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Humidity-corrected Arrhenius equation: The reference condition approach

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ABSTRACT

Accelerated and stress stability data is often used to predict shelf life of pharmaceuticals. Temperature, combined with humidity accelerates chemical decomposition and the Arrhenius equation is used to extrapolate accelerated stability results to long-term stability. Statistical estimation of the humidity-corrected Arrhenius equation is not straightforward due to its non-linearity. A two stage nonlinear fitting approach is used in practice, followed by a prediction stage. We developed a single-stage statistical procedure, called the reference condition approach, which has better statistical properties (less collinearity, direct estimation of uncertainty, narrower prediction interval) and is significantly easier to use, compared to the existing approaches. Our statistical model was populated with data from a 35-day stress stability study on a laboratory batch of vitamin tablets and required mere 30 laboratory assay determinations. The stability prediction agreed well with the actual 24-month long term stability of the product. The approach has high potential to assist product formulation, specification setting and stability statements.

1. Introduction

Predicting shelf life of solid-dose pharmaceutical products based on accelerated and stress stability data is often desired in order to avoid long development times and costs, associated with real-time stability testing. Arrhenius equation is the base for extrapolation of stability data from elevated temperature to the actual storage condition. Although some non-isothermal methods have been published (Fernandez de Aranguiz et al., 2007; Oliva et al., 2006), the majority of applications involve accelerated aging isothermally at temperatures up to 80 °C (do Nascimento et al., 2013; Gil-Alegre et al., 2001). Humidity was recognized as a major driver of instability and thus an additional humidity term was included into the Arrhenius equation (Genton and Kesselring, 1977; Waterman et al., 2007; Yoshioka and Stella, 2000). This approach has further been refined to non-isothermal and non-isohumid ageing (Li et al., 2008).

Stability prediction is essentially an extrapolation beyond the range, covered by actual data. Degradation rate is extrapolated from high temperatures to the actual storage temperature according to the Arrhenius equation and the kinetics of degradation (reaction order) is assumed not to change from the initially observed one (Naversnik and Bohanec, 2008). Humidity corrected Arrhenius equation Eq. (1) imposes additional assumptions on how degradation rate depends on moisture (exponential with respect to relative humidity) and independence of temperature and humidity terms. Degradation rate constant (k) dependence on temperature (T, °K) and humidity (RH, % relative humidity) is assumed to be according to Eq. (1) (Waterman, 2011).

$$k = A \times e^{-\frac{E_a}{R\times T}+B\times \mathrm{RH}} \quad (1)$$

$$\ln(k) = \ln(A) - \frac{E_a}{R\times T} + B \times \mathrm{RH} \quad (2)$$

Eq. (2) is a linearized version, where B represents moisture sensitivity, E_a is the activation energy, R is the gas constant (8.314 J/Mol K) and A is the pre-exponential term. The equation can either be applied to disappearance of the active drug component (assay decrease) or increase in degradation product(s). Some have also applied it to nonspecific measures of change, such as heat flow (Simoncic et al., 2008) or physical changes (Goh, 2010; Ochiai and Danjo, 2011).

Statistical estimation of stability parameters and uncertainty is not straightforward, since Arrhenius equation is not linear with respect to temperature and humidity (Eq. (1)). A two stage approach is often used in practice (Li et al., 2008; Fu et al., 2015; Patterson et al., 2014). Degradation rate constants (according to a

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predefined order of degradation kinetics) are estimated in the first stage at various temperature/humidity levels. The second stage consists of bivariate regression of rate constants according to the Arrhenius equation (or its linearized version). Weighted regression may be required in order to accurately reflect the error structure in degradation rate constants (Bentley, 1970; Klicka and Kubácek, 1997; Sundberg, 1998). It is reasonable to have a procedure that directly estimates stability parameters from concentration data in order to improve statistical efficiency (Yoshioka and Uchiyama, 1986). In this way, all data are used at once to estimate the Arrhenius parameters and a much more precise estimate of these parameters is obtained (Van Boekel, 2008).

The parameters of interest for a stability prediction are usually $k_{298,60}$ (degradation rate at 298 °K and 60% relative humidity) or $t_{90\%}$ (time to reach 90% of initial assay). The estimation process needs to result in point estimates along with their uncertainty (standard errors). Data fitting according to Eq. (1) results in estimates for parameters A,E_a and B, which need to be converted into $k_{298,60}$ or $t_{90\%}$. Whilst an easy calculation for point estimates, this is not straightforward for calculation of standard errors. Examples from the literature are scarce: Taylor series expansion (Boxenbaum et al., 1974), assuming a multivariate normal sampling distribution (Nagy and Turányi, 2011), bootstrapping (Fan and Zhang, 2015) and Monte Carlo simulation (Waterman et al., 2007; Van Boekel, 2008). A strong correlation between parameters of the Arrhenius equation additionally complicates uncertainty estimation (Van Boekel, 2008; Nagy and Turányi, 2011; Héberger et al., 1987). Several reparametrizations have been proposed to overcome this issue (Van Boekel, 2008; King et al., 1984; Rodionova and Pomerantsev, 2005; Schwaab and Pinto, 2007).

Extrapolation to room temperature will result in high uncertainty, as evident by wide confidence intervals for predicted degradation rates (Darrington and Jiao, 2004), particularly for non-isothermal experiments (Oliva et al., 2006). It is thus important to have an efficient statistical procedure, which results in narrow confidence intervals for the predicted parameter ($k_{298,60}$).

The goal of our work was to evaluate performance of a new statistical approach for stability prediction according to the humidity corrected Arrhenius equation. We have set up an accelerated stability protocol for a vitamin tablet formulation and used this data to predict room-temperature degradation rates. Our intention was to develop a statistical approach to directly estimate the parameter of interest together with its statistical uncertainty. We aim to compare the new approach with two existing approaches and provide a ready-to-use set of programming code for the open source statistical software R (RDC Team, 2008).

2. Materials and methods

Vitamin tablets were manufactured by direct compression which resulted in a dry product with water activity aw = 0.05. A portion of the batch was exposed to 60% relative humidity for 3 days, which increased moisture to aw = 0.58.

Accelerated stability studies were performed by sealing tablets (two moisture levels) in glass vials and exposing them to elevated temperatures for periods up to 35 days. The sampling periods were calculated based on preliminary stability data (not shown) in order to obtain about 10% decrease in assay (isoconversion principle) (Waterman et al., 2007). The assay results are shown in Fig. 1 and Table 1.

$$C = C_0 - t \times k \tag{3}$$

Vitamin assay was the stability parameter of interest. A zero order kinetic model (Eq. (3)) was assumed, where vitamin assay (C) is a function of initial assay (C_0) and time (t) with a constant degradation rate (k, %/day). Vitamin assay was determined by HPLC and expressed as % of labeled value per tablet (Table 1). A composite, consisting of ten tablets was assayed each period. Initial (unstressed) assay was determined in nine replicates. Analyses of stability samples were performed in one replicate.

These data were then evaluated according to three statistical procedures:

- standard two-stage model, based on the linearized Arrhenius equation
- direct nonlinear fit
- a new “reference condition” approach.

Data fitting and statistical simulation was performed in statistical package R (RDC Team, 2008).

Long-term stability data according to ICH protocol was later available for 9 batches (three per strength) in Al–Al blisters (product moisture was low throughout shelf life) and PVDC blisters

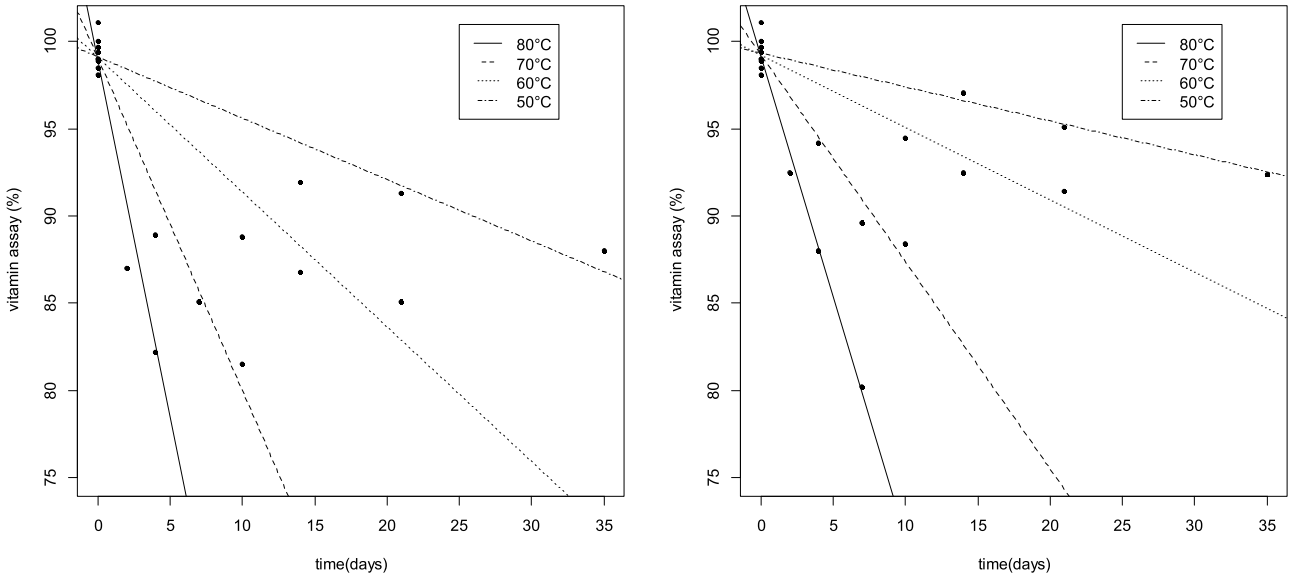

Fig. 1. Assay decrease over time at 58% relative humidity (left) and 5% relative humidity (right) for various temperatures.