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Degradation Rate Observations as a Function of Drug Load in Solid-State Drug Products

Steven W. Baertschi [1], Allison L. Dill [2,*], Timothy T. Kramer [3], Garry Scrivens [4,*], Miroslav Suruzhon [4]

[1] Baertschi Consulting, LLC, Carmel, Indiana 46033
[2] Eli Lilly and Company, Lilly Research Laboratories, Small Molecule Design and Development Indianapolis, Indiana 46285
[3] Eli Lilly and Company, Lilly Research Laboratories, Global Statistical Sciences Indianapolis, Indiana 46285
[4] Analytical Research and Development, Pfizer Inc., Sandwich, UK

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ABSTRACT

Degradation rates of solid-state drug products generally increase as the drug load decreases. A model for quantifying this effect based on surface area ratios is proposed here. This model relates the degradation rate to an estimate of the proportion of drug substance in contact with the excipient, and that the drug substance in contact with excipients degrades more quickly. Degradation data from previously published case studies and from 5 new case studies were found to be consistent with our proposed model; our model performed better than similar previously published models. It was also found that the relationship between degradation rate and drug load is largely independent of the temperature and humidity conditions, suggesting that drug load solely affects the pre-exponential factor of the Arrhenius equation and does not significantly affect the activation energy of the degradation process. A second method for calculating the proportion of the drug substance surface in contact with the excipient surface is presented in the Supplementary Material. Fundamentally, the 2 methods are very similar and provide almost identical fits to the experimental data.

Introduction

One of the areas critical to the development of pharmaceutical products is chemical stability sufficient to deliver an acceptable shelf life. Progress has been made in the rapid modeling of solid-state degradation kinetics via short-term accelerated stability studies using a humidity-modified Arrhenius equation.[1-3] Such models, while increasingly being recognized as effective tools for speeding development by reducing the time it takes to predict the shelf life of a product, are valid only for the specific solid dosage formulation and strength (i.e., drug load). There would be increased value if predictive models were available for relating degradation kinetics to drug load so that degradation rates associated with 1 or 2 drug loads could be used to predict degradation rates for a broad range of potential or actual drug loads.

It is widely accepted that the stability of drug substances can be affected by excipient interactions[4] and that the rate of degradation of a drug product is dependent on the dosage strength, with the rate increasing significantly as the drug load decreases. Two approaches for quantitatively modeling the rate of degradation of the drug substance as a function of drug load have recently been proposed.[5,6] Both models propose that the rate of degradation is faster at the interface between drug substance and excipient. The first of these approaches used a "quasi-liquid" model to calculate the proportion of drug substance at the interface; the quasi-liquid model assumes that the small drug substance particles randomly fill in the interstitial spaces between larger excipient particles and essentially act as one large fluid particle. From this, a power-law (allometric) relationship between the contact surface area (and hence the rate of degradation) and the volume fraction of the drug substance was derived (Eq. 1).

$$Ln(k) = \alpha * Ln(\%Drug\ Substance) + Ln(k_0) \quad (1)$$

It was suggested that the slope, α, is expected to be between zero, when excipient interactions do not influence degradation,

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* *Correspondence to:* Garry Scrivens (Telephone: +44 01304 649578) and Allison L. Dill (Telephone: +1-317-476-1588).
E-mail address: garry.scrivens@pfizer.com (G. Scrivens).

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and −2/3, when excipient interactions influence degradation, because the slope follows the surface-to-volume ratio of the drug particles present. (Note on logarithms: throughout this article we use natural logarithms [base "e" denoted by "Ln"] for all logarithmic relationships, whereas previous literature sources have used base 10 logarithms. The choice of logarithm type does not fundamentally affect the equation and has no effect on factors such as a as long as the same logarithm type is used for both the x and y axes.) The derivation of this "allometric" model and the proposed limits for "α" were shown to be invalid by Deepika and Dewan,[7] who later went on to propose a different allometric model[6]:

$$Ln(k) = \alpha * Ln\left(\frac{\%Excipient}{\%Drug\ Substance}\right) + Ln(k_0) \quad (2)$$

The possibility of a quantitative relationship between drug load and degradation rate is an intriguing and potentially powerful observation that is worthy of further investigation. Therefore, we decided to evaluate this relationship for a number of other drug substances and excipient types and a wider range of drug loads. Our evaluation used several case studies of drugs formulated at different dosage strengths, in development at Lilly. In addition, the degradation rates for a broad range of drug loads for 2 binary mixtures were studied at Pfizer to get detailed information about the relationship between drug load and degradation rate. As a result of these investigations and after carefully analyzing similar previously published experimental data,[5,6] we propose a third model that we believe has the strongest rationale and provides the best overall fit to the experimental data across different drug products.

Experimental

Case Study 1

The sample tablets were packaged in nitrogen-inerted, cold-form foil blisters and stored at conditions of 25°C/60% relative humidity (RH), 30°C/75%RH, and 40°C/75%RH and analyzed for total degradation products using a stability-indicating reversed-phase HPLC method after 1 month, 3 months, and 6 months of storage to determine the rate of degradation.

Case Studies 2, 3, and 4

The sample tablets for these case studies were stored in open dish containers and stored at various temperature and humidity conditions as described below in the Results and Discussion section. They were subsequently analyzed for total degradation products or, for case study 3, individual degradation products. Product-specific, stability-indicating, reversed-phase HPLC methods were used for analysis. Degradation rates were determined from the slopes of the degradation amount versus time plots for each condition.

Case Study 5

Powder blend binary mixtures of drug substance D and dicalcium phosphate ("A-TAB anhydrous" grade) were prepared by simple mixing. Bulk samples with nominal drug loads of 1%, 5%, 10%, 25%, 40%, 50%, and 80% were prepared by weighing the 2 components, combining, and then tumbling gently for ~2.5 h using a Turbula T2F blender. The bulk blends were stored in an open container at 70°C/75%RH. At various timepoints, multiple aliquots were sampled from the bulk blend into pre-tared HPLC vials. An accurate volume of sample diluent was added to each of the HPLC vials using an Autorep pipette. The volume added was calculated to achieve a concentration of ~0.5 mg/mL (as required by the analytical method); this calculation is based on the nominal drug load and the tare-weight of blend added to the HPLC vial. The HPLC vials were shaken for 30 min to fully extract the analytes and the insoluble excipient was allowed to settle before injection. The HPLC method determined the amount of degradation product as area% and determined the actual drug load (%w/w) of the subsample. The drug load (%w/w) is calculated from the parent compound assay quantified using external standards and using the mass of blend added to the HPLC vial and the accurate volume of sample diluent added. Samples were tested after 4.8, 8.8, 19.8, 29.6, 36.6, 48.5, 81.2, and 122.9 days of storage at the accelerated conditions.

Case Study 6

Powder blend binary mixtures of drug substance E and microcrystalline cellulose ("Avicel PH-101" grade) were prepared by simple mixing. Triplicate samples with nominal drug loads of 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, and 100% (pure drug substance) were prepared in 4-dram vials by weighing the 2 components, combining, and then tumbling gently for ~2.5 h using a Turbula T2F blender. Each of the blend samples was stored in an open vial at 80°C/40%RH. At various timepoints, certain vials were removed from the stability cabinet and a sample of the blend was weighed into 8-dram vials and an accurate volume of sample diluent was added to each of the vials in order to achieve a desired concentration of ~0.1 mg/mL (as required by the analytical method); the volume of diluent added was calculated based on the nominal drug load and the weight of blend added to the 8-dram vial. Following extraction, the supernatant was transferred to an HPLC vial for analysis. The HPLC method determined the amount of degradation product as area% and determined the actual drug load of the subsample. The drug load (%w/w) is calculated from the main band assay quantified using external standards and using the mass of blend and the accurate volume of sample diluent added. Samples were tested after 29.8 days and 53.5 days of storage under the accelerated conditions.

Results

Case Studies/Example Data

Case Study 1

A pediatric formulation of prasugrel (Effient®) was studied (see Fig. 1 for structure); the current approved tablets are 5 mg and 10 mg with a drug load of greater than 5%, while the pediatric tablets

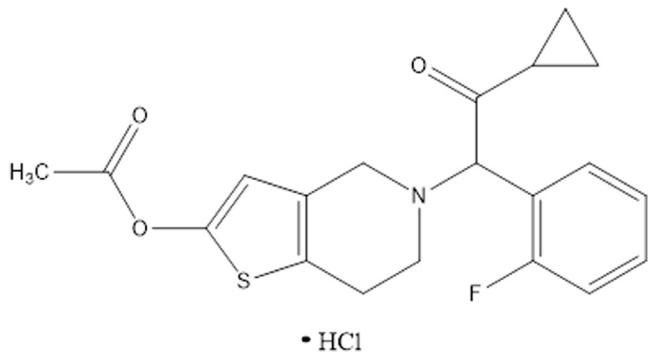

Figure 1. Chemical structure of prasugrel hydrochloride.

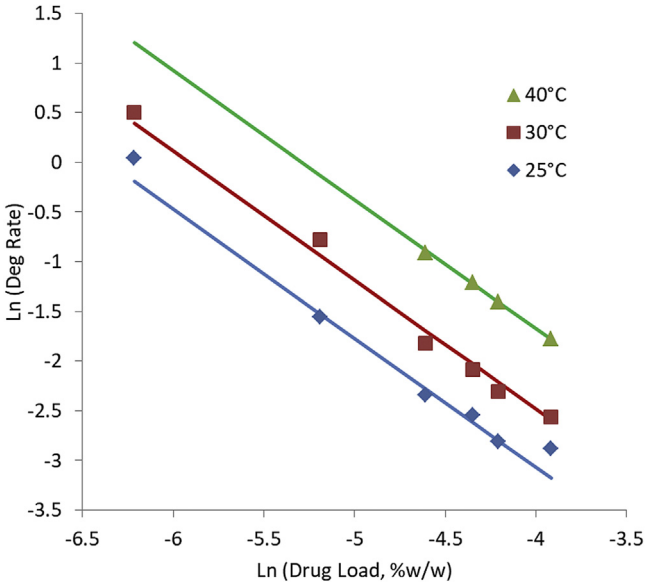

Figure 2. Relationship between observed Ln(degradation rate) and Ln(drug load) over a range of temperatures for case study 1.

studied had a dose range of 0.2 to 5 mg with drug loads ranging from 0.2% to 2%. The drug substance is micronized in the pediatric tablets and the main excipients are mannitol and starch. This dosage flexibility is necessary when dosing pediatric patients who could range in age from 2 to 18 years. Due to the larger range of dosage strengths and the dosing flexibility required in the pediatric space, it is advantageous in terms of both cost and time to be able to determine the stability of multiple dosage strengths quickly and without the need to test each strength. Stability studies of the various drug loads at 25°C/60%RH, 30°C/75%RH, and 40°C/75%RH stored in cold-form foil, nitrogen-inerted blisters were conducted as described in the experimental section, and degradation rates based on the total amount of degradation were obtained. Figure 2 shows Ln(degradation rate), where degradation rate is determined from the slope of the %degradation over 6 months, plotted against the Ln(%drug load). As can be seen in Figure 2, the degradation rate data follow the linear pattern predicted by Equation 1. In addition, the lines associated with each temperature appear nearly parallel. When a common slopes model is fit using all the data across all temperatures, the common slope is approximately −1.06.[4] (A common slope model characterizes a dependent [response] variable as a linear function of one variable with intercepts dependent on one or more other independent variables. For case study 1, Ln(k) is a linear function of Ln(drug load) with intercepts that depend on temperature. In subsequent case studies, the intercepts will depend on both temperature and relative humidity.) The model proposed by Deepika and Dewan[6] performed equally well for this dataset, with similarly linear curves being obtained when Ln(degradation rate) is plotted against Ln(%excipient load/%drug load), where %excipient load is 100%-% drug load.

Case Study 2

Compound A, with a formulation consisting of drug loads of 5% and 10%, was assessed for stability in an open dish study by measuring total degradation at storage conditions of 50°C/65% RH, 50°C/75% RH, 60°C/45% RH, 70°C/30% RH, and 70°C/45% RH. The main route of degradation is hydrolysis of the ester group. Degradation rates for the different dosage strengths obtained from the stability study were plotted in the same manner described in case study 1. Because there were only 2 drug loads, straight lines were fit to Ln(degradation rate) versus Ln(drug load) at each storage condition. The availability of only 2 points per line limits the ability to test drug load degradation models; however, it can be seen that increasing drug load leads to a decrease in the degradation rate, consistent with previous studies. Figure 3 shows that the lines obtained for the various storage conditions are nearly parallel. The effect of temperature appears to be consistent with case study 1 in which temperature appears to affect the intercept, Ln(k_0), but not the slope, α. In addition, this case study also suggests that humidity similarly affects only Ln(k_0) and not α. When a common slopes model is applied, using all the data, across all temperature and humidity conditions, the common slope is approximately −0.35.

Case Study 3

Compound B has a tablet formulation with drug loads of 2.5% and 20%; degradation rates (as measured by the increase in the degradation of 2 degradation products during an open dish study) were assessed at storage conditions of 65°C/75% RH, 70°C/70% RH, 70°C/75% RH, 75°C/60% RH, and 75°C/75% RH. This molecule has 2 main degradation pathways and the rates of degradation were determined separately for each of the 2 degradants (degradant 1 and degradant 2). Degradant 1 is formed by an intramolecular cyclization to create a 6-member ring with loss of water. Degradant 2 is formed through oxidation of thiol ether to the sulfoxide. Because there were only 2 drug loads, straight lines were fit to Ln(degradation rate) versus Ln(drug load) at each storage condition. As with case study 2, the availability of only 2 points per line limits the ability to test drug load degradation models. When a common slopes model is applied, using all the data, across all temperature and humidity conditions, the common slope is approximately −1.32 for degradant 1 and −1.36 for degradant 2; these slopes are outside the range of 0 to −0.67 suggested by the quasi-liquid allometric model.[5] Figures 4 and 5 show Ln(degradation rate) plotted against Ln(drug load) for degradant 1 and degradant 2, respectively. It can be seen in these plots that the lines obtained for the different storage temperature and humidity conditions are approximately parallel. The effects of temperature and humidity appear to be consistent with the previous case studies in which temperature and humidity appear to affect the intercept, Ln(k_0), but not the slope, α.

Case Study 4

Compound C has a formulation with drug loads of 3% and 9%; degradation rates (as measured by total degradation during an

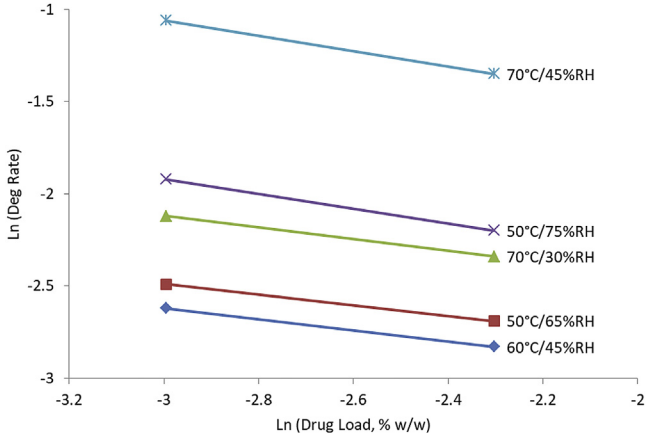

Figure 3. Relationship between observed Ln(degradation rate) and Ln(drug load) over a range of temperatures and humidity conditions for case study 2.

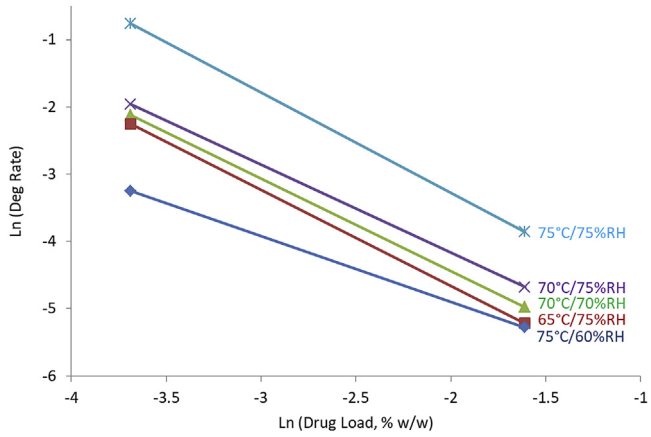

Figure 4. Relationship between observed Ln(degradation rate) of degradant 1 and Ln(drug load) over a range of temperatures and humidity conditions for case study 3.

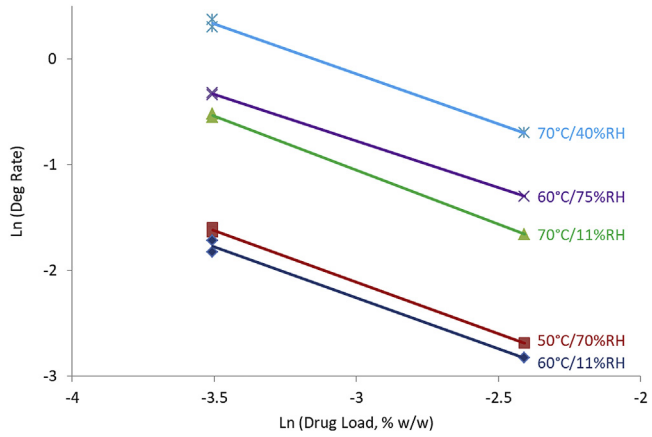

Figure 6. Relationship between observed Ln(degradation rate) and Ln(drug load) over a range of temperatures and humidity conditions for case study 4.

open dish study) were assessed at storage conditions of 50°C/70% RH, 60°C/11% RH, 60°C/75% RH, 70°C/11% RH, and 70°C/40% RH. The main route of degradation is the N-formylation of the secondary amine. Figure 6 shows Ln(degradation rate) plotted against Ln(drug load). It can be seen in Figure 6 that the lines obtained for the different storage temperature and humidity conditions are approximately parallel. The effects of temperature and humidity appear to be consistent with the previous case studies in which temperature and humidity appear to affect the intercept, Ln(k_0), but not the slope, α. When a common slopes model is applied, using all the data, across all temperature and humidity conditions, the common slope is approximately −0.96.

Case Study 5

In this case study, it was decided to focus the investigation on the relationship between the drug load of compound D and its degradation rate by studying a very large number of drug loads across a very wide range at a single storage condition. A number of drug substance:dicalcium phosphate binary blend mixtures were prepared and subjected to degradation at a single open-dish accelerated storage condition of 70°C/75%RH. Compound D undergoes a hydrolytic degradation pathway as shown in Figure 7 and the rate of degradation was calculated by dividing the degradation (%w/w) by the number of day's storage.

In Figure 8, the 2 models previously proposed in the literature are evaluated[5,6]: In panel (a), Ln(degradation rate) is plotted against Ln(drug load) while in Figure 8b it is plotted against Ln(excipient load/drug load). Figure 8a shows that, over narrow ranges of drug loads (i.e., over approximately 1 order of magnitude), Equation 1 fits the data as indicated by an approximately linear relationship, but over a wide range of drug loads the plot is clearly curved with the tangential gradient varying between approximately −0.7 and −3.7. Figure 8b demonstrates that Equation 2 models the data from case study 5 very well and superior to Equation 1, but on close inspection some curvature in Figure 8b can also be discerned, with the tangential gradient varying between approximately 0.6 and 1.2. At each drug load, the rate of degradation decreases with time; in Figures 8a and 8b, this manifests as a decrease in the vertical offset in the data, but the duration of exposure does not appear to otherwise affect the overall relationship between drug load and degradation rate.

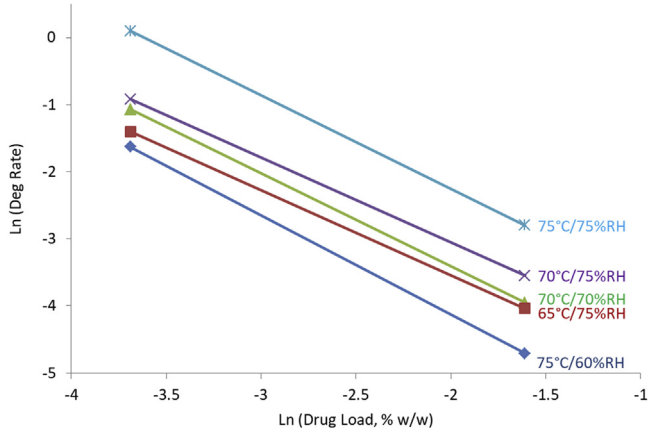

Figure 5. Relationship between the observed Ln(degradation rate) of degradant 2 and Ln(drug load) over a range of temperatures and humidity conditions for case study 3.

Case Study 6

Similar to the previous case study, this investigation focused only on the relationship between drug load (of compound E) and its degradation rate by studying a large number and wide range of drug loads. Binary blend mixtures of drug substance:microcrystalline cellulose were prepared and subjected to degradation at a single open dish accelerated storage condition of 80°C/40%RH. Compound E undergoes a complex degradation pathway involving isomerization, hydrolytic, and possibly oxidative chemistry; the overall transformation is represented in Figure 9.

As with the previous case study, the 2 models proposed in the literature were evaluated and compared graphically (Fig. 10). Over narrow drug load ranges, both models may be interpreted as fitting the data as indicated by approximately linear relationships, but over wider drug load ranges both models clearly generate nonlinear plots indicating that neither Equation 1 nor Equation 2 fully satisfactorily describe the drug load-degradation rate relationship. The

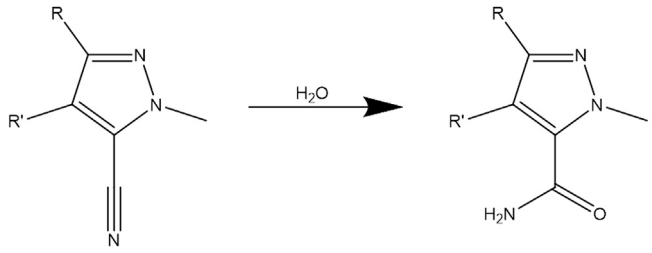

Figure 7. Hydrolytic degradation pathway for compound D.

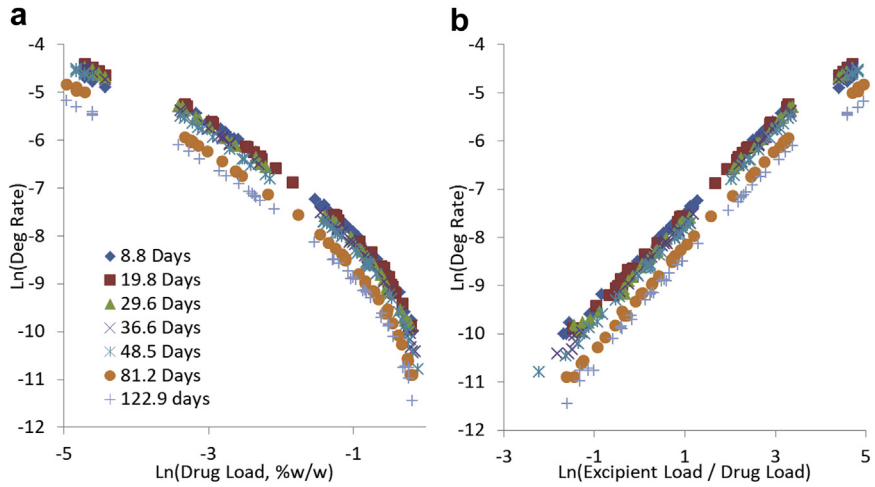

Figure 8. Relationship between Ln(degradation rate) and Ln(drug load) (panel a) and between Ln(degradation rate) and Ln(excipient load/drug load) (panel b) measured at 70°C/75%RH at multiple timepoints for case study 5.

tangential gradient varies between approximately −0.1 and −3 in Figure 10a and between approximately 0.1 and 1 in Figure 10b.

Discussion

Summary of Case Studies

These case studies show that across relatively narrow drug load ranges, the previously published allometric models (Eqs. 1 and 2) can be useful empirical models for estimating the effect of drug load on the degradation rate. Case studies 1 to 4 show that changing the temperature or humidity changes the degradation rate and therefore the relative position (vertical offset) of the lines but does not appear to affect the slope or the curve shape of Ln(k) versus Ln(drug load) or of Ln(k) versus Ln(excipient load/drug load) plots. The nonlinear relationships of these plots observed for case study 5 and particularly case study 6 show that these allometric models do not hold across wide drug load ranges for the drug products studied. Therefore, the rationalization of these allometric models in terms of fundamental principles is likely to be flawed and these case studies support the search for a more accurate model for the relationship between degradation rate and drug load. The rationalization of Equation 1 has already been disputed by Deepika and Dewan,[7] but their rationalization of Equation 2 has not yet been studied in detail. As with Equation 1, the rationalization of Equation 2[6] is based on the assumption that drug substance particles degrade much faster when in direct contact with excipient particles. Taking this fundamental assumption as a starting point our understanding of their rationalization of Equation 2 can be summarized as follows.

(a) The observed rate of degradation of the drug substance is directly proportional to the concentration of the excipient, which according to Deepika and Dewan is synonymous with the excipient load expressed as percent weight (%w/w).
(b) The observed rate of degradation of the drug substance is also inversely proportional to the concentration of the drug substance. The justification for this according to Deepika and Dewan is because "the concentration of the drug substance declines with time due to degradation by the excipients." As with point (a), the concentration of the drug substances is taken to be synonymous with drug load (%w/w).
(c) Combination of points (a) and (b) predicts that the degradation rate should be proportional to excipient load/drug load; therefore, expressing this in logarithmic form, a plot of Ln(rate) versus Ln(excipient load/drug load) should have a slope of 1. However, Deepika and Dewan also introduce a factor "α" to allow for slopes other than 1, resulting in Equation 2. The introduction of the "α" factor is justified "in case a power-law relation exists" between Ln(degradation rate) and Ln(excipient load/drug load).

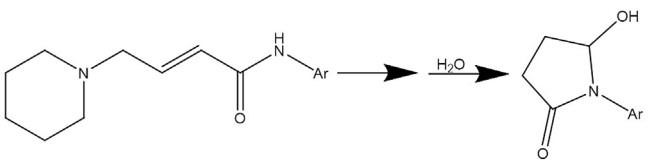

Figure 9. Hydrolytic degradation pathway for compound E.

We believe this rationalization of Equation 2 is not fully satisfactory in a number of ways. Firstly, the concept of "excipient concentration" as referred to in point (a) requires careful consideration when applied to solid powder blends and we believe it is not directly synonymous with excipient load (% w/w). In the context of degradation in the solid state, the excipient "concentration" of relevance is the amount of excipient present *per* "unit" *of drug substance*. (It is not stated here what measure is used to quantify the "amount" of excipient or what specifically is meant by a "unit" of drug substance, but it is described later how these quantities are perhaps best considered as surface areas.) Therefore, the "concentration" of excipient relevant to degradation may be expected to be related to excipient load/drug load, that is, this definition of excipient concentration automatically accounts for the relationship between degradation rate and excipient load and the inverse relationship between degradation rate and drug load. We believe this rationalization of the inverse relationship between degradation rate and drug load is preferable to that provided in point (b), which refers to a "time-related" effect. Secondly, the justification for introducing the log-log slope factor "α" [point (c)] is "in case a power-law relation exists" between degradation rate and excipient load/drug load, but there was no explanation why a power-law relation may be relevant: the authors acknowledge that a power-law relation is difficult to imagine theoretically. It appears

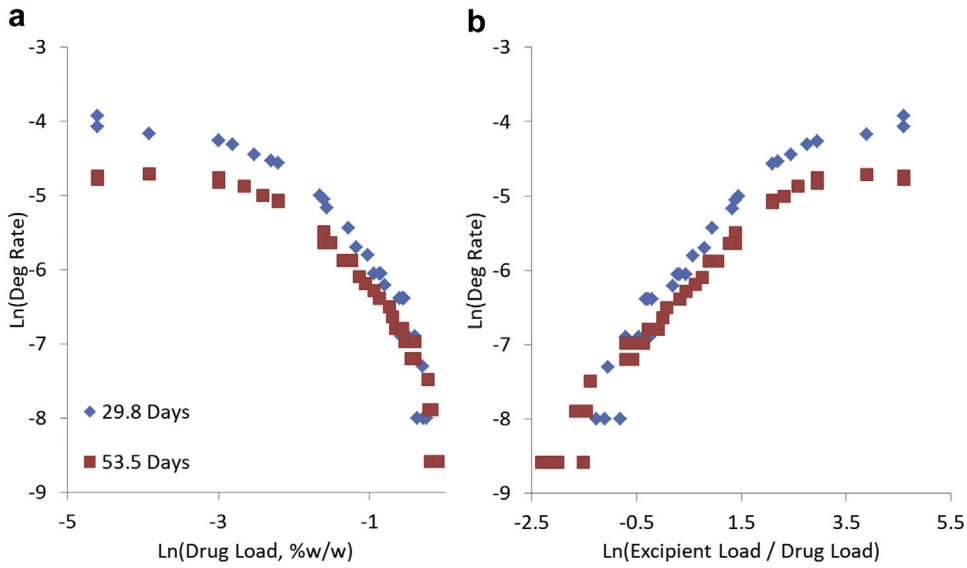

Figure 10. Relationship between Ln(degradation rate) and Ln(drug load) (panel a) and between Ln(degradation rate) and Ln(excipient load/drug load) (panel b) measured at 80°C/40%RH at 29.8 and 53.5 days for case study 6.

that the authors allow for the possibility of a power-law relation despite having invalidated the rationale for a power-law relation provided by Waterman et al.; that is, there appears to be no good rationale for a power-law relation.

Equations 1 and 2 were only partially successful in describing the relationship between degradation rate and drug load for all case studies, and the above rationalization of Equation 2 does not take into account important considerations such as the surface areas of the drug substances and excipients. These considerations are explored further in the next section and an alternative degradation rate versus drug load model that is consistent with the observed data is proposed.

The Surface Area Contact Model: An Alternative Degradation Rate Versus Drug Load Model

This model (as with previous models) is based on the assumption that degradation is accelerated by contact between drug substance and excipient particles and as the drug load is decreased, the excipient:drug substance ratio increases and a higher percentage of the drug substance particles come in contact with excipient. Specifically, the model assumes that the degradation rate is proportional to the fraction of the total surface area of all of the individual drug substance particles in contact with excipient, $f_{contact}$. A simple calculation for estimating the surface area contact fraction ($f_{contact}$) is presented below. An alternative calculation is presented in the Supplementary Material; despite being mathematically different, the resulting degradation rate-drug load model is virtually identical.

Modeling Surface Area Contact Fraction, $F_{contact}$, as a Function of Drug Load

Consider a sample of drug substance with mass m_{DS} (units, g) with a specific surface area of S_{DS} (units, m^2g^{-1}) mixed with a sample of excipient with mass m_E and specific surface area S_E. This model assumes that after mixing the fraction of drug substance surface area in contact with excipient, $f_{contact}$ is proportional to the surface area of the excipient divided by the total surface area of the mixture, that is,

$$f_{contact} \propto \frac{Surface\ Area\ of\ Excipient}{Total\ Surface\ Area\ of\ Sample} = \frac{m_E \cdot S_E}{(m_E \cdot S_E) + (m_{DS} \cdot S_{DS})} \tag{3}$$

Drug load, L, is defined as in Equation 4, and excipient load (1−L) can be calculated as in Equation 5:

$$L = \frac{m_{DS}}{m_{DS} + m_E} \tag{4}$$

$$(1 - L) = \frac{m_E}{m_{DS} + m_E} \tag{5}$$

Substituting Equations 4 and 5 into Equation 3 and simplifying gives Equation 6:

$$f_{contact} \propto \frac{(1 - L) \cdot S_E}{(1 - L) \cdot S_E + (L \cdot S_{DS})} \tag{6}$$

Note that Equation 6 does not require size or shape information of either the drug substance or excipient particles because the model is based purely on a consideration of surface areas. If a term R_{SSA} is defined as the ratio of the specific surface areas (Eq. 7), then the contact fraction equation simplifies further to Equation 8.

$$R_{SSA} \propto \frac{S_{DS}}{S_E} \tag{7}$$

$$f_{contact} \propto \frac{(1 - L)}{(1 - L) + R_{SSA} \cdot L} \tag{8}$$

When the degradation is much faster in contact with excipients and the rate of degradation in the absence of excipient is negligible, the degradation rate can be assumed to be proportional to $f_{Contact}$ as follows:

$$Degradation\ Rate = k_{limit} * f_{contact} = k_{limit} * \frac{(1 - L)}{R_{SSA} * L + (1 - L)} \tag{9}$$

where k_{limit} is the rate of degradation at L = 0, that is, an infinitely dilute drug substance:excipient mixture.

Examination of Equation 9 reveals that it is very similar to the nonlogarithmic form of Equation 2: the only differences are that Equation 9 has α fixed at 1 and has an extra (1−L) term in the denominator (note that k_0 and %excipient from Eq. 2 are expressed as k_{limit}/R_{SSA} and (1−L), respectively, in Eq. 9). Also note that our derivation of Equation 9 does not provide any rationale for a power-law relation between drug load and degradation rate, that is, this derivation provides no justification of α values other than 1 and so there is no need to express it in a logarithmic form.

When the surface area of the excipient is very low relative to that of the drug substance such as in situations where the drug substance is micronized and the drug load is high (that is, when R_{SSA}*L >> [1−L]), Equation 2 (shown below in nonlogarithmic form with $\alpha = 1$) provides a good approximation to Equation 9:

$$Degradation\ Rate = k_{limit} * \frac{(1-L)}{R_{SSA} * L + (1-L)} \approx k_0 * \frac{(1-L)}{L} \qquad (10)$$

However, when the surface area of the excipient is similar to or higher than that of the drug substance (that is, when R_{SSA}*L is not significantly higher than [1−L]), then our analysis would suggest that Equation 2 would perform less well in modeling the degradation rate versus drug load relationship. This provides a possible rationale why Equation 2 performs well for some products (such as in case studies 1 and 5) but less well for other products (such as in case study 6). Further evidence for this was provided by a reexamination of the previously published raw data presented by Waterman et al., discussed later.[5]

In cases where the pure drug substance exhibits a non-negligible degradation rate, then Equation 9 can be adjusted to account for the degradation of drug substance that occurs in the absence of excipients as follows:

$$Degradation\ Rate = k_{DS} + k_{limit} * f_{Contact} = k_{DS} + k_{limit} * \frac{(1-L)}{R_{SSA} * L + (1-L)} \qquad (11)$$

where k_{DS} is the rate of degradation of pure drug substance (i.e., when L = 1).

It is possible to rearrange Equation 11 to allow for a linear regression approach to model the degradation rate versus drug load relationship as follows:

$$\frac{1}{k - k_{DS}} = \left(\frac{R_{SSA}}{k_{limit}}\right) * \frac{L}{(1-L)} + \frac{1}{k_{limit}} \qquad (12)$$

where k is the degradation rate at drug load L. Therefore, a plot of $1/(k-k_{DS})$ versus $L/(1-L)$ should give a straight line; obtaining the degradation rate at 2 or more different drug loads can be used to predict the degradation rate at any other drug load by linear extrapolation/interpolation as long as all other factors remain the same. Equation 12 also provides a means of obtaining k_{limit} and R_{SSA} by linear regression: k_{limit} is the reciprocal of the intercept and R_{SSA} is the slope divided by the intercept. However, a drawback of plotting the reciprocal degradation rate (as in Eq. 12) is that a high statistical weighting is applied to datapoints with very low rates of degradation (observed at high drug loads), where the experimental scatter is high. Also, the k_{limit} and R_{SSA} values obtained using this approach can be different from those obtained by nonlinear regression because the 2 approaches result in different statistical weightings being applied to the input data.

The derivation of Equations 9, 11, and 12 is based on a consideration of drug substance and excipient surface interactions. In most scenarios, it is likely that a significant proportion of the drug substance will not be on the particle surface, and that a proportion of the drug substance on the surface will not be in contact with either other drug substance particles or excipient particles (i.e., adjacent to "voids" in the sample). Also, there is likely to be different affinities between drug substance and excipient surfaces. These considerations are not explicitly included as factors in Equation 11 but are accounted for because they affect the apparent magnitudes of k_{limit} and R_{SSA}.

Note that R_{SSA} has been defined in Equation 7 as being proportional to S_{DS}/S_E and as such, it is unlikely that R_{SSA} can be calculated solely from surface area measurements because other factors will also affect R_{SSA}. For example, as stated above, it is likely that a proportion of the drug substance surface area will be inaccessible to the excipient. Therefore, the appropriate value for R_{SSA} is most likely determined empirically, that is, from degradation studies of different drug loads in which it is obtained as a "best-fit" parameter.

The presence of water may increase the proportion of drug substance that is in contact with excipient, for example, by (a) increasing molecular mobility, (b) providing a bridge between particle surfaces, or (c) increasing the depth of the reactive "surface" of the molecules.

Case Study Evaluation of the Surface Area Contact Model

Case studies 1, 5, and 6 provide sufficient data on degradation rate versus drug load to enable comparison of the models. For the surface area contact model, k_{limit} and R_{SSA} can be fit to the experimental data using linear regression (Eq. 12) or nonlinear regression (Eq. 11) with an optimization tool, such as the Excel Solver tool.

Case Study 1

The surface area contact ratio parameter, R_{SSA}, when estimated by nonlinear regression, was found to be extremely large for this case study. Also, the range of drug loads studied in this case study was relatively narrow and across very low drug loads (between 0.2% w/w and 2% w/w) such that Equation 1 approximates to Equation 2. The result of this is that all models can be expected to perform equally well for this product unless a power-law relation is observed (in which case the surface area contact model would perform worse). Figure 2 showed that Equation 1 fits the data well and Equation 2 performed equally well because of the reasons described above.

Figure 11 shows that the surface area contact model (evaluated by linear regression using Eq. 12) also works reasonably for case study 1 and it is not possible to clearly discriminate which model provides the best fit of the data above the experimental scatter. The intercept of the plot in Figure 11 is very close to zero which is an alternative indication that k_{limit} and R_{SSA} are extremely large for this case study.

Case Study 5

It was seen in Figure 8 (panel b) that the model proposed by Deepika and Dewan (Eq. 2) performed well in fitting the experimental data for this case study over the full range of drug loads: a linear trend indicates a model fit and only very slight curvature is discernable. In Figure 12, the same plot is shown for only the 48.5-day data for clarity, together with the prediction obtained using the surface area contact model (Eq. 11). It can be seen that the surface area contact model also provides an excellent fit but additionally successfully predicts the small amount of curvature obtained in this plot for this case study. Excellent agreements between the surface area contact model and the observed degradation rates were obtained for the other timepoints. The surface area contact model parameter, R_{SSA}, was estimated to be approximately 163; this relatively high value reflects the linearity of Figure 12.

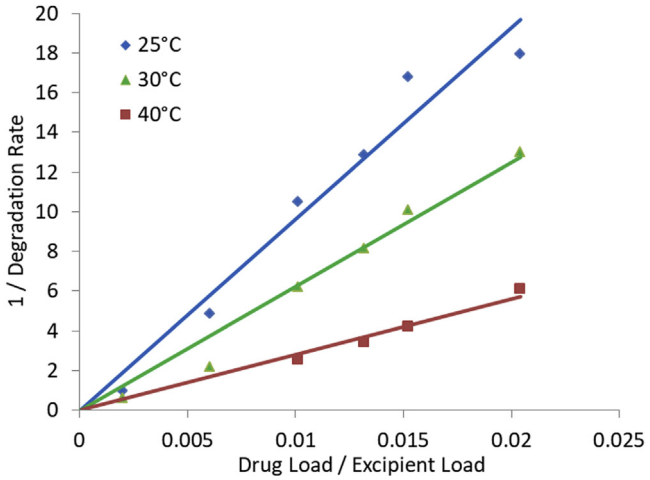

Figure 11. Model evaluation using degradation rate and drug load obtained from case study 1; individual points are the observed data, and the solid lines represent the relationship predicted by the surface area contact model (Eq. 12).

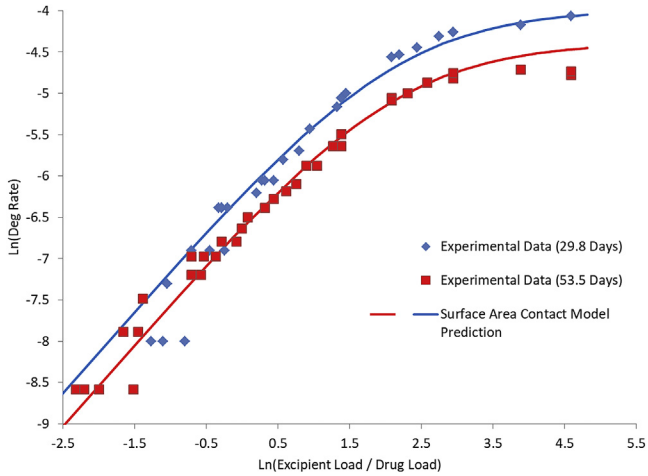

Figure 13. Evaluation of the model predictions from the surface area contact model (Eq. 11) obtained for case study 6.

Case Study 6

It was seen in Figure 10 that neither of the previously published models (Eqs. 1 and 2) managed to account for the experimental data from this case study across the entire range of drug load studies. Figure 13, on the other hand, shows there is good agreement between the surface area contact model predictions and the observed degradation rates: the surface area contact model accurately describes the curvature seen in Figure 13. The surface area contact model parameter, R_{SSA}, was estimated to be approximately 8.5, which is much lower than the previous case study; this might suggest that the previously published models did not perform well because the surface area of the excipient is relatively high in comparison with that of the drug substance in this case study when the excipient load is high (at low drug loads). The surface area contact model predicts that plots such as Figure 13 will asymptote to a horizontal line at very high excipient loads because in these scenarios modest changes in the excipient load will not significantly change the excipient environment surrounding each drug substance particle and so the degradation rate per drug substance particle remains approximately constant. In Figure 13, this effect appears to manifest significantly when Ln(excipient load/drug load) is greater than ~1.5 (which equates to drug loads of less than ~20% w/w).

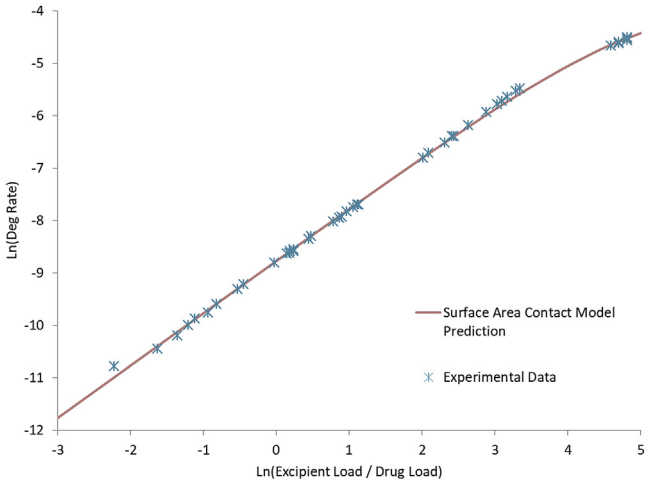

Figure 12. Evaluation of the model predictions from the surface area contact model (Eq. 11) obtained for case study 5. For clarity, only data from the 48.5-day timepoint are shown.

Reexamination of Previously Published Drug Load Versus Degradation Rate Data Using the Surface Area Contact Model

In the drug load versus degradation rate investigation previously described by Waterman et al.,[5] 2 products were studied: CP-481715 (which had 2 major degradation products) and methylprednisolone (in which the major degradation product was referred to as "Deg A"). In all cases, the surface area contact model (Eq. 11) performs very well at describing the degradation rate versus drug load relationship (not shown, but available on request), although the 2 previously published allometric models (Eqs. 1 and 2) also perform well for all but one of the cases. The case where methylprednisolone degrades to Deg A is particularly noteworthy because Equations 1 and 2 were unsatisfactory in describing the degradation rate across the full range of drug loads studied when the drug substance had a larger particle size. In the methylprednisolone study, 2 different drug substance particle sizes were investigated; when the drug substance had a particle size of 7 μm (i.e., higher surface area), all models (Eqs. 1, 2, and 11) provide a good description of the degradation rate versus drug load relationship, but in the case where the drug substance had a particle size of 42 μm (i.e., lower surface area), the previously published models produced nonlinear plots when Ln(degradation rate) was plotted against Ln(100%/drug load) or Ln(excipient load/drug load). Figure 14 (panel a) shows that the surface area contact model (Eq. 11) successfully accounts for the curvature seen in these plots, and panel b shows that when the data are plotted according to Equation 12, a linear relationship is obtained. The ratio of the accessible surfaces of drug substance and excipient, R_{SSA}, was found to be ~169 when the methylprednisolone had a particle size of 7 μm, and ~68 when the methylprednisolone had a particle size of 42 μm; this change in R_{SSA} is as expected, but it should be noted that different excipients were also used in these different scenarios which will also affect the magnitude of R_{SSA}. The general observation that the previously published allometric models were successful at modeling the degradation rate versus drug load behavior of methylprednisolone when the drug substance has a small particle size (high surface area) but were less successful when the drug substance has a large particle size (low surface area) provides

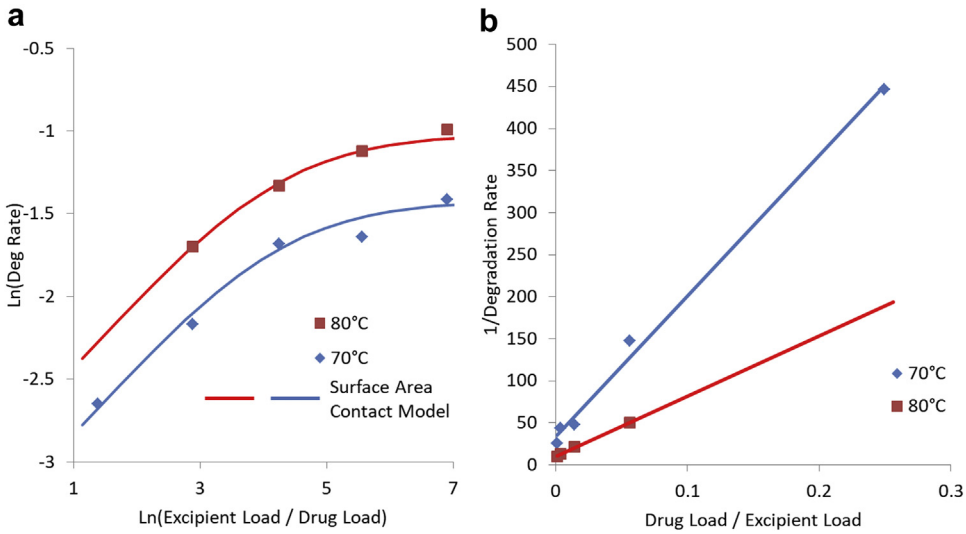

Figure 14. Evaluation of the surface area contact model for the degradation of methylprednisolone (particle size 42 μm) to Deg A: panel a shows that this model successfully accounts for the curvature observed when plotted according to Equation 2 and panel b shows the linear relationship predicted by Equation 12.

evidence in support of our model and its rationalization presented in this article.

The Combined Effects of Effect of Drug Load, Temperature, and Humidity on the Degradation Rate

It was observed in case studies 1 to 4 that changes in temperature generally result in changes in degradation rates (as indicated by the vertical offset seen in plots of Ln(k) versus Ln(drug load)), with no significant change in the slope (Figs. 2-6). Because these plots are based on a logarithmic *y*-axis, a constant vertical offset for all drug loads indicates that increasing the temperature multiplies the rate of degradation by a constant factor for all drug loads. Similarly, changes in relative humidity (H) also appear to produce a vertical offset in plots of Ln(degradation rate) versus Ln(drug load), with no significant changes in the slope (as seen in case studies 2 to 4). Relating these observations back to the extended (humidity-corrected) Arrhenius equation (Eq. 13),[1,2] it would appear that, for these examples, the drug load alters the pre-exponential term, Ln(A), but does not significantly affect the activation energy, E_a, nor the humidity sensitivity coefficient, B, as inferred from the parallel curves in the Ln(k) versus Ln(drug load) plots (Figs. 2-6).

$$Ln(k) = Ln(A) - \frac{E_a}{RT} + B^*H \tag{13}$$

In other words, both k_0 and k_{limit} (from Eq. 9) appear to vary with temperature and humidity according to Equation 13. From this observation, it may be inferred that changes in drug load affect the *amount* of drug substance in the reactive environment but not the *nature* of that reactive environment.

In cases where the degradation rate of the pure drug substance is extremely slow (i.e., k_0 is negligible), the lack of interaction between the effects of temperature, humidity, and drug load observed in these studies indicates that an additional term to account for the effects of drug load can simply be added to the existing humidity-modified Arrhenius equation as shown in Equation 14. Note that Equation 14 is obtained by substituting in Equation 13 for k_{limit} in Equation 11 and taking logarithms.

$$Ln(Deg\ Rate) = Ln(A) - \frac{E_a}{R^*T} + B^*H + Ln\left(\frac{1-L}{R_{SSA}{}^*L + 1 - L}\right) \tag{14}$$

For drug products in which the pure drug substance exhibits non-negligible degradation rates (i.e., $k_{DS} \neq 0$), k_{DS} can also be substituted by the humidity-modified Arrhenius equation into Equation 11, although the A, E_a, and B terms for k_{DS} are likely to be different from those used for k_{limit}.

Conclusions

This drug load-degradation rate dependency study provides evidence that direct contact with excipients can dramatically increase the degradation rate of drug substances. In the 6 cases studies presented in this article, this phenomenon was observed for a reasonably wide range of common and relatively inert excipients such as microcrystalline cellulose, hydroxypropyl methylcellulose, starch, mannitol, lactose, and dicalcium phosphate, and for a reasonably wide diversity of drug substances and chemical degradation pathways such as hydrolysis, oxidation, condensation, isomerization, cyclization, and N-formylation. The wide applicability of these observations among a diversity of drug products suggests that the increased rate of degradation in contact with excipients is caused by a physical interaction between drug and excipient rather than by a direct chemical reaction.

In this study, a "surface area contact model" (Eq. 9) was derived solely from a consideration of the surface areas of the drug substance and excipient and should be applicable to particles of any size or shape. This model has been demonstrated to be applicable to all the drug products studied so far (6 case studies presented in this article and 2 previously published case studies, although case studies 2, 3, and 4 had insufficient data to allow a full evaluation of the model). In this context, the term "surface area" refers only to the surface area of a particle that is accessible for contact with other particles: it is likely that a significant proportion of the surface area of a particle is inaccessible for chemical interactions with other particles. It is therefore unlikely that a single analytical or particle characterization technique will be able to provide a direct measurement of the "accessible surface area" relevant to degradation rate or of R_{SSA}.

The underlying assumption of this surface area contact model is that the drug substance present in a drug product is either in a reactive environment (i.e., on the surface of the particle and in contact with the excipient) or in a nonreactive environment (i.e., not in contact with the excipient). This simple "2-state" model is

likely to be an oversimplification because at the molecular, crystal, and particle length-scales, solid-state products are likely to be highly heterogeneous in nature, with a multitude of different drug substance environments that may be expected to exhibit a broad distribution of chemical degradation rates; nevertheless, this simple model provided surprisingly good fits to the experimental data for these case studies.

These studies suggest that there is a linear relationship between reciprocal degradation rate and "L/(100−L)" (where L is the drug load %w/w); this linear relationship should provide a simple and general-purpose means of predicting the degradation rate of drug products with other drug loads if the degradation rate is known at 2 or more drug loads and all other factors remain the same. However, this approach may be susceptible to high degrees of experimental scatter when the rate of degradation is very slow, and therefore nonlinear modeling approaches may be preferable.

Degradation rate versus drug load models proposed in previous studies[5,6] were based on power-law (allometric) relationships between drug load and degradation rate; these models have shown varying degrees of success for different drug products across wide ranges of drug loads. The rationale for the surface area contact model provides no justification for a power-law relationship and suggests that the previously published allometric models would only work well in cases where the accessible drug substance surface area is significantly higher than that of the excipient (such as when the drug substance is micronized). Experimental evidence for this was obtained from a reexamination of previously published degradation rate versus drug load data obtained for drug products that contained either small or large particle size drug substance.

The effects of temperature, humidity, and drug load appear to act independently of each other, resulting in Equation 14. None of the case studies exhibited significant changes in their sensitivity to temperature (E_a) or to humidity (B) at different drug loads; however, if there were a significant contribution to the overall degradation rate from 2 or more environments (e.g., if k_{DS} and k_{limit} were both significant), and those different environments have different E_a and B terms, then this would lead to an apparent shift in E_a and B across different drug loads.

It is hoped that this work has provided some useful insights into chemical degradation in solid-state drug products and has provided a useful model for estimating rates of degradation as a function of drug load based on measuring the rates of degradation at different drug loads of a given formulation. It is intended that these studies will be extended to other solid drug products (including multicomponent systems), to other drug product types (such as lyophiles), and to investigate the effects of other factors such as compaction and particle size.

Acknowledgment

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