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Research Article

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Guest Editors: Ajaz S. Hussain, Kenneth Morris, and Vadim J. Gurvich

Using Manufacturing Design Space Concepts for Stability Risk Assessment—Gabapentin NIPTE/FDA Case Study

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Abstract. A quantitative, model-based risk assessment process was evaluated using Bayesian parameter estimation to determine the posterior distribution of the probability of a model tablet formulation's (gabapentin) ability to meet end-of-expiry stability criteria-based manufacturing controls. Experimental data was obtained from an FDA-supported, multi-year project that involved researchers at nine universities working collaboratively with industrial and governmental scientists under the leadership of the National Institute for Pharmaceutical Technology and Education (NITPE). The risk assessment process involved the development of a design space manufacturing model and shelf life stability model that shared stability-related critical quality attributes (CQAs). Monte Carlo simulations of the design space and shelf life models that uses model parameter uncertainty to estimate the probability of shelf life failure as a function of manufacturing control. The resultant linked design space and shelf life stability models were tested by comparing model predicted and observed long-term stability data generated under a variety of pilot scale production conditions.

KEY WORDS: risk assessment; stability; design space; Bayesian modeling; Monte Carlo simulation.

INTRODUCTION

The US FDA Quality-by-Design (QbD) initiative and associated design space definition have stimulated the use of quantitative methods, mathematical and statistical models, and designed experimentation in drug product and manufacturing development and licensure. Design space may be interpreted as the constrained region of the drug product composition and manufacturing operating variable space within which assurance can be provided that drug product quality specifications will be met. Defining design space in a meaningful and practical manner should include quantitative assessment of quality assurance risk. By its very nature, risk is probabilistic. Thus maintaining manufacturing operations within an acceptable region of a design space is necessarily associated with some risk of quality failure. Central issues arising from the probabilistic nature of risk are estimating realistic failure rates and then obtaining a consensus on what is "acceptable" risk. Some traditional risk assessment methods rely on qualitative metrics and historical knowledge (1). The use of mathematical models and, in particular, Monte Carlo simulation for linking product quality to product safety and efficacy has been proposed (2,3). The objective of this case study report is to describe a process for assembling the needed modeling and simulation methods to relate manufacturing design space to the risk associated with shelf life stability failure.

Gabapentin was used as model drug substance for studying the connection between manufacturing-related stress and drug product stability in an FDA-supported, multi-year project entitled *Development of Quality by Design (QbD) Guidance Elements on Design Specifications Across Scales with Stability Considerations* that involved researchers at nine universities working collaboratively with industrial and governmental scientists under the leadership of the National Institute for Pharmaceutical Technology and Education (NITPE). The overarching objective of this research was to incorporate stability and unit operation scaling issues into a QbD paradigm for manufacturing quality control. Gabapentin is an ideal model compound for this project because of its proclivity to exist in various physical forms, its propensity to undergo structural disorder when subjected to mechanical stress and the susceptibility of the disordered material to chemical degradation by intramolecular cyclization (4–7).

In this manuscript, we present an unpublished case study resulting from this NIPTE project wherein a quantitative,

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model-based risk assessment was evaluated using the Bayesian parameter estimation to determine the posterior distribution of the probability of the product meeting quality specifications associated with shelf life. This case study demonstrates a process for linking QbD design space models to stability quality assurance risk by identifying key process stress-related stability factors to incorporate into an environmental storage-stress degradation model. The resultant linked design space and degradation models were tested by comparing model predicted and observed long-term stability data generated under a variety of pilot scale production conditions. The overall process involved the following key steps:

1. Defining shelf life stability failure: The USP limit for gabapentin-lactam is 0.4%, thus critical stability failure occurs when the level of gabapentin-lactam exceeds 0.4%. (4,5)
2. Identifying metrics (critical quality attributes (CQAs)) arising from manufacturing process that relate to product stability: We have previously reported on the relationship between the initial levels of gabapentin-lactam (gaba-L_0) and crystal-disordered gabapentin (gaba*$_0$) obtained immediately after the completion of manufacturing and the long-term stability of gabapentin (4–7), thus the stability-related CQAs are gaba-L_0 and gaba*$_0$.
3. Developing a design space manufacturing model that predicts stability CQAs as a function of manufacturing controls
4. Developing a shelf life stability model based on long-term and accelerated stability data that incorporates stability CQAs and environmental storage conditions.
5. Monte Carlo simulations of the design space and shelf life models that uses model parameter uncertainty to estimate the probability of shelf life failure as a function of manufacturing control.

The materials, analytical methods, and stability methods used in generating the experimental data for this case study have been previously reported (4,5) and are briefly described here. Modeling and simulation methods are described in the "RESULTS AND DISCUSSION" section of this report.

METHODS AND MATERIALS

Development of the Manufacturing (Design Space) Model

Gabapentin tablet formulations included 600-mg active pharmaceutical ingredient (API), 80-mg hydroxypropyl cellulose, 22-mg crospovidone NF, 60-mg pregelatinized cornstarch NF, 7-mg magnesium stearate NF, 100-mg microcrystalline cellulose NF (Avicel PH102), and 9-mg talc USP extra-fine. The manufacturing process included blending API and 40-mg hydroxypropyl cellulose (HPC) with 2.5–5.5% moisture content with median particle size from 160 to 270 μm. Then these blends were subjected to high shear wet granulation at various spray rates (12–18 g/min) and impeller speeds. The resultant granules were put into fluidized bed for drying to different target moisture end point (0.5–1.0%) with various environmental equivalency factors. The granules then were milled, sieved, and blended at low and high blending speed and different fill ratios (60 and 80%). The initial blends and final blends were compressed into tablets (12 mm, round, flat-faced) under different forces from 5 to 15 kN (5).

Upon completion of the manufacturing process, the initial levels of gaba-L and gaba* (*i.e.*, gaba-L_0 and gaba*$_0$) due to different levels of manufacturing processing stress were estimated either by direct HPLC analysis (gaba-L_0) or from the initial rate of gaba-L formation (gaba*$_0$) under controlled accelerated conditions (24 h at 50°C and 5% RH). These data were used to correlate the stability-related CQAs to manufacturing control parameters as described in the "RESULTS AND DISCUSSION" section.

Development of the Shelf Life Stability Model

The manufacturing methods described above were used to prepare API/HPC granules and gabapentin tablets (using the complete list of excipients). Aliquots of the granules were sampled after milling and sieving and then stored under controlled environment conditions (25, 40, 50 and 60°C at both 5 and 30% RH) for 6 months. Samples of 50 mg of dried granules were removed from storage periodically, subjected to water extraction of the highly soluble API, followed by HPLC testing of gabapentin and its lactam content as described above. In addition, gabapentin tablets were stored under the same conditions, sampled periodically, subjected to water extraction, and analyzed for gabapentin and lactam content. The HPLC analysis used Waters μBondapak CN-RP, 3.9 × 300-mm column with flow rate at 1.0 mL/min and detection at 210 nm. The percentage lactam was calculated on a molar basis. In addition, prior to long-term stability storage, both HPC/API granule and tablet batches were analyzed for gaba-L_0 and gaba*$_0$ as described above.

The stability data obtained from the samples (both tablet and granule) stored at 40, 50 and 60°C was used to train the shelf life stability model (*i.e.*, parameterize the model), whereas the 25°C data was used to demonstrate the model predictability (*i.e.*, validate the model) as described in the "RESULTS AND DISCUSSION" section.

RESULTS AND DISCUSSION

Developing a Design Space Manufacturing Model

Preliminary screening analysis of manufacturing variables demonstrated that tableting mean compression force and granulation water content had a significant effect on the stability-related CQAs (gaba-L_0 and gaba*$_0$). Twenty-two samples from 14 batches were used to establish a design space model that correlated the stability-related CQAs to compression force and water content (Fig. 1a, b). Gaba*$_0$ was more sensitive to manufacturing condition than gaba-L_0; the squared correlation coefficients were 0.80 and 0.40, respectively. For the gaba-L_0 model, the water content by compression force interaction term was not significant ($p = 0.66$) and compression force term was marginally significant ($p = 0.08$), whereas the water content term had a p value less than 0.03. For the gaba*$_0$ model, the water content by compression force interaction term was again not significant ($p = 0.92$), but both primary effects were significant ($p < 0.001$). The summary of fit, analysis of variance, and parameter estimates for both models are presented in Table I.

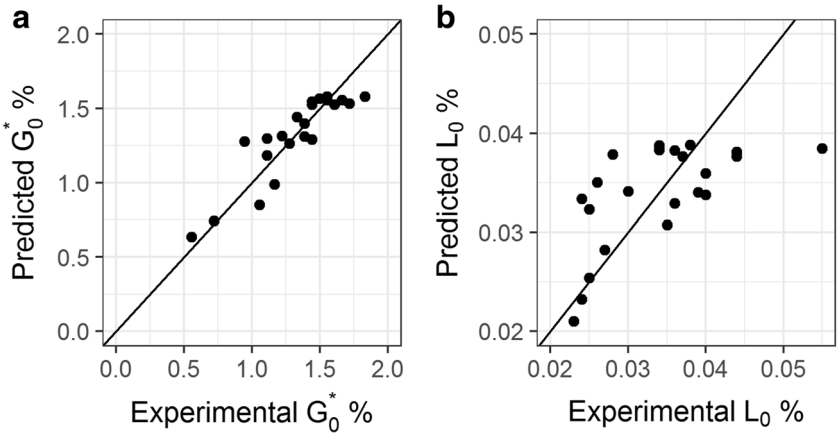

Fig. 1. Manufacturing model parity plots comparing the model predicted and experimentally determined values for the stability-related CQAs: **a** gaba* and **b** gaba-L

Developing a Shelf Life Stability Model

We have previously presented detailed models for the formation of gaba-L from gabapentin that incorporate autocatalytic branching, spontaneous dehydration, and moisture-induced recovery as temperature and humidity sensitive degradation processes (5,6). These models described the complete degradation of gabapentin including physical state transformations that contribute to the chemical conversion of the gabapentin to its degradation product, gaba-L. These models were developed using extreme manufacturing stress (extended milling) and rigorous thermal stress ($\leq 60°C$). However, the long-term stability of gabapentin tablets manufactured under much more mild mechanical stress (limited milling) and stored with limited thermal stress ($\leq 40°C$) facilitated the development of a simplified shelf life stability model based on initial rate assumptions. The concentration time profiles for the appearance of gaba-L (upon which these models were based) showed two phases. The first phase was characterized by the relatively rapid, first-order appearance of gaba-L directly from gaba*$_0$. The subsequent phase in the gaba-L concentration time profiles was attributed to the Prout-Thompkins autocatalytic degradation of non-manufacturing damaged gabapentin. For long-term stability of tablets manufactured with minimal stress and stored under mild environmental conditions, the initial phase of gaba-L formation predominates chemical instability over the entire duration of storage. In other words, the formation of gaba* during manufacturing is largely responsible for the subsequent formation of gaba-L during long-term storage. At the first-order expiry, the amount of gaba-L present is due to the gaba-L formed during manufacturing (gaba-L$_0$) and that portion of gaba*$_0$ that converts to gaba-L during long-term storage.

In the original detailed degradation model (5), reversible formation of gaba* by autocatalytic branching and moisture-induced crystal recovery is followed by spontaneous dehydration to yield gaba-L. Thus the two rate processes as described as follows: where G, G^*, and L represent gabapentin, gaba*, and gaba-L, respectively:

$$\begin{aligned} \text{Rate}_1 &= k_1 G(G^* + L) - k_3 G^* G \\ \text{Rate}_2 &= k_2 G^* \end{aligned} \tag{1}$$

In the early stages when total conversion is low,

$$\begin{aligned} G(t) &\approx G_0 \approx 100 \\ L(t) &\approx 0 \end{aligned}$$

Table I. Summary of Manufacturing Model Statistics

$\text{gaba}_0^* = \beta_0 + \beta_{WC}\text{water\_content} + \beta_{CF}\text{Compression\_force} + \beta_{WC\times CF}\text{water\_content} \times \text{Compression\_force}$
$R^2 = 0.80$
Parameter estimates

Term	Estimate	Std error	*t* ratio	Prob >|t|
Intercept	−0.307305	0.240486	−1.28	0.2175
Water content (%)	0.282563	0.050688	5.57	<.0001
Mean compression force	0.0275207	0.006882	4.00	0.0008
(Water content) × (compression force)	0.0008168	0.008078	0.10	0.9206

$\text{gaba\_L}_0 = \gamma_0 + \gamma_{WC}\text{water\_content} + \gamma_{CF}\text{Compression\_force} + \gamma_{WC\times CF}\text{water\_content} \times \text{Compression\_force}$
$R^2 = 0.41$
Parameter estimates

Term	Estimate	Std error	*t* ratio	Prob >|t|
Intercept	0.0024493	0.010073	0.24	0.8106
Water content (%)	0.0050123	0.002123	2.36	0.0297
Mean compression force	0.0005423	0.000288	1.88	0.0762
(Water content) × (compression force)	0.0001524	0.000338	0.45	0.6579

Thus the net rate of change of G^* is given by,

$$\frac{dG^*}{dt} = \text{Rate}_1 - \text{Rate}_2 \approx k_1 G_0 G^* - k_3 G^* G_0 - k_2 G^* = G^*(k_1 G_0 - k_3 G_0 - k_2),$$

and a new complex first-order rate constant can be defined which accounts for loss of G^*

$$k_1 G_0 - k_3 G_0 - k_2 = -k_{obs}$$

The ordinary differential equation that describes the rate of gaba* change can be analytically solved by separation of variables, letting $G^*(0) = G_0^*$

$$\frac{dG^*}{G^*} = -k_{obs} dt$$
$$G^*(t) = G_0^* \exp[-k_{obs} t]$$

Since the rate of lactam formation is known, the conversion of $G^* \rightarrow L$ in the simplified model is given by

$$\frac{dL}{dt} = \text{Rate}_2 \approx k_2 G^* = k_2 G_0^* \exp[-k_{obs} t]$$

which can also be solved by separation of variables

$$L = \frac{k_2 G_0^*}{-k_{obs}} \exp[-k_{obs} t] + C$$

The constant of integration is determined by incorporating the initial condition, $(0) = L_0$.

The relationship between G_0^* and STS (V_0) has been previously reported, where STS is the initial rate of lactam formation at standard conditions (5% RH and 50°C for 24 h) (5,8).

$$\text{STS} = \left.\frac{dL}{dt}\right|_{t=0} = k_2[T_0, \text{RH}_0] G_0^*$$

The rate constant k_2 can be parameterized with respect to temperature and humidity by considering the offset of the temperature and humidity.

$$k_2 = \frac{\text{STS}}{G_0^*} \exp\left[-\frac{\text{STS}}{G_0^*}\left(\frac{\text{STS}}{G_0^*} - 1\right) + B_{\text{Form.}_{k_2}}(\text{RH} - \text{RH}_0)\right]$$

k_{obs} is an effective rate constant wherein a modified Arrhenius equation can account for the variation in k_{obs} with respect to temperature and humidity due to the relatively small range of these storage conditions. The rate constant k_{obs} was offset to standard conditions—namely RH_0= 5% and $T_0 = 50^\circ$C. The subscript "Form" was used because the HPC comilled granules and tablet formulations have different humidity dependencies.

$$k_{obs} = k_{obs}^0 \exp\left[-\frac{E_{a,k_{obs}}}{\text{RT}_0}\left(\frac{E_{a,k_{obs}}}{\text{RT}_0} - 1\right) + B_{\text{Form.}_{k_{obs}}}(\text{RH} - \text{RH}_0)\right]$$

The final model is given by

$$L = L_0 + \frac{k_2 G_0^*}{k_{obs}}(\exp[-k_{obs} t] - 1)$$
$$k_2 = \frac{\text{STS}}{G_0^*} \exp\left[-\frac{E_{a,k_2}}{\text{RT}_0}\left(\frac{T_0}{T} - 1\right) + B_{\text{Form.}_{k_2}}(\text{RH-RH}_0)\right]$$
$$k_{obs} = k_{obs}^0 \exp\left[-\frac{E_{a,k_{obs}}}{\text{RT}_0}\left(\frac{T_0}{T} - 1\right) + B_{\text{Form.}_{k_{obs}}}(\text{RH-RH}_0)\right]$$

and requires seven parameters to be estimated.

$$E_{a,k_2}, B_{\text{granule.}_{k_2}}, B_{\text{Tablet.}_{k_2}}, k_{obs}^0, E_{a,k_{obs}}, B_{\text{granule.}_{k_{obs}}}, \text{and } B_{\text{Tablet.}_{k_{obs}}}$$

These parameters were estimated from stability data collected over 6 months from 1-kg scale batches of tablets and granules stored at temperatures 30–60°C and relative humidity 5 and 30%.

The Bayesian parameter estimation was used to estimate the joint posterior of the simplified shelf life model parameters (8–10). Briefly, non-informative priors were employed with a delayed rejection Markov Chain Monte Carlo sampler as implemented in the FME package of R (11,12). Assuming normally distributed error in the gaba-L measurements, 110,000 samples of the posterior were drawn in a single chain with 10,000 samples discarded as burn-in. The posteriors are summarized in Table II and the marginal densities are shown in Fig. 2.

As shown in Table II, the column labeled "Best" is the sample with the highest likelihood. The central 95% interval captures 95% of the probability density, with equal 2.5% of the total area above and below. Importantly, these ranges include the mean and the best points. That the "Best" point is never more than 1.5 standard deviations from the mean is also a sign of good convergence of this single long chain.

The marginal distributions, plotted as kernel densities in Fig. 2, also indicate a mostly smooth posterior. We note the heavy tails in $\log_{10}(k_{obs}^0)$, $E_{a,k_{obs}}$, and $B_{\text{Tablet.}_{k_{obs}}}$. These parameters all effect the apparent rate of lactamization and are highly correlated with each other. A joint marginal distribution of these parameter pairs (not shown) indicates a high degree of correlation consistent with a compensation effect. Despite this concern with model identifiability, the predictions from this model are acceptably tight for illustration purposes.

In Fig. 3, we show an example fit (a) and an example prediction (b) of the model. We stress that the 25°C data were not used to train the model and represent a validation of the model predictive ability. The 95% intervals are shown to indicate how the model parameter uncertainty propagates to a predicted distribution of the amount of lactam as a function

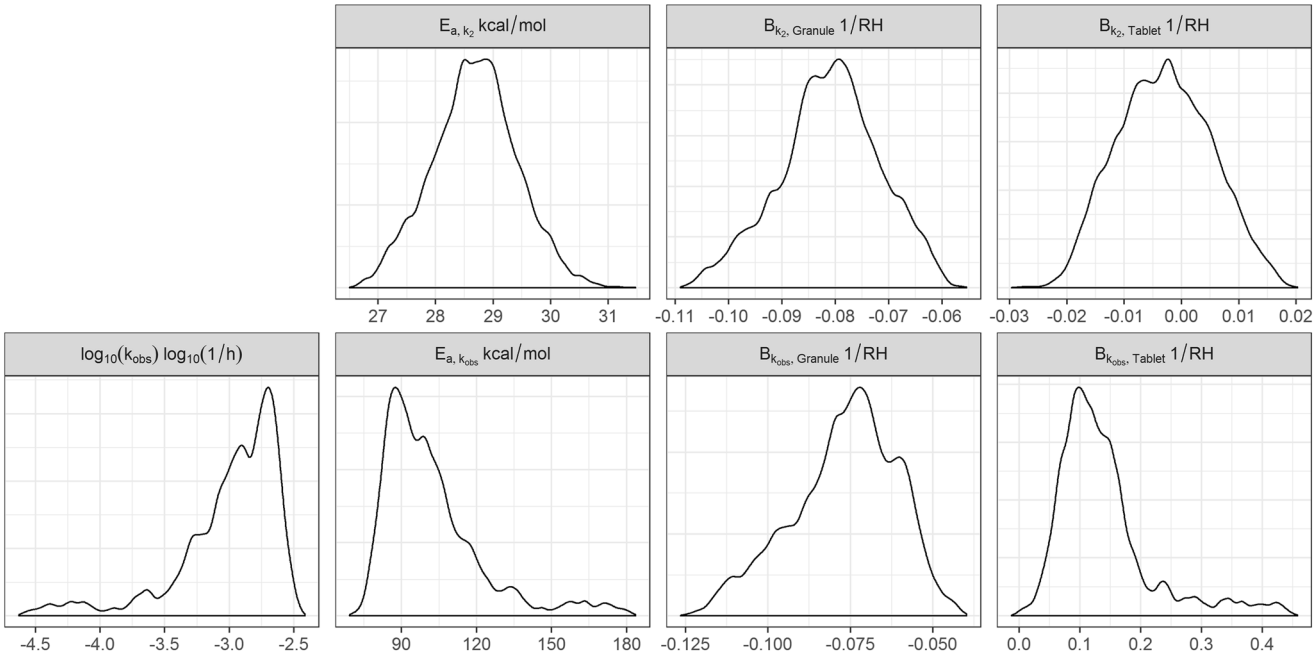

Fig. 2. Posterior marginal distributions for shelf life model parameters obtained by Bayesian estimation and generated by 110,000 samples of the posterior using the MCMC sampler

of shelf life storage time. This distribution was used to define the shelf life stability risk as described below.

Coupling the Manufacturing Model and Shelf Life Model

The manufacturing model relates two key process conditions, namely, granulation water content and tablet compression force to the initial amount of gaba* and the initial amount of gaba-L. Assuming perfect control of the process parameters, the uncertainty in the manufacturing model parameters propagates to the outputs. This uncertainty is independent of the uncertainty in the shelf life model parameters, the posteriors of the shelf life model and the manufacturing model were independently sampled. As a further conservative assumption, any covariance in the manufacturing model parameters was neglected, and a normal distribution with mean and standard deviation equal to the manufacturing model estimates and standard errors as listed in Table I was used to obtain the 100,000 samples of the posterior of the shelf life model. The manufacturing levels evaluated included granulation water contents of 3, 4, and 5% and tablet compression forces of 5, 12.5 and 20 kN. The storage condition used for risk predictions was 25°C and 30% RH. The coupled model was thus solved for each set of the

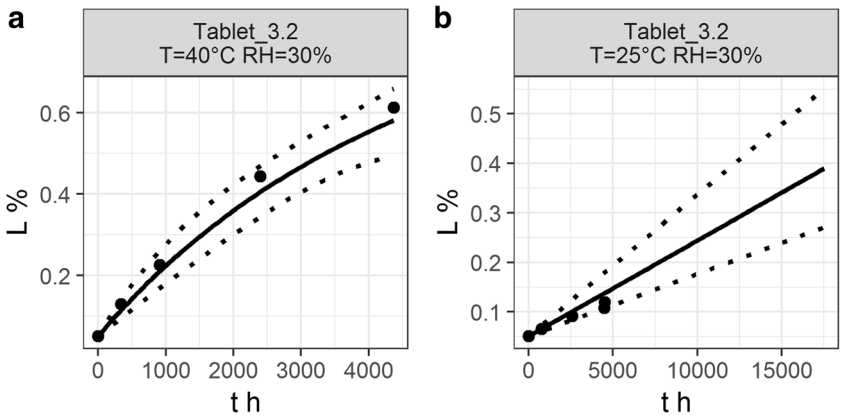

Fig. 3. Shelf life model predictions for the accumulation of gaba-L during long-term storage. **a** Illustrates an example fit to a gabapentin tablet batch stored at 40°C and 30% RH for 6 months. These data were part of the data used for parameter estimation. Mean model predicted gaba-L accumulation (solid curve) is compared to experimental data and the dotted curves represent the 95% intervals based on repeated simulations. **b** Illustrates the model-predicted (solid curve) and observed data for a tablet batch stored at 25°C and 30% RH. The data obtained at this condition were not used to train the model but only for model validation. The dotted curves represent the 95% intervals based on repeated simulations

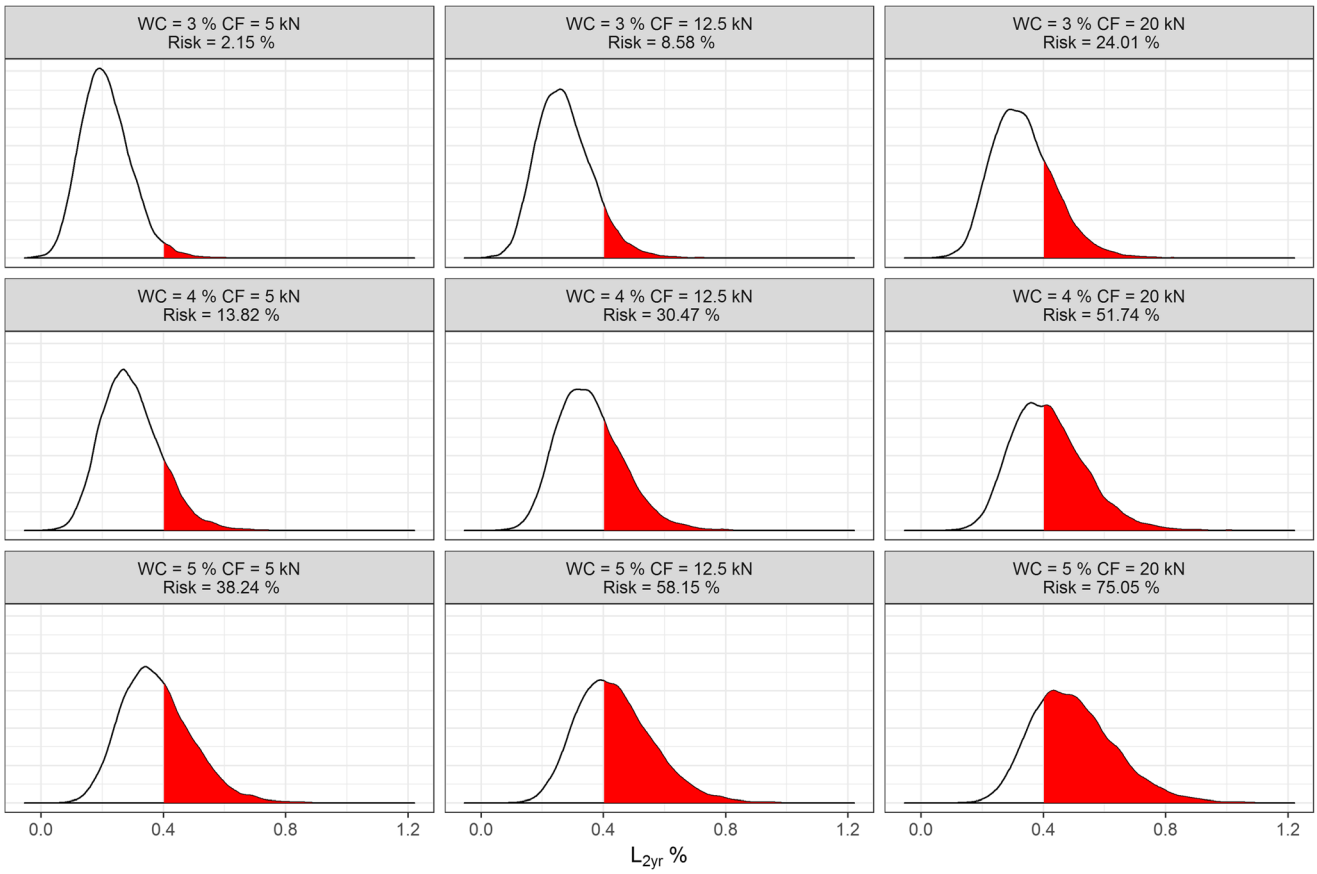

Fig. 4. Probability distributions for the predicted level of gaba-L after 2 years of storage at 25°C and 30% RH obtained for batches of gabapentin tablets manufactured at ranges of water content (WC, 3–5%) and tablet compression force (CF, 5–20 kN). The risk percentage is indicated by the shaded regions of the probability distributions wherein the accumulated level of gaba-L exceeds 0.4% (the critical value according the USP specification). Probability distributions were obtain from 100,000 simulations using Monte Carlo sampling of the uncertainty associated with manufacturing and shelf life model parameters

parameters and the resulting gaba-L probability distribution at 2 years is plotted. We define shelf life risk as the probability of failing the requirement of not more than 0.4% gaba-L:

$$\text{Risk} = Pr\left(L(\text{WC}, \text{CF}; t = 2\text{yr}) > 0.4\%\right)$$

which is computed from the model predictions from all the samples drawn.

Figure 4 shows the distribution of gaba-L at nine different processing conditions. Low instability risk was effectively achieved when both the granulation water content and tableting compression force were low. Although low compression force would be expected to result in a lesser degree of mechanical stress and therefore decreased instability, the role of granulation water content on gabapentin stability is somewhat counter intuitive given that gabapentin is known to degrade faster at low residual water content than when the residual water content is high (4). But the destabilizing effect of water added during granulation may be account for by noting that the granules were dried to the same target residual water content regardless of the amount of water added during granulation. Thus the extended thermal stress associated with removal of excess granulation water may explain this counter intuitive result. In short, higher levels of manufacturing stress (*i.e.*, higher water content [leading to more thermal stress during drying] and higher compression force) substantially increased the shelf life risk.

Table II. Summary of Posterior Distributions for the Gabapentin Shelf Life Model

Parameter	Unit	Best	Mean	Standard deviation	Central 95% LB	Central 95% UB
E_{a,k_2}	kcal/mol	27.54	28.68	0.74	27.20	30.13
$B_{granule.k_2}$	1/ % RH	− 0.0811	− 0.0810	0.0094	− 0.101	− 0.0633
$B_{Tablet.k_2}$	1/ % RH	− 0.0116	− 0.0029	0.0082	− 0.0179	0.0130
$\log_{10}(k^0_{obs})$	$\log_{10}$(1/h)	− 2.707	− 3.005	0.40	− 4.234	− 2.549
$E_{a,k_{obs}}$	kcal/mol	86.39	102.2	20.16	78.51	163.5
$B_{granule.k_{obs}}$	1/ % RH	− 0.0696	− 0.0768	0.0159	− 0.112	− 0.0506
$B_{Tablet.k_{obs}}$	1/ % RH	0.0832	0.1398	0.0799	0.0395	0.382

LB lower bound
UB upper bound

While the present model suggests that the lower water content and compression force, the lower the stability risk; these concerns must be balanced with the competing requirements such as maintaining appearance with sufficient tablet hardness. All of the requirements could be modeled with posterior distributions, and the product of those posterior probabilities could be used to define the probability of failure as a risk metric. It would then be left as a management risk tolerance exercise to determine which operating point exposes the product to the least acceptable amount of risk.

CONCLUSIONS

As illustrated by this case study, quantitative risk assessment can provide very useful insight for obtaining a rational consensus decision on what is "acceptable" risk. The utility of this approach to risk assessment is dependent on the quality and quantity of the manufacturing and stability data, the reliability of the models and the rigor of the model development and validation methods employed. There is nothing in the present methodology that necessitates a linear manufacturing model. In the present example, a simple correlation was able to illustrate the manufacturing model; a Bayesian fitting was not pursued as it would not have afforded different predictions. In principal, one could employ the Bayesian parameter estimation on a mechanistic model and then sample from the resulting posterior in the same way as was done here. Indeed, mechanistic models, models, where available should always be preferred for risk analysis.

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