change in dissolution after storage of the tablets packaged in Aclar® blisters would be insignificant after storage for 12 months at the intended storage condition (25 °C/60 % RH). We will continue to the monitor the stability of these formulations with a view to establishing a two-year shelf life, a period over which predictions made by the ASAP*prime*® software indicated that the dissolution of the two drugs would be well within typical specifications (Q = 80 % at 20 min) for an immediate release product.

Conclusions

In this study, we have clearly demonstrated that the computer program, ASAP*prime*®, originally developed to predict the rates of degradation of SDFs arising from chemical reactions can also be used to predict changes in dissolution. Experiments conducted under various conditions of elevated temperature and relative humidity accurately predicted that the reduced rates of dissolution of two APIs in an SDF, IR tablet seen under accelerated conditions would not translate into any measurable changes in dissolution over the shelf life of the product (up to two years at 25 °C/60 % RH or 30 °C/75 % RH). Furthermore, the software predicted accurately that no special precautions are necessary to protect the product from moisture and that there is no need to control the water content of the tablets in the drug product specification. The methodology described here adds great value to the overall Quality by Design approach to tablet development.

Methods

Materials

Chemicals and reagents

All chemicals and reagents, obtained from various commercial sources, were reagent grade, except for the HPLC solvents, which were HPLC grade. Deionized water was prepared in-house.

Tablets

The article used to test the hypothesis was an investigational, solid dosage form (SDF) tablet[3] containing two active pharmaceutical ingredients, API 1 and API 2: both drugs were small molecules with molecular weights of less than 1000.

Procedures

Dissolution procedure

Tablet dissolution testing was performed on three tablets stored at each condition using USP Apparatus 2 in 900 mL of dissolution media at 37 °C. Due to their

Table 5 Predicted and observed dissolution of the two active pharmaceutical ingredients after 20 min at different storage conditions of temperature (T) and relative humidity (RH)

Study	Storage Conditions			Amount Dissolved (LC%)					
	T (°C)	RH (%)	Time (months)	API 1			API 2		
				Initial (T0)	Final (6 or 12 mo)		Initial	Final (6 or 12 mo)	
					Predicted	Observed		Predicted	Observed
1[a]	25	60	12	95.9	95.9	95.7	85.5	84.9	87.4
	30	65	12		95.8	96.4		84.8	86.7
	40	75	6		94.7	92.5		84.6	85.6
	40	75	12		92.7	92.5		83.9	84.8
2[b]	25	60	6	92.9	92.8	94.1	86.3	NT[c]	NT[c]
	25	60	12		92.7	93.2		84.8	87.1

[a]Tablets packaged in Aclar® blisters. Initial water content 2.1 %
[b]Open dish study. Initial water content 4.1 %
[c]Not tested

different aqueous solubilities, the dissolution profile of API 1 was obtained with pH 1.5 media, and the dissolution profile of API 2 was obtained with pH 6.8 media. Dissolution profiles were collected at 5, 10, 15, 20, 30, 45 and 60 min at 75 rpm and 65 rpm, respectively for API 1 and API 2, with an "infinity spin" from 60-75 min at 200 rpm.

Sample analysis

Samples (1.5 mL) were removed and filtered immediately through a polyvinylidene fluoride (PVDF, 10 μm,) filter at the sampling times listed above and analyzed for API content by HPLC. The HPLC procedure was validated for accuracy, precision and linearity and found to be suitable for the intended application. The system was calibrated using external standards containing concentrations of API 1 and API 2 equivalent to 100 % of the label claims (LC) of each API.

Stability studies

In one set of experiments the tablets were pre-equilibrated to constant water content at various relative humidity (RH) values ranging from 30 % to 75 % at 25 °C sealed in aluminum foil pouches and stored for various periods of time (Table 2) at 50 °C and 60 °C. In a second set of experiments tablets were stored in petri dishes (open dish) at 40 °C/75 % RH. Detailed experimental conditions and durations are listed in Table 1. The samples were stored in calibrated stability chambers.

Water content

The water content of the tablets was determined by automated Karl Fischer titration.

Water sorption isotherm

The water sorption isotherm of the tablets was determined using a dynamic water sorption analyzer.

Data analysis

The concentrations of the dissolved APIs at each sampling point ($C_{1,t}$ and $C_{2,t}$) were expressed as a percentage of the label claim ($LC\%_{1,t}$) (Eq. 17) and plotted against time, t to generate the dissolution profiles ($LC\%_{1(\text{or } 2),t}$ vs. t).

$$LC\%_{(1or2),\,t} = \frac{C_{1(or2),t}}{LC_{1(or2),t}} 100\% \tag{17}$$

The relationships between the values of $LC\%_{1,20}$ and $LC\%_{2,20}$, temperature (T) and relative humidity (RH) were established by fitting the data Eq. 2 to calculate the regression coefficients, A, E_a, and B, using the ASAP-*prime*® software (version 3, FreeThink Technologies, Inc. Montvale, NJ 06405).

Endnotes

[1]Additional stability data at 40 °C/60%RH for API 1 from a separate, unrelated study were also included in the modeling for API 1. The inclusion of the data does not change the overall conclusion for API 1. Data for API 2 at 40 °C/60%RH were not available.

[2]The software uses the GAB equation developed by Guggenheim, Anderson and de Boer as described by Timmerman (Waterman 2009) to simulate the water sorption isotherm. The GAB Equation parameters are provided in Appendix 2.

[3]The structures of the APIs and the composition of the tablets are proprietary; however, disclosure of this information is not necessary to understand how the study was conducted, the hypothesis tested or the conclusions.

Appendix 1

Table 6 ASAP data input for API 1 – dissolution at 20 min

Time (days)	T (°C)	%RH	%LC at 20 min	SD (%)
0	60	60	98.1	0.9
3	60	60	82.9	3
0	60	75	96.2	0.9
3	60	75	76.8	3
0	40	75	96.3	0.9
90	40	75	90.9	3
180	40	75	86.7	3
0	60	30	98.4	0.9
7	60	30	90	3
14	60	30	85.6	3
0	60	50	98.1	0.9
3	60	50	87.6	3
7	60	50	85.8	3
0	60	65	97.5	0.9
3	60	65	79.9	3
7	60	65	76.4	3
0	50	60	98.1	0.9
7	50	60	92.4	3
14	50	60	88.9	3
0	50	65	97.5	0.9
7	50	65	87	3
14	50	65	76.4	3
0	40	60	96.2	0.9
90	40	60	94.8	3
180	40	60	93.7	3

Table 7 ASAP data input for API 2 – dissolution at 20 min

Time (days)	T (°C)	%RH	%LC at 20 min	SD (%)
0	60	60	84.9	1.1
3	60	60	77.3	3
0	60	75	84.7	1.1
3	60	75	70.5	3
0	40	75	86.3	1.1
90	40	75	80.6	3
0	60	30	85.5	1.1
7	60	30	85.5	3
14	60	30	84.2	3
0	60	50	85.9	1.1
3	60	50	80	3
7	60	50	79.3	3
0	60	65	83.4	1.1
3	60	65	76	3
7	60	65	76.3	3
0	50	60	84.9	1.1
7	50	60	83.8	3
14	50	60	82.7	3
0	50	65	83.4	1.1
7	50	65	80.8	3
14	50	65	80.8	3

Appendix 2

Table 8 GAB parameters used based on DVS of SDF tablets

W_m	C	K
2.758	7.67	0.785

Abbreviations

A: Collision frequency factor; API: Active pharmaceutical ingredient; ASAP: Accelerated stability assessment program; B: Humidity sensitivity factor; C: Temperature sensitivity factor; E_a: Activation energy; $F_{\Delta RH}$: Factor by which the IC changes for given change in RH at fixed T; $F_{\Delta T}$: Factor by which the IC changes for given change in T at fixed value of RH; HPLC: High performance liquid chromatography; IC: Isoconversion time; IR: Immediate release; LC: Label claim; LC%: Percentage label claim; MVTR: Moisture vapor transmission rate; Q: USP acceptance criteria; R: Gas constant; RH: Relative humidity; SDF: Solid dosage form; T: Temperature

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Declarations

Dissolution predictions and results described herein do not relate in any way to unexpected effects of combining two APIs on the dissolution rate of each individual API.

Authors' contributions

HL conducted the experimental work. DN was involved in the study's conception and design. HL and CMR analyzed the data and prepared the abstract, introduction, experimental, results and discussion and conclusions sections. DN and AK reviewed and edited the manuscript. All authors have read and approved the final manuscript.

Competing interests

Christopher M. Riley, Ph.D. Editor-in-Chief, *AAPS Open*, was not involved in the review process of this article or in the decision to publish.

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References

Baertschi S (2007) Pharmaceutical Stress Testing: Predicting Drug Degradation. Informa Healthcare, New York
Colgan S, Hofer R, Vuoviski K, Waterman K, Norris (2015) Lean Stability, AAPS Newsmagazine, 14-18 Sept. The Timmerman. vol 220 (1–3)
Huynh-Ba K (2008) Handbook of Stability Testing on Pharmaceutical Development: Regulations, Methodologies and Best Practices. Spirnger, New York
Karstensen J (1990) Drug Stability: Principles and Practices. Marcel Dekker, New York
MacDonald KW (2010) Package selection for moisture protection for solid, oral drug products. J Pharm Sci 99:4437–4452
Stella SY (2000) Stability of Drugs and Dosdage Forms. Kluwer Academic/Plenum, New York
Timmerman E (2003) Multilayer sorption parameters: BET or GAB values. Colloid Surf A: Physiochem Eng Asp: 220(1-3):235–360
Waterman K (2009) Understanding and Predicting Pharmaceutical Proruct Shelf-Life. In: Huynh-Ba K (ed) Handbook of Stability Testing in Pharmaceutical Development: Regulations, Methodlogies and Best Practices. Springer, New York, pp 115–135
Waterman K (2011) The application of accelerated stability assessment program (ASAP) to quakity by design (QbD) for drug product stability. AAPS PharmSciTech 12(3):932–937
Waterman KC, Carella AJ (2007) Improved protocol and data analysis for accelerated shelf-life estimation of solid dosage forms. Pharm Res 24:780–790
Waterman KC, Swanson JT (2014) A scientific and statisitical analysis of accelerated aging of pharmaceuticals. Part 1: accuracy of fitting methods. J Pharm Sci 103:3000–3006