Regular Article

Impact of Magnesium Stearate Content: Modeling of Drug Degradation Using a Modified Arrhenius Equation

Kousuke Tamura,*[,a] Makoto Ono,[b] Takefumi Kawabe,[a] and Etsuo Yonemochi*[,c]

[a] *Analytical and Quality Evaluation Research Laboratories, Daiichi Sankyo Co., Ltd.; 1–2–58 Hiromachi, Shinagawa-ku, Tokyo 140–8710, Japan:* [b] *Quality Assurance Department, Daiichi Sankyo Co., Ltd.; 3–5–1 Nihonbashi Honcho, Chuo-ku, Tokyo 103–8426, Japan: and* [c] *Graduate School of Pharmaceutical Sciences, Hoshi University; 2–4–41 Ebara, Shinagawa-ku, Tokyo 142–8501, Japan.*

Received May 24, 2020; accepted August 5, 2020

To accelerate drug development, the pharmaceutical industry is working to shorten and improve studies on stability. The Accelerated Stability Assessment Program (ASAP) incorporating the humidity-corrected Arrhenius equation as an accelerated methodology has been proposed for both drug substances and drug products. In this study, the effect of magnesium stearate (MgSt) content on the chemical stability of acetylsalicylic acid was evaluated as a model system of drug–excipient compatibility studies using ASAP. In the acetylsalicylic acid powder blends, temperature and humidity showed a first-order linear response to the natural logarithm of the reaction rate constant, and MgSt content also showed a first-order linear response. A polynomial model was built in which temperature, humidity, and MgSt content were independent each other. The fitting index of the model, the coefficient of determination, was 0.9567, which was a good fit. In the long-term stability study (25°C/60% relative humidity, 6 months), there was good agreement in total between measured values and model-predicted values. Using this model, we inferred that the degradation rates were depended on MgSt content at the fixed temperature and humidity because the micro-environmental pH of the excipient was catalytically affected. Applying this model equation can significantly reduce the duration of formulation design and stability studies and save time and costs in drug development.

Key words chemical stability; drug–excipient interaction; mathematical model; solid-state; kinetics

Introduction

In drug substance and drug product applications, it is essential to conduct stability studies based on the International Conference on Harmonization (ICH) Q1A(R2) guideline.[1)] For the stability studies based on ICH guidelines, the long-term stability studies under the assumption of actual storage are time-consuming, and there are problems such as difficulty in extrapolation to long-term stability studies from accelerated and stress studies. In addition, while regulatory authorities are working to shorten the review system for an accelerated development of innovative new drugs, there is a lack of understanding of changes in quality with the shortening of stability studies.[2)] Moreover, since the drug applications for very short-term stability data have been approved in the early stage of development such as Phase I, the development of accurate stability predictions through short-term stability studies is crucial for the successful establishment and production of pharmaceuticals.[3)]

The Arrhenius equation is known as a correlation between a reaction rate constant and the temperature of a chemical reaction and has been used for the evaluation of the stability of pharmaceuticals. However, humidity is also known to be an important factor for the stability of pharmaceuticals but has not been evaluated using the conventional Arrhenius equation. Thus far, the Accelerated Stability Assessment Program (ASAP) (Eq. 1) capable of assessing humidity has been proposed, and research has been conducted with the aim of shortening and improving the accuracy of stability prediction.[4,5)]

$$\ln k = \ln A - E_a/(R \cdot T) + B(\%\mathrm{RH}) \quad (1)$$

where, k is the reaction rate; A is the frequency factor; E_a is the activation energy; R is the gas constant; T is the absolute temperature; B is the humidity sensitivity constant; and %RH is relative humidity (RH). Although the ASAP is empirical, it has been reported that the model equation fits well for a number of pharmaceuticals.[5)] In addition, as an extension of the Arrhenius equation in chemical stabilities, the effect of the content of the drug load,[6,7)] reactive excipient in solid dispersions,[8)] oxygen concentration in capsules containing oil components,[9)] and reactive impurities in polyethylene glycol have been reported.[10)] Also reported is the short-term stability evaluation of dissolution slow down owing to physical changes in immediate-release tablets as an extension of the Arrhenius equation.[11)] The incorporation of various unstable factors into the Arrhenius equation has led to efforts to understand quality more quickly and accurately.[12)]

A number of cases have been reported in chemical incompatibilities between formulation components.[13)] In particular, it has been reported that magnesium stearate (MgSt), which is commonly used as a lubricant for tablets, has chemical incompatibilities with many drugs, including acetylsalicylic acid,[14)] eprazinone hydrochloride,[15)] and angiotensin-converting enzyme inhibitors.[16,17)] In addition, MgSt is known to cause salt disproportionation in the salt form of a weakly ionizable drug.[18,19)] Although many cases of chemical interactions with MgSt in pharmaceuticals have been reported, there are no theoretically predicted multiple interactions using the Arrhenius equation for rapid formulation design and stability studies. In this study, we focused on the MgSt content in the formulation components and confirmed the effect of MgSt content on

* To whom correspondence should be addressed. e-mail: tamura.kousuke.aa@daiichisankyo.co.jp; e-yonemochi@hoshi.ac.jp

chemical stability. In addition, the correlation of temperature, humidity, and MgSt content with the reaction rate constant at each temperature and humidity condition was modeled by statistical analysis. The correlation between the prediction from the model equation and the actual long-term stability study was evaluated, and the possibility of the stability prediction by the change in MgSt content was examined.

Experimental

Materials Acetylsalicylic acid (Fig. 1) of a special grade was obtained from Kanto Chemical Co., Inc. (Tokyo, Japan). D-mannitol Parteck M200 was purchased from Merck KGaA (Darmstadt, Germany). MgSt NF NON-BOVINE HyQual was purchased from Mallinckrodt Pharmaceuticals (Dublin, Ireland). Lithium chloride, magnesium chloride hexahydrate, sodium bromide, and sodium chloride were purchased from Kanto Chemical Co., Inc. Britton–Robinson buffer solutions (pH 2.0 to 12.0, ionic strength: 1.0) were of a special grade and obtained from Nacalai Tesque, Inc. (Kyoto, Japan). Phosphoric acid of a special grade and acetonitrile of HPLC grade were purchased from Kanto Chemical Co., Inc. Purified water for LC-MS was purchased from FUJIFILM Wako Pure Chemical Corporation (Osaka, Japan). All other chemicals and reagents were commercial products of analytical grade.

Preparation of Acetylsalicylic Acid Powder Blends Powder blend mixtures of acetylsalicylic acid, D-mannitol, and MgSt were prepared by simple mixing. The components and composition of acetylsalicylic acid powder blends are described in Table 1. Acetylsalicylic acid was ground using a mixer mill (MM200; RETSCH GmbH, Haan, Germany) at the frequency of 25 Hz for a total of 2 min. For the procedure, 2-mL Eppendorf tubes (DNA LoBind; Eppendorf AG, Hamburg, Germany) and two zirconium dioxide balls (3 mm i.d.) were used. The powder X-ray diffraction pattern of the ground sample showed the diffraction peaks (data not shown). Acetylsalicylic acid, D-mannitol, and MgSt were sieved using Japanese Pharmacopoeia mesh No. 100 screens (Tokyo Screen Co., Ltd., Tokyo, Japan). These components were stirred in an agate mortar and a pestle. Each of the blend samples was divided into a 20 mg portion and stored in a 10 mL screw-capped GC glass vial. Control samples were stored at −20 °C in a freezer.

MgSt comprises a mixed composition of magnesium salts of stearic acid and palmitic acid, and it has been reported that physical properties differ between manufacturers and lots.[20] It is speculated that batch-to-batch differences can also occur in this degradation model. In this experiment, the same manufacturer and the same lot of MgSt were used. In addition, the % (w/w) MgSt used in the pharmaceutical formulation is generally approximately 1% (w/w) by total weight; however, a high concentration was used to confirm the effect of the content while ensuring good content uniformity in this experiment.

Stability Study of Acetylsalicylic Acid Powder Blends in Solid-State The powder blend samples with five different MgSt content (0, 1, 2, 3, and 4% (w/w)) were exposed to three different temperature conditions (35, 40, and 50 °C) and four different %RH (10, 30, 50, and 75%RH) for a maximum 10 d. For all conditions, the samples were placed in a sealed glass jar containing saturated salt solution that was stored in a temperature-controlled oven. Saturated lithium chloride solution was used to maintain the %RH environment at approximately 10%RH, saturated magnesium chloride hexahydrate solution was used for approximately 30%RH, saturated sodium bromide solution was used for approximately 50%RH, and saturated sodium chloride solution was used for approximately 75%RH. A temperature-humidity logger (KT-255U, Fujita Electric Works, Ltd., Kanagawa, Japan) was used for actual temperature and relative humidity data acquisition. For the long-term stability study, the samples were stored at a condition of 25 °C/60%RH for 1 to 6 months in a temperature-humidity controlled room.

Stressed and unstressed powder blend samples were added to approximately 8 mL of water–acetonitrile (1 : 1 (v/v)) and sonicated for 5 min. The solution was filtered with a 0.45 μm membrane filter (Millex-LCR hydrophilic polytetrafluoroethylene membrane, Merck KGaA). The first 1 mL of the filtrate was discarded and the remaining filtrate collected. The sample solution was set at the concentration of 0.5 mg/mL.

Stability Study of Acetylsalicylic Acid in Solution Acetylsalicylic acid was dissolved in a mixture of water–acetonitrile (1 : 1, v/v), mixed with the Britton–Robinson buffer solution (pH 2.0 to pH 12.0, ionic strength: 1.0), and was adjusted to a concentration to 1.0 mg/mL. The solution was stressed at 40 °C and sampled periodically. The sample solution was diluted 2-fold with a mixture of water–acetonitrile (1 : 1, v/v) before analyses.

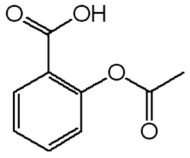

Fig. 1. Chemical Structure of Acetylsalicylic Acid

Measurement

HPLC Analysis The Shimadzu Nexera X2 LC system (Shimadzu Corporation, Kyoto, Japan) equipped with a photodiode array detector was used for HPLC analysis. An ACQUITY Ultra Performance LC (UPLC) BEH C8 column (2.1 mm i.d. × 75 mm, 1.7 μm particle size, Waters Corporation, Milford, MA, U.S.A.) was used as the analytical column.

Table 1. Components and Composition of Acetylsalicylic Acid Powder Blends

Components and composition	1	2	3	4	5
Acetylsalicylic acid (g) (for a drug substance)	20.0	20.0	20.0	20.0	20.0
D-Mannitol (g) (for a bulking agent)	80.0	79.0	78.0	77.0	76.0
Magnesium stearate (g) (for a lubricant)	0.0	1.0	2.0	3.0	4.0
Magnesium stearate to total weight ratio (% (w/w))	0.0	1.0	2.0	3.0	4.0
Magnesium stearate to acetylsalicylic acid ratio (% (w/w))	0.0	5.0	10.0	15.0	20.0

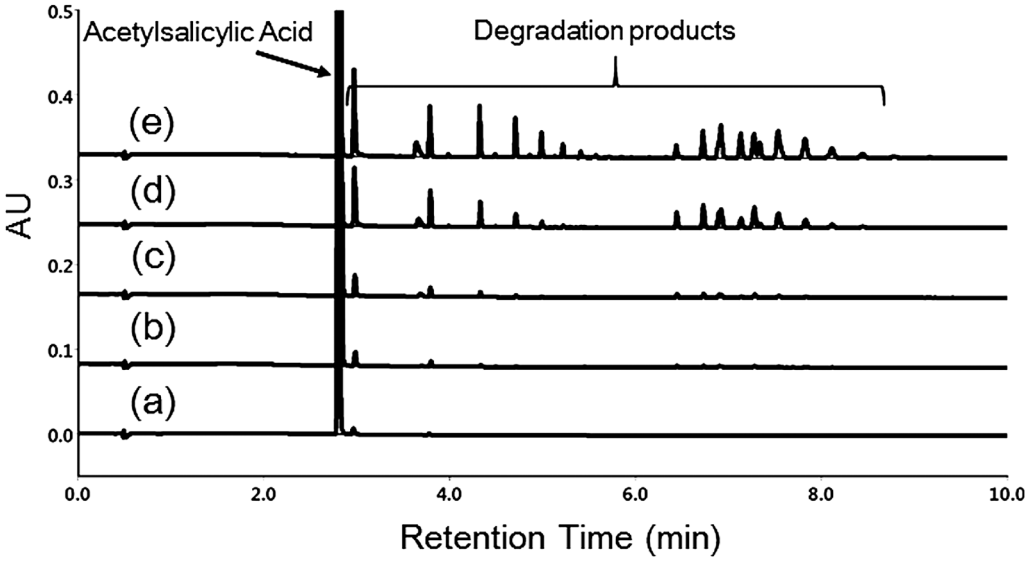

Fig. 2. Representative HPLC Chromatograms of Acetylsalicylic Acid Powder Blends with 4% (w/w) MgSt: (a) Initial; (b) 35 °C/12%RH for 7 d; (c) 35 °C/30%RH for 7 d; (d) 35 °C/47%RH for 7 d; (e) 35 °C/76%RH for 7 d

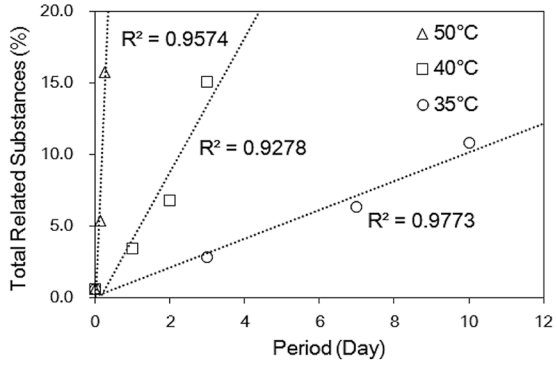

Fig. 3. Effect of Temperature on Degradation Level at Approximately 50%RH (4% (w/w) MgSt)

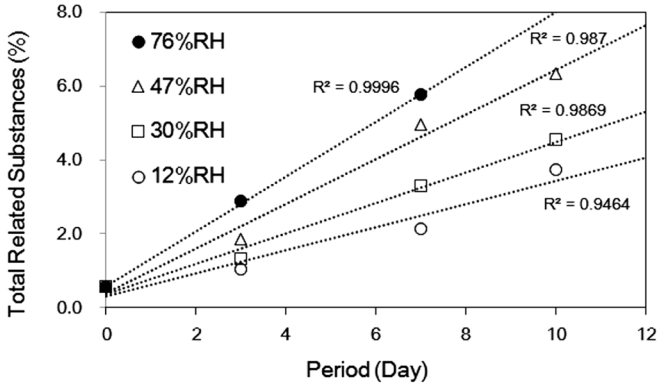

Fig. 4. Effect of Related Humidity on Degradation Level at 35 °C (3% (w/w) MgSt)

The temperature of the column oven was set at 40 °C. UV detection was performed at 227 nm. The mobile phase A was 5 mmol/L phosphoric acid in water, and the mobile phase B was acetonitrile. The flow rate was set at 0.5 mL/min. Gradient elution was conducted as follows: the step gradient by changing the percentage of mobile phase B at different times, T (min)/% mobile phase B = 0/5, 5/85, 10/85, 10.1/5, 14/5. The injection volume was 2 μL. Empower 3 (Waters Corporation) was used for data acquisition.

Statistical Evaluation and Kinetic Modeling of Degradation Rate Statistical evaluation and kinetic modeling was performed using JMP version 14.0.0 (SAS Institute Inc., Cary, NC, U.S.A.) based on a previous report.[21] The degradation rates were determined from the slopes of the degradation amount *versus* time plots for each condition. Experimental Ln k data were fit with a linear combination of temperature ($-1/T$), %RH, and % (w/w) MgSt variables to give the calculated formula using multiple regression with standard least squares fitting and effect leverage.

Results and Discussion

Solid-State Stability of Acetylsalicylic Acid Powder Blends The results of the solid-state stability of the acetylsalicylic acid powder blends under various conditions are shown in Tables S1, S2, and S3, Supplementary Materials. Representative HPLC chromatograms of the solid-state stability study of the acetylsalicylic acid powder blends are shown in Fig. 2. Salicylic acid (relative retention time 1.09), a hydrolysate of ester, was observed as a primary degradation product, and many other degradation products were also observed. Though these secondary degradation products are presumed to be multimers in the previous reports,[14] they are all derived from salicylic acid, and it is reported that the total amount of related substances is observed as a zero-order degradation curve of up to approximately 20 area%. Therefore, this study focused on the total amount of related substances as an extrapolation of the Arrhenius equation, and verified the degradation rate in each condition. In addition, the powder X-ray diffraction pattern of the representative samples of the stressed powder blends showed the diffraction peaks at the same position as that of the initial control sample (data not shown). Acetylsalicylic acid was suitable for the model compound because of anhydrous crystalline free form and highly soluble at each pH buffer solution.

The total amount of related substances of various temperatures at fixed %RH (approximately 50%RH) and % (w/w)

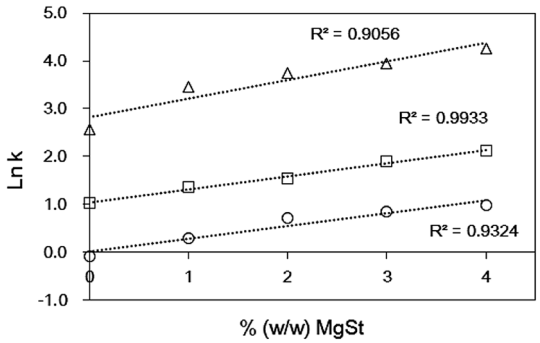

Fig. 5. Relationship between Lnk and MgSt Content (% (w/w)) at Fixed Temperature and Related Humidity Conditions: (○ 40 °C/32%RH, □ 40 °C/77%RH, △ 50 °C/75%RH)

MgSt (4% (w/w)) is shown in Fig. 3. A zero-order degradation curve of up to approximately 20 area% was observed for the increase in the total amount of related substances, indicating a linear relationship between the total amount of related substances and time over the temperature range investigated. At fixed temperature (35 °C) and % (w/w) MgSt (3% (w/w)), the relationship between the total amount of related substances and %RH is shown in Fig. 4. A zero-order degradation curve was observed for the increase in the total amount of related substances, indicating a linear relationship between the total amount of related substances and time over the %RH range investigated. In addition, as previously reported, temperatures ($1/T$) and %RH showed first-order linear responses to the logarithm of k.[5] Therefore, it is suggested that temperature and %RH in this degradation mechanism can be modeled with the moisture-modified Arrhenius equation. The plots of ln k at each temperature/%RH against % (w/w) MgSt are shown in Fig. 5. % (w/w) MgSt exhibited a first order linear responses

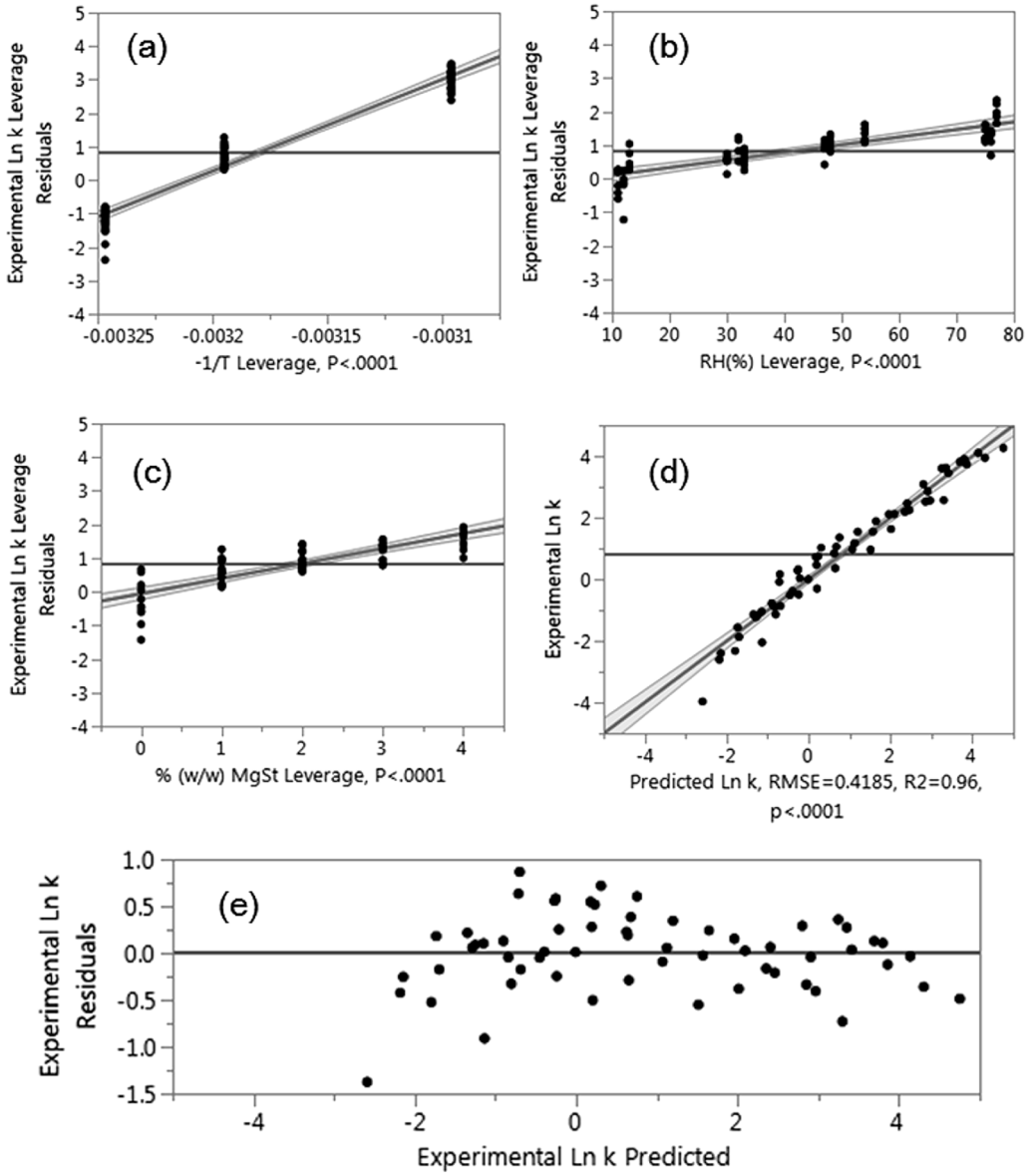

Fig. 6. Results of Statistical Modeling Using Multiple Linear Regression Analysis: (a) the Effect Leverage Plot of $-1/T$ on Ln k; (b) the Effect Leverage Plot of %RH on Ln k; (c) the Effect Leverage Plot of MgSt Content (% (w/w)) on Ln k; (d) The Plot of the Experimental Ln k *versus* Predicated Ln k; (e) Experimental Ln k Residual Plot

Table 2. Multiple Linear Regression Analysis

	p-Values		
	$-1/T$ and %RH	$-1/T$, %RH and % (w/w) MgSt	$-1/T$, %RH, % (w/w) MgSt, $(-1/T)\times$%RH, $(-1/T)\times$% (w/w) MgSt, and %RH$\times$% (w/w) MgSt
Intercept (ln *A*)	<0.0001	<0.0001	<0.0001
$-1/T$	<0.0001	<0.0001	<0.0001
%RH	<0.0001	<0.0001	<0.0001
% (w/w) MgSt	—	<0.0001	<0.0001
$(-1/T)\times$%RH	—	—	0.8404
$(-1/T)\times$% (w/w) MgSt	—	—	0.4234
%RH$\times$% (w/w) MgSt	—	—	0.3937
Coefficients			
Intercept (ln *A*)	86.8624	85.9695	85.9868
$-1/T$	27360	27360	27366
%RH	0.0227	0.0227	0.0227
% (w/w) MgSt	—	0.4465	0.4465
$((-1/T)-(-0.003179))\times((\%RH)-42.3333)$	—	—	7.5771
$((-1/T)-(-0.003179))\times((\%\text{ (w/w) MgSt})-2)$	—	—	−499.77
$((\%RH)-42.3333)\times((\%\text{ (w/w) MgSt})-2)$	—	—	−0.001410
Model performance			
R^2	0.8512	0.9567	0.9579
RMSE	0.7692	0.4185	0.4245

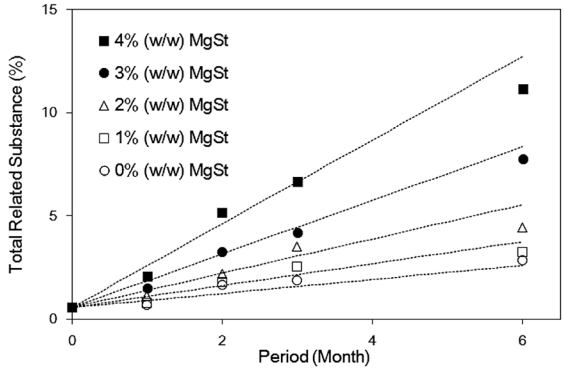

Fig. 7. Results of Stability Study of Acetylsalicylic Acid Powder Blends in Solid-State at 25 °C/60%RH

Dotted lines are a predicted values by the model. Markers are an experimental data.

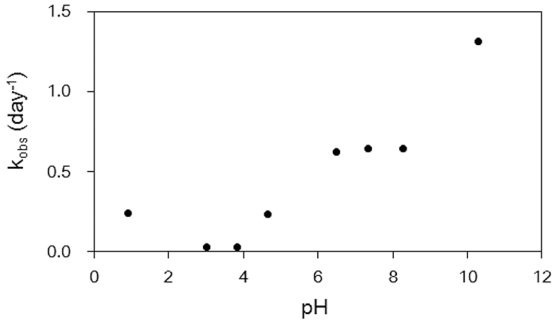

Fig. 8. Effect of pH on the Degradation Rate of Acetylsalicylic Acid in Various Buffer Solutions at 40 °C

to ln *k*, suggesting that % (w/w) MgSt can be modeled as a first-order function in the Arrhenius equation.

Modeling the Modified Arrhenius Equation of Acetylsalicylic Acid Mixture Powders The results of the evaluating models in which % (w/w) MgSt was added to the moisture-modified Arrhenius equation using JMP 14.0.0 for the obtained *k* under 60 conditions (Tables S1, S2, and S3) are shown in Fig. 6 and Table 2. We assessed whether all factors fit first-order linear models from the experimental results of the relationships between ln *k* and % (w/w) MgSt. The results showed that the *p*-value indicating the effect of the factor on *k* was <0.0001 in all factors, which was found to be significant. The fitting index of the models, the coefficient of determination (R^2), was 0.9567, and ln *k* residues were found to be uniformly distributed (Fig. 6). The accuracy measure, root mean square error (RMSE), was 0.4185, which was a good fit in this model. Thus, a polynomial model was determined in which the 1/*T*, %RH, and % (w/w) MgSt represented by Eq. 2 were independent each other.

$$\ln k = \ln A - E_a/(R\cdot T) + B(\%RH) + C\left(\%\text{ (w/w) MgSt}\right) \quad (2)$$

where, *C* is the MgSt sensitivity constant. In this experiment, the activation energy $E_a = 54.4$ (kcal·mol^{-1}), the humidity sensitivity constant $B = 0.0227$, and MgSt sensitivity constant $C = 0.4465$ were calculated from Table 2. It was confirmed that temperature had the largest effect on the degradation rate, and the % (w/w) MgSt had the next largest effect. When modeled only using 1/*T* and %RH, R^2 was 0.8512, and it was confirmed that it was inferior in terms of accuracy of the prediction model. In addition, the model including the interaction of 1/*T*, %RH, and % (w/w) MgSt was evaluated, and R^2 was slightly improved to 0.9579 (Table 2). However, it was a very complicated model equation, and the *p*-value of each interaction was not significant (>0.4); therefore, it was judged to be inappropriate as a model.

The results of plotting the model predicted values *versus* the measured values up to 6 months in the long-term stability test (25 °C/60%RH) condition for model validity assessment are shown in Fig. 7. Good fit was observed between the predicted and actual values of the models for the various % (w/w)

MgSt. Therefore, it was inferred that the model was shown by Eq. 2 and that the degradation rate could be predicted well for the variations in various temperatures, %RH, and % (w/w) MgSt. Acetylsalicylic acid powder blend samples with different MgSt contents are a complicated reaction such as a multistep decomposition reaction, and it may be predicted with higher accuracy in the case of a simpler reaction.

Consideration of Drug Degradation with Excipients To clarify the effect on the degradation mechanism, the solution stability test of acetylsalicylic acid in various pH conditions was conducted. The results are shown in Fig. 8. The degradation rates were determined as pseudo-first-order kinetics from the slopes of the degradation amount *versus* time plots for each condition. Acetylsalicylic acid decomposed significantly under a basic condition, whereas MgSt is known to be a basic excipient. In this degradation model, it was presumed that the degradation rates were depended on MgSt content at the fixed temperature and humidity because the micro-environmental pH of MgSt was catalytically affected.[22)]

From these results, the influence of the reactive excipient on chemical stability was modeled using the modified Arrhenius equation as a factor independent of temperature and humidity. As many pharmaceuticals are affected by reactive excipients, it is suggested that the application and refinement of this model equation for formulation and storage condition changes during actual drug development would allow efficient and rapid stability predictions.

Conclusion

In this study, the effect of temperature, relative humidity, and the content of MgSt on the degradation rate was modeled for acetylsalicylic acid powder blends with various MgSt content. No significant interactions were found for each factor, and multiple linear regression analyses found a polynomial model independent of each factor. It was judged to be a good prediction model because $R^2 = 0.96$. In fact, a better fit was observed when the predicted values from the models were compared with the actual values from the long-term stability test (25 °C/60%RH). MgSt is known to be a basic excipient, and in this case, it was inferred that the degradation rates were depended on MgSt content at the fixed temperature and humidity owing to the influence of micro-environmental pH on MgSt.

The model equation proposed here is simple and is considered to be highly practical because it mimics actual drug products, such as those containing a bulking agent. Applying this model equation can significantly reduce the duration of formulation design and stability studies and save time and costs in drug development. To speed up drug development and overcome severe international competition, it is important for the pharmaceutical industry to establish accelerated testing and work toward promoting an understanding of stability performance.

Acknowledgments The authors thank Ms. Hisae Yuasa (Daiichi Sankyo Co., Ltd.) for preparing samples and for HPLC analyses and Dr. Tetsuya Araki (Daiichi Sankyo Co., Ltd.) for helpful discussions.

Conflict of Interest Kousuke Tamura, Makoto Ono, and Takefumi Kawabe are currently employees of Daiichi Sankyo Co., Ltd., respectively.

Supplementary Materials The online version of this article contains supplementary materials.

References

1) International Conference on Harmonization (ICH). Topic Q1A(R2). "Stability Testing of New Drug Substances and Products.": ‹http://www.ich.org/›, cited 6 February, 2003.
2) Nagai S., *Int. J. Mol. Sci.*, **20**, 3801 (2019).
3) Li Q. C., Cohen K., Tougas T., Qiu F., Li J., McCaffrey J., Purdue T., Song J. J., Abelaira S. S., *J. Pharm. Innov.*, **8**, 56–65 (2013).
4) Waterman K. C., Adami R. C., *Int. J. Pharm.*, **293**, 101–125 (2005).
5) Waterman K. C., Carella A. J., Gumkowski M. J., Lukulay P., MacDonald B. C., Roy M. C., Shamblin S. L., *Pharm. Res.*, **24**, 780–790 (2007).
6) Waterman K. C., Gerst P., Dai Z., *J. Pharm. Sci.*, **101**, 4170–4177 (2012).
7) Baertschi S. W., Dill A. L., Kramer T. T., Scrivens G., Suruzhon M., *J. Pharm. Sci.*, **108**, 1746–1755 (2019).
8) Patterson A., Ferreira A. P., Banks E., Skeene K., Clarke G., Nicholson S., Rawlinson-Malone C., *Int. J. Pharm.*, **478**, 348–360 (2015).
9) Tang C., Sinchuk N., Flavier K., Waterman K. C., Waterman A., Krisch M. J., Poster presented at the American Association of Pharmaceutical Scientists Annual Meeting 2019 PharmSci 360, San Antonio, TX, November 2019.
10) Robnik B., Likozar B., Wang B., Stanić Ljubin T., Časar Z., *Pharmaceutics*, **11**, 452 (2019).
11) Scrivens G., *J. Pharm. Sci.*, **108**, 506–515 (2019).
12) Qiu F., Scrivens G., "Accelerated Predictive Stability (APS): Fundamentals and Pharmaceutical Industry Practices," Academic Press, Cambridge, MA, 2018.
13) Narang A. S., Desai D., Badawy S., *Pharm. Res.*, **29**, 2660–2683 (2012).
14) Mroso P. V., Li Wan Po A., Irwin W. J., *J. Pharm. Sci.*, **71**, 1096–1101 (1982).
15) Yamamura T., Ohta T., Taira T., Ogawa Y., Sakai Y., Moribe K., Yamamoto K., *Int. J. Pharm.*, **370**, 1–7 (2009).
16) Stanisz B., Paszun S., Strzyzycka N., Ptaszyński E., *Acta Pol. Pharm.*, **67**, 99–102 (2010).
17) Stanisz B., Regulska K., Kania J., Garbacki P., *Drug Dev. Ind. Pharm.*, **39**, 51–61 (2013).
18) Nie H., Xu W., Ren J., Taylor L. S., Marsac P. J., John C. T., Byrn S. R., *Mol. Pharm.*, **13**, 3541–3552 (2016).
19) Patel M. A., Luthra S., Shamblin S. L., Arora K. K., Krzyzaniak J. F., Taylor L. S., *Int. J. Pharm.*, **546**, 226–234 (2018).
20) Swaminathan V., Kildsig D. O., *AAPS PharmSciTech*, **2**, 73–79 (2001).
21) Fu M., Perlman M., Lu Q., Varga C., *J. Pharm. Biomed. Anal.*, **107**, 370–377 (2015).
22) Badawy S. I., Hussain M. A., *J. Pharm. Sci.*, **96**, 948–959 (2007).