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Application of iChemExplorer in pharmaceutical pH stress testing

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ABSTRACT

pH stress testing is an integral part of pharmaceutical stress testing and is a regulatory requirement for validating a stability indicating analytical method and elucidating degradation products and degradation pathways. This paper reports the results of an evaluation of iChemExplorer (ICE) for drug substance and drug product pH stress testing in comparison with the conventional (manual) approach. ICE is a simple and inexpensive technology, and through real case studies it was demonstrated that ICE is an efficient and "fit-for-purpose" alternative in conducting pharmaceutical pH stress testing. In addition, when using a non-isothermal ICE protocol, it is feasible to estimate the pH degradation kinetics (e.g., E_a) using the ICE software.

1. Introduction

"Stress testing of the drug substance can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used" [1]. pH stress testing is to "evaluate the susceptibility of the drug substance to hydrolysis across a wide range of pH values [1]" and is an integral part of pharmaceutical stress testing. The conventional (manual) approach in conducting pH stress testing is placing the samples under various pH conditions in an isothermal oven or water bath until a predefined level of degradation (e.g., 5–20% assay loss) or a predefined maximum duration is reached (from hours to weeks depending on the stability of the drug and the stress temperature). This approach usually requires manual pulling of the samples periodically to check the degree of degradation; as a result, it can be quite labor intensive. Naturally, applications of commercially available or home made automated or semi-automated systems have been attractive in stress testing [2,3]. These automated or semi-automated systems can be extremely helpful in automating the repetitive operations and save the scientists' time for more value added work. However, the disadvantage is that these systems are often sophisticated and costly, and require dedicated experts to operate. Automation brings in efficiency when there are sufficient numbers of stress studies to be performed on a routine basis, and works best with a centralized laboratory dedicated to high volumes of stress testing. However, for most pharmaceutical companies, a centralized stress testing laboratory is either undesirable or unnecessary due to cost/benefit considerations. A "fit for purpose" alternative with some automated features therefore can be very attractive in a decentralized stress testing environment.

In the past few years, the authors evaluated a simple yet innovative technology iChemExplorer® (Reaction Analytics Inc., Wilmington, DE, USA) for pH stress testing of drug substances and drug products with a focus on early clinical development applications, where turnaround time and material saving can be critical. This manuscript reports the result of the evaluation.

2. Experimental

2.1. Instruments and materials

A 1290 Infinity LC system (Agilent Technologies, Santa Clara, CA, USA) with a PDA detector was used for all experiments. Empower II software (Waters Corporation, Milford, MA, USA) was used for experimental setup, data acquisition and process. The LC methods were previously developed and validated for each of the drug substance or product evaluated; however, the development or validation of these methods is out of the scope of this paper.

iChemExplorer® (ICE) is a simple add-on device to the Agilent HPLC systems. The iChemExplorer® hardware includes a specially designed sample tray and a control unit. When the ICE is installed, this sample tray replaces the original one in the HPLC autosampler. The control unit is placed directly under the autosampler,

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Fig. 1. The iChemExplorer (ICE) hardware, which includes a specially designed sample tray replacing the original sample tray of an Agilent (U)HPLC and a control unit installed directly under the Agilent (U)HPLC autosampler (courtesy of Reaction Analytics, Inc.).

as shown in Fig. 1. The temperature of the sample tray is set up using the iChemExplorer software. The ICE also allows magnetically controlled stirring if necessary.

For drug substance applications, crimp vials with a PTFE/silicone/PTFE septum (Waters P/N: PSL404231) were used.

For drug product applications, ChemGlass filter vials (part # PF-1011-150LP, which includes: 12 mm × 32 mm crimp seal vial (PF-1011-251LP), Teflon ferrule/holder for vial and filter (PF-1011-252LP), and micro coarse fritted insert (PF-1011-253LP), ChemGlass Life Sciences, Vineland, NJ, USA) and Thompson filter vials (part # 35544-500-ML, Thomson Instrument Co., Oceanside, CA, USA) were used.

Drug substance and drug product samples were all small molecule investigational drug candidates from internal sources. Drug substance or drug product stock solutions were prepared at concentrations according to the procedure for that drug substance or drug product using the diluents specified in the procedure. For acid and base stress testing, typically, a 1 N HCl and 1 N NaOH aqueous solutions were prepared, respectively. The final stress solution was prepared by mixing appropriate aliquots of the drug substance or drug product stock solution and the 1 N HCl or 1 N NaOH solution in a volumetric flask to make a 0.1 N HCl or 0.1 N NaOH stress solution with a concentration of the drug ranging from 0.1 to 1 mg/ml in accordance with the analytical procedure. Likewise, a stress solution at pH 7.4 was prepared using phosphate buffer. For ICE studies, the pH stress solution was then transferred to a regular crimp vial or a filter vial in the case of drug product.

A more comprehensive pH stability study was performed with 8 pH values: pH 1.3, 2, 3, 4.5, 6, 6.8, 7.4, and 8. In this case all samples were prepared using phosphate buffer except pH 4.5 which was prepared using citrate buffer.

For pH stress testing using the conventional (manual) approach, stress solutions were prepared in volumetric flasks, which then were placed in an oven preheated to 40 °C.

All solvents (e.g., water, methanol, acetonitrile) were HPLC grade. All chemicals (e.g., NaOH, HCl and phosphate buffer) were ACS grade.

2.2. pH stress testing protocols

pH stress studies were carried out using both the conventional and ICE approaches for comparison. The experimental designs of both approaches are summarized in Table 1. For optimization of the ICE approach, two ICE protocols were initially evaluated.

For ICE studies, the temperature program was set up using the ICE software. Empower II software was used for HPLC instrument control and data processing. If applicable, the data were also processed with the iChemExplorer software for additional information (e.g., kinetic estimation).

3. Results and discussion

3.1. Design and application of the ICE protocol

ICH Q1A recommends stress testing including pH stress testing [1], however, the specifics on the conditions and durations of the stress testing are left to the individual pharmaceutical company. Internally, we adopted a general pH stress testing protocol (which henceforward is referred to as the conventional protocol) as shown in Table 1. pH stress testing is carried out at 40 °C for a maximum of 2 weeks or 5–20% degradation, whichever is achieved first. This protocol is in line with the industry's best practice in performing pH stress testing [4–6] although a quicker turnaround time is always desirable. To take full advantage of the flexibility of the ICE in temperature programming and evaluate the feasibility of its use in pH stress testing, the following were considered when designing an ICE protocol:

(1) Maintain the same level or slightly excessive stress with that of the conventional approach so that the extent of the pH stress would not be significantly altered due to the use of ICE.
(2) A higher temperature than 40 °C would be evaluated to shorten the duration of the ICE stress studies; however, the temperature would be increased gradually from room temperature to a higher temperature as needed for achieving the target level of degradation. In this way, degradation products only formed at high temperature can be monitored and thus differentiated from the more relevant degradation products (those that are readily formed at ambient or moderate temperature).
(3) The highest temperature would be 70 °C to limit the potential for formation of irrelevant degradation products or secondary degradation products, as 70 °C has been generally accepted as an appropriate temperature for stress testing in the pharmaceutical industry [5,6].

The equivalency of the ICE approach to the conventional approach was estimated by applying the principle of Arrhenius equation. It has been reported that the activation energies for pharmaceutical degradations are mostly in the range of 12–30 kcal/mol or higher [6,7]. Without knowing the actual activation energy of a compound, an activation energy of 12 kcal/mol can be considered an extremely conservative estimation. At this activation energy, the rate increase roughly follows the "2 for 10" rule-the rate approximately doubles with every 10 °C temperature increase.

Two ICE temperature protocols were initially evaluated. The first protocol used a staged isothermal approach:

(1) Keep the temperature at 40 °C for up to 48 h,
(2) If the target level of degradation is not reached after 48 h at 40 °C, increase the temperature rapidly (in 10 min) to 55 °C,
(3) If the target level of degradation is still not reached after 24 h at 55 °C, increase the temperature rapidly (in 10 min) to 70 °C and keep it for up to 24 h,
(4) Stop the stress testing after 24 h at 70 °C regardless the level of degradation.

This 4-day ICE protocol is roughly equivalent to a 13-day stress at 40 °C estimated according to the "2-for-10" rule. The second ICE protocol is consisted of the following steps:

Table 1
Experimental design of the pH stability studies.

	Conventional[a]	iChemExplorer[a]	
Temperature	40 °C	Ramp from ambient to 70 °C in 24 h, hold at 70 °C for another 24 h	40 °C for up to 2 days, 55 °C for up to 1 day, and 70 °C for up to 1 day
Maximum duration	2 weeks		
pH values	0.1 N HCl, pH 7.4, 0.1 N NaOH		
Endpoint	5–20% assay loss or maximum duration, whichever occurs first		
Pull time	Manual pull samples at t = 0, 4 h, 8 h, day 1, day 3, day 7 and day 14	Samples were pulled automatically and periodically based on the cycle time for all stress conditions.	

[a] Control samples were injected under ambient temperature before heating.

(1) Ramp the temperature from ambient temperature to 70 °C in 24 h,
(2) If the target level of degradation is not reached, then holding at 70 °C for up to 24 h,
(3) The stress testing is terminated after holding at 70 °C for 24 h regardless the level of degradation.

This 2-day partially non-isothermal protocol (henceforward it is referred to as the non-isothermal protocol) is roughly equivalent to a 10-day stress testing at 40 °C according to the "2-for-10" rule. The less than 14-day-equivalence design of both ICE protocols is based on the conservative nature of the "2 for 10" rule. Because an activation energy of 12 kcal/mol is possible but uncommon for pharmaceutical compounds, it was expected and experimentally demonstrated through all actual studies we did so far that both ICE stress protocols were indeed slightly more stressful than the 40 °C 2-week conventional protocol.

As an example, Fig. 2 compares the results obtained with the conventional and the ICE protocols. The compound of interest (drug substance A) is very stable under basic (0.1 N NaOH) and neutral (pH 7.4) stress conditions and did not yield any reportable degradation products (method quantitation limit = 0.05%) with either the conventional or the ICE protocols (data not shown). Under the acidic stress condition (0.1 N HCl), a single degradation product was formed at about 0.6% after 2 weeks at 40 °C with the conventional protocol, while slightly more of the same degradation product was formed under either of the ICE conditions after 4 and 2 days, respectively. Considering the purpose of the pH stress testing-elucidation of degradation products and validation of stability indicating method, all three protocols can be considered equivalent.

In addition to programmable temperature control, the ICE can also provide magnetically controlled stirring. The effect of stirring for pH stress testing was therefore examined. Not surprisingly, as shown in Table 2, slightly more degradation was observed when the sample was stirred during the stress. Degradant RRT 0.95, which is the same as that depicted in Fig. 2, was formed at 2.40% with stirring comparing to 2.02% without stirring after 96 h with the 4-day ICE protocol. Further, a new degradation product RRT 1.24 appeared at the last time point on day 4 with stirring. By examining the data, it was determined that the difference between stirred and non-stirred pH stress testing was not significant considering the purpose of pH stress testing. The additional peak formed only under stirring was at very low level and only formed at high temperature (70 °C on day 4 of the 4-day protocol), thus would not be considered as a relevant degradation product. Hence, to simplify the protocol, stirring is not recommended for the routine pH stress testing.

Table 2
Comparison of acid degradation of API A with/without stirring.

Time (h)	Area%/without stir	Area%/with stir	
	RRT 0.95	RRT 0.95	RRT 1.24
0	ND	ND	ND
6	ND	ND	ND
16	0.09	0.16	ND
24	0.12	0.14	ND
48	0.23	0.29	ND
72	0.80	1.03	ND
96	2.02	2.40	0.11

ND: not detected.

The non-isothermal ICE protocol was eventually selected as the default ICE pH stress protocol because of the shorter turnaround time and more importantly because of the convenience of obtaining kinetic information of the pH degradation (details are discussed in Section 3.2). With this protocol, the maximum duration for pH stress testing is 2 days. In practice, the actual duration is determined on a case by case basis depending on the pH stability of the drug substance or product under the conditions tested. For an unstable compound, the stress testing can be terminated at any time point once the desired level of degradation is achieved. On the other hand, for a stable compound, the stress is terminated at the end of the 2 day program regardless whether the target level of degradation is achieved or not.

Fig. 3 shows the data of drug substance B obtained under 0.1 N HCl using the full 2-day non-isothermal ICE protocol. By examining the data, it was observed that the same two peaks RT 9.69 and RT 16.07 remained the major degradation products (which were defined according to the internal practice for identification

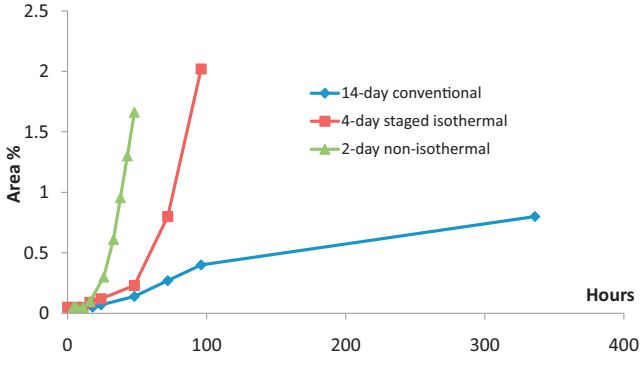

Fig. 2. Comparison of acid stress results of API A obtained using the conventional and the two ICE protocols, respectively.

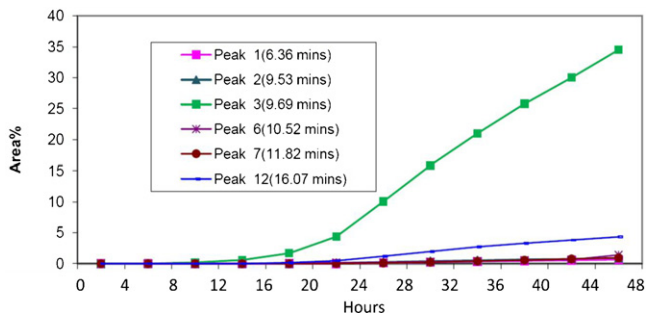

Fig. 3. Results of API B acid stress testing using the non-isothermal ICE protocol.

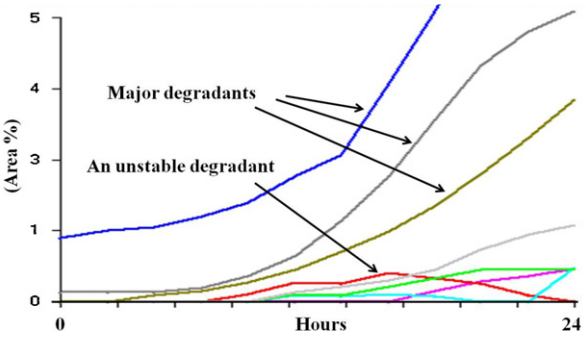

Fig. 4. ICE plot (partial) of degradants of API C formed under base stress condition (0.1 N NaOH). Major degradants are those exceeding the internal identification thresholds for solution stress testing. (For interpretation of the references to color in the text, the reader is referred to the web version of this article.)

of degradants formed during solution stress testing: greater than both the ICH identification threshold and 1/10 of total degradation) [8] through the whole course of the study. By the end of the non-isothermal portion of the protocol after 24 h, about 5% total degradation was formed, of which RT 9.69 was about 4.4% and RT 16.07 was about 0.5%, which is just above the internal identification threshold for solution stress testing. By the end of the study, RT 9.69 increased to about 34.5%, and RT 16.07 increased to about 4.3%, which is still just slightly above this identification threshold for solution stress testing. None of the other degradation products were above this threshold at any time during the stress. This example demonstrated that once the degradation product reached a level that is sufficient for the purpose of the pH stress testing (e.g., 5–20% degradation), then the timing of termination (e.g., at 5% or 20% degradation) of the stress testing might not change the assignment of major degradants that should be identified, unless the major degradation product is unstable. This type of behavior is rather common; as similar observations were made for all the compounds we tested using these protocols.

Since the temperature and time of each testing point are recorded by the ICE software, the time or temperature at which a degradation product appears or disappears can be conveniently tracked. This feature is useful in tracking and identifying a degradation product formed only under a high temperature or a secondary degradation product. In contrast, during a conventional pH stress testing, because the sample pulls are relatively infrequent due to the manual operation, sometimes a degradation product observed in one pull in the middle of the stress testing but not in the rest can confuse the interpretation of the degradation pathway.

Avoiding this problem, Fig. 4 shows an example of how an unstable degradation product can be monitored using the ICE approach. In this case, three major degradation products of API C were readily formed under basic condition (0.1 N NaOH) soon after the stress was started, and about 20% total degradation was reached in 24 h. Several minor degradation products were observed at higher temperatures but remained below the internal identification threshold for solution stress testing. Among the minor degradation products, one degradation product (the red trace) was apparently unstable. It was detected at around 35 °C and reached maximum concentration at around 50 °C (around 15 h in Fig. 4), and then it started to decrease until it was no longer detectable when the temperature increased to 70 °C (24 h in Fig. 4).

To assist preformulation development, a more comprehensive pH stability study is often conducted under more pH conditions (typically between pH 1 and 7.5) in order to obtain more pH stability information. To evaluate the feasibility of ICE in this type of application, API D was stressed under 8 different pH values: 1.3, 2.0, 3.0, 4.5, 6.0, 6.8, 7.4, and 8.0, using the non-isothermal ICE

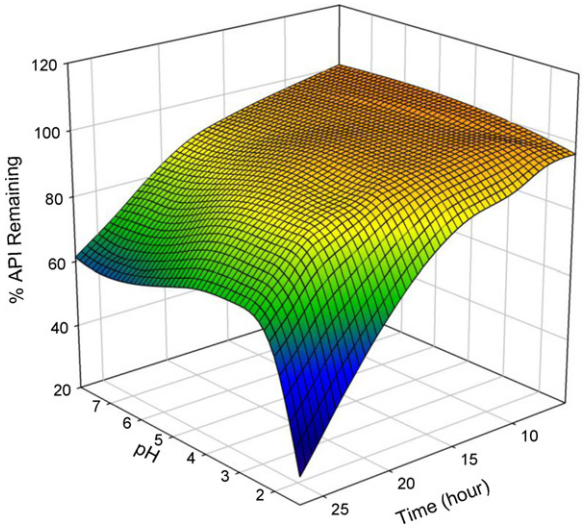

Fig. 5. 3-Dimensional plot of pH stability results of API D. The *X* axis is the pH value, the *Y* axis is the stress time in hours and *Z* axis is the percent of parent compound remaining during the course of pH stress. The remainder of the parent compound (%) is a reflection of the stability of the compound under the pH conditions.

protocol. Significant degradation products were formed in 24 h under the majority of the conditions, so the stress was terminated at the 24-h time point. Fig. 5 shows the results (plotted using SigmaPlot software, Systat Software, Inc., San Jose, CA, USA) from this study. In 24 h, the pH stability profile of the compound was established. The compound was relatively more stable at around pH 3–4 in the pH range tested.

3.2. Evaluation of degradation kinetics

Knowledge of degradation kinetics is valuable to enhance the overall understanding of chemical stability and degradation of the drug. Unfortunately, this type of information cannot be obtained during conventional pH stress testing for the purpose of validating an analytical method or elucidating potential degradation products because a one temperature study under the stress testing condition is not sufficient to predict the degradation kinetics of the drug under the long term storage temperature. In order to predict the pH degradation kinetics of the drug under the long term storage temperature, the activation energy (E_a) of the pH degradation across a temperature range must be established. Typically, this is achieved through a separate study with multiple temperature conditions during preformulation development. Because the samples are typically manually pulled from multiple parallel isothermal conditions during an extended period, this type of study requires a significant commitment in both time and labor.

The use of the non-isothermal ICE protocol makes it possible to estimate the pH degradation activation energy E_a and other kinetic information using the same data generated during the non-isothermal part of the study. It has been demonstrated by many authors that a non-isothermal approach can be much more efficient in getting the activation energy with accuracy comparable to that from a conventional isothermal study [3,9–12]. The feasibility of using a non-isothermal ICE protocol to estimate the degradation activation energy and the associated accuracy were demonstrated previously using famotidine as a model compound [13]. Hence, in this paper, comparison of kinetic results from ICE approach and the conventional isothermal approach was not performed. Fig. 6 shows the kinetic report of the pH 1.3 sample from the pH stability study of API D discussed above, in which the estimated apparent activation energy (E_a) based on the loss of the API, rate constant

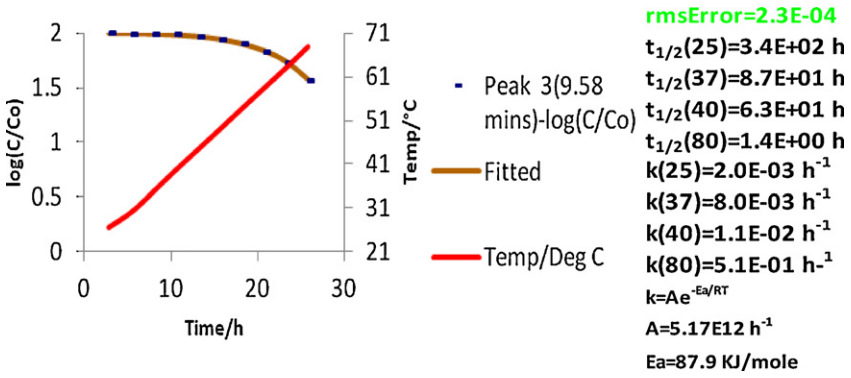

Fig. 6. Kinetic report of the pH 1.3 sample of API D by the ICE software. The *Y* axis (shown in the left) is the logarithm of ratio of API peak area (C) divided by the API peak area at time 0 (C_0) expressed in percent value as typically the API remaining or loss during a stability testing is expressed in percent (e.g., when $C = C_0$, $\log(C/C_0)$ is expressed as $\log 100 = 2$).

(k) and half life ($t_{1/2}$) at various temperatures are provided. This information is extremely useful in predicting the solution stability of the API (e.g., in this case the half life of the pH 1.3 API solution at 25 °C is 340 h–14 days), the in use stability of PfOS (powder for oral solution drug product) reconstituted solution, and the shelf life of a liquid formulation, etc. Even for SOF (solid oral formulation) drug product, this knowledge is useful in selecting a stable pH range and hence the type of excipients during formulation development.

Fig. 7 shows the estimated activation energies (E_a) as a function of the pH values. Comparing with Fig. 5, as expected, a correlation can be made in that the activation energies (or the rate constant (k) and the half life ($t_{1/2}$) at various temperatures (not shown)) estimated using the ICE software and the level of API (%) remaining during the course of the stress testing as shown in Fig. 5 plotted using SigmaPlot software displayed the same trend of pH stability: the greatest stability observed in Fig. 5 and the highest activation energies observed in Fig. 7 occur at around the same pH range 3–4. Note that without comparison to the results from a multiple temperature conventional isothermal kinetic study, it is not possible to know how accurate these kinetic data are in an absolute sense; however, this correlation demonstrates the usefulness of this estimate at least from a relative point of view, which may be sufficient at the early development stage.

It is worthwhile to mention that currently the ICE software uses the absolute area of the API peak at different pulling points for the kinetic estimation; therefore, when the degradation is insignificant or the accuracy/precision of the injection is compromised due to various reasons (e.g., solvent loss), it was noticed that the accuracy of this estimation can be problematic.

In order to use the ICE software to graph the degradation and perform kinetic estimation, the testing at different time points must be performed on the stressed sample from the same vial. It is thus important to use crimp vials with durable septa that can withstand repeated injections under strong acid or base at elevated temperature to maintain effective closure and thus prevent solvent loss during the stress testing. An evaluation on the precision of repeated injections using one of the ICE protocols was conducted using API A dissolved in only the diluent (50/50, v/v, acetonitrile/water) in a crimp vial with a PTFE/silicone/PTFE septum (Waters P/N: PSL404231); the results are exhibited in Table 3. The peak area of the API A was quite consistent throughout the whole course of the stress testing. According to internal practice, 50% is the highest level of organic co-solvent used in solution stress testing. Injection precisions of solutions with lower level of organic co-solvent was not tested, however, it is not unreasonable to assume that the lower the level of the organic phase, the less a problem for solvent evaporation.

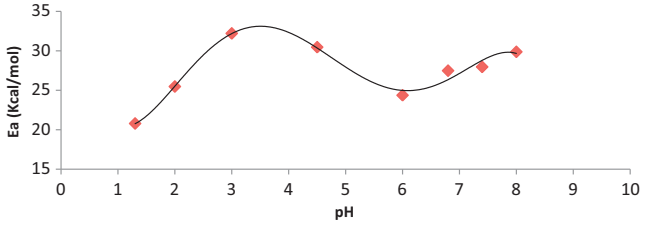

Fig. 7. Correlation of pH values and pH degradation activation energies of API D.

3.3. Drug product applications

Insolubility of certain excipients/coating materials, etc., of a formulated product in the aqueous solution is a common issue when conducting drug product pH stress testing. To ensure an uninterrupted analysis, the drug product solutions are usually manually filtered or centrifuged prior to the HPLC/UPLC analysis. To simplify the ICE workflow for drug product pH stress testing, it is possible to eliminate this manual step by using commercially available filter vials. Two types of filter vials were evaluated for pH stress of several drug products under both basic and acidic (data not shown because the outcome was comparable to that of the basic) condition. The results of base stress are shown in Table 4. It was observed that both filter vials effectively prevented needle clogging during the ICE stress without having to manually filter or centrifuge the product solutions prior to the study.

Also, in general, the results from the ICE approach with both filter vials and that from the conventional approach are qualitatively comparable. Similar to the observations made without using filter vials, the ICE approach generates slightly more degradation products than the conventional approach because of the assumption of

Table 3
Precision of 10 repeated injections from the same vial.

Time (h)	Peak area
0	5721.77
7.6	5778.43
18.6	5855.69
28.2	5853.84
37.9	5851.45
42.7	5810.97
55.9	5796.64
66.9	5900.54
80.1	5753.95
91.8	5884.49
Average	5820.78
STDEV	58.13
% RSD	1.0

Table 4
Comparison of the results of three drug product tablets basic stress (0.1 N NaOH) obtained using the conventional approach and iChemExplorer.

Tablet	Conventional	iChemExplorer	
		ChemGlass vial	Thomsen vial
Product M[a]	2.1%	2.2%	4.3%
Product X[a]	3.6%	8.7%	3.6%
Product N	RRT 0.85 = 0.4% RRT 1.03 = 0.4%	RRT 0.85 = 1.0% RRT 1.03 = 0.7% RRT 1.15 = 0.2%	RRT 0.85 = 0.6% RRT 1.03 = 1.1% RRT 1.15 = 0.1%

[a] Only one degradation product was formed.

the 12 kcal/mol E_a when correlating between ICE and conventional approaches. In addition, a slight difference was observed between the results of the two filter vials, however, the statistical significance of these differences was not evaluated as it was determined that the difference was not significant considering the purpose of the pH stress testing. Note that the additional peak at RRT 1.15 from product N is below the internal identification threshold for drug product solution stress [8]; therefore, the significant degradation products for all products with both approaches are identical.

4. Conclusions

The results of multiple studies demonstrated that the ICE approach is a simple, inexpensive, yet innovative alternative in conducting pH stress testing of drug substances or drug products. The ICE approach improved the efficiency and reduced the sample requirement. A full ICE pH stress testing can be done in less than 2 days to achieve appropriate levels of stress that fits the purpose of the pH stress testing. Low milligram levels of drug substance can be sufficient for an ICE pH stress testing because the entire sample required is a single solution in an HPLC vial. Combining the use of filter vials and ICE, manual filtration or centrifugation can be eliminated. In addition, when using a non-isothermal ICE protocol, pH degradation kinetics can be estimated utilizing the same data generated during the pH stress testing without a separate, time consuming kinetic study.

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