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Lifetime Assessment of POCT Strips through Accelerated Degradation Test

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Abstract

In general, single parameter, i.e. temperature, as an accelerating parameter is used to assess the accelerated stability of Point-of-Care Testing (POCT) diagnostic devices. However, humidity also plays an important role in deteriorating the strip performance since major components of test strips are proteins such as enzymes. 5 different Temp/Humi conditions were used to assess the lifetime of strips. Degradation of test strips were studied through the accelerated stability test and the lifetime was assessed using commercial POCT products.

The failure time of the test strips was determined to be the time when the concentration at the time of the measurement was out of the range of ± 15% of the initial concentration value, by following the degradation pattern in an exponential fashion. For the combined Temp/Humi accelerated conditions, the lifetime prediction was made by adopting a modified Eyring Eq. Model for Stress-Life relationship, and the B10 lifetime (with CL=90%) was estimated to be 505 h (lower limit) when Weibull distribution was applied as the lifetime distribution of strips.

Keywords: Accelerated degradation test; Lifetime assessment; Diagnostic device; Strip; POCT

Abbreviations: β: Shape Parameter; *φ*: Parameters to be Determined; *b*: Parameters to be Determined; *A*: Constant; AF: Acceleration Factors; CL: Confidence Level; Ea: Activation Energy (eV); L: Lifetime; $L_{accelerated}$: The Life at the Accelerated Stress Level; L_{USE}: The Life at Use Stress Level; *U*: Relative Humidity (Decimal or Percentage); U_A: Accelerated Humidity Level; U_u: Use Humidity Level; *V*: Temperature (in Absolute Units); V_A: Accelerated Temperature Level; V_u: Use Temperature Level

Introduction

The number of diabetic patients is drastically increasing every year, which makes the point-of-care testing important in daily life [1-3]. Among other POCT devices, glucose-monitoring devices are the most popular and available ones and their fast response and convenience in use are driving their market share not limited only in hospital but expanding in home healthcare. Therefore, it is important to assess the performance of those devices, most importantly the accurateness. Storage condition is the main key factor in maintaining their performance since the major functionality comes from the proteins immobilized on the test strips. The strip stability is determined by evaluating the period during which the performance of the product is maintained under the storage condition recommended by the manufacturer. EN 13640 and CLSI EP25-A are generally used for the evaluation of the strip stability [4,5]. EN 13640 includes the real-time monitoring and the accelerated test of the stability of strips. In real-time monitoring methods, all conceivable conditions such as transportation, storage, and etc. are considered. In accelerated tests, physical and chemical degradations are accelerated by exposing the strips under accelerated environmental conditions in order to evaluate the storage lifetime, which makes the manufacturers choose this method based on the economic point of view. In general, single parameter, i.e. temperature or humidity, as an accelerating parameter is used to assess the accelerated stability of Point-of-Care Testing (POCT) diagnostic devices [6-9]. In the present research, the degradation model and the lifetime prediction were systematically studied under combined accelerated stress conditions of temperature and humidity as stress factors.

Materials and Method

Commercial glucose-monitoring device and test strips (ACCU-CHEK® and ACCU-CHEK® Active Strip) were purchased from Roche Diagnostics GmbH, Germany. The control solution (Meter Trax™ Control) was purchased from Bio-Rad, USA and was used as a standard material for the degradation of strips under the combined stress conditions. 5 different Temp/Humi conditions were used as shown in Table 1. The strips were completely exposed to the stress conditions such that the strips were taken out from the vials and kept in the Temp/Humi chamber for the accelerated stress tests. For measurement of the strips which had been exposed in the Temp/Humi conditions, the strips were allowed to reach room temperature by keeping them in an ambient environment for 1 h. 1 μL of control solution was used for each measurement.

Strips of identical lot number were used for all the present experiments in order to minimize the variables which can be caused

Control Solution	Temp/Humi	Failure Determination
Bio-Rad, USA	30°C/70% RH	value at the time of measurement is out of the range of ± 15% of initial value
	40°C/70% RH	
	50°C/70% RH	
	50°C/50% RH	
	50°C/30% RH	

Table 1: Conditions of accelerated stability test on diagnostic device strips.

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during the production. 5 test strips were used per each measurement.

Failure of strip was set at the point in which the measurement reading was out of the range of ± 15% of initial reading, which is required for the FDA approval. For the estimation of lifetime of strips in normal use condition (25°C/30% RH), a statistical approach was adopted by using a commercial software program, ALTA® (ReliaSoft, USA). The failure time was determined by following the degradation pattern of the strips in the exponentially decreasing fashion. Weibull distribution was applied as the lifetime distribution of the strips in the present study. Lifetime of strips in normal use condition was predicted using the lifetime data obtained from the accelerated degradation tests by adopting a modified Eyring model [7-9].

Results and Discussion

Scatter diagrams of strips under 5 different Temp/Humi conditions were shown in Figure 1, for which each measurement was made by recording the concentrations of the control solutions at each different exposure time to the stress conditions. It was found that the measured values of the control solution decreased as the exposure time increased. Particularly, it was observed that the degradation proceeded in the following orders: i) 30°C/70% RH<40°C/70% RH<50°C/70% RH under varied temperature conditions by setting the humidity constant, ii) 50°C/30% RH<50°C/50% RH<50°C/70% RH under varied humidity conditions by setting the temperature constant, respectively. It could be seen that the degradation occurred very rapidly in the present study, which was similar to the findings from Bamberg et al. [10] and Gonzales and Kampa [11]. This was because the test conditions in the present study were the same as the open-vial condition of their studies. It is interesting to note that the accuracy was more strongly affected by the humidity condition than the temperature condition since the accuracy decreased more drastically as the humidity increased, which indicated that the stability of protein, the core sensing material for the detection of glucose, was more affected by humidity than temperature.

The degradation of test strips under stress condition of temperature have been extensively studied and could be found in the literature [8,9]. However, the present research not only studied the degradation pattern under temperature/humidity stress but also estimated the lifetime of the test strips using a statistical method. The degradation of test strips was estimated using ALTA® as shown in Figure 2. The degradation was exponentially decreased in all the stress conditions. The failure time was collected by setting the failure at the point in which the measurement reading was out of the range of ± 15% of initial reading. In order to estimate the failure time of strips, an exponential model in the form of y=b*exp(a*x) was adopted in the ALTA® software program, which was represented in the solid lines in the exponentially decreasing fashion. Thus, the failure time was determined to be the ones which touched the ± 15% of initial reading lines represented in the solid purple lines. By using the failure time estimated in Figure 2, the relationship between life *vs*. stress was plotted in Figure 3, for the temperature and humidity stress conditions, respectively. In Figure 3(a), the temperature was changed from 30°C to 50°C while the humidity maintained at 70% RH and it was found that the degradation time decreased as the temperature increased. In Figure 3(b), the humidity was changed from 30% RH to 70% RH while the temperature maintained at 50°C and it was found that the degradation time decreased as the relative humidity increased. The unreliability and scale parameter lines were shown in straight lines. The upper top line indicated the 99% unreliability line while the lowest line indicated the 1% unreliability line, respectively. The middle line indicated the scale parameter line. For example, the reliability began to drop at 30°C approximately after 100 h, and the reliability began to drop at 50% RH approximately after 80 h. Therefore, the lifetime of the strips was getting shorter in both the temperature and humidity conditions as the stress levels were getting more severe, which could be verified by the area of the parabola of each stress condition since the lifetime represented by the area was appearing in the shorter time as the stress levels were getting more severe. In addition, the upper limit of lifetime was also appearing in the shorter time as the stress levels were getting more severe.

The behavior of probability density function and failure rate with time was shown in Figure 4 when the Weibull distribution was applied as the lifetime distribution of the strips in the present study. Particularly, Figure 4(a) indicated that most of the strips failed in a relatively short time since the maximum of the probability density function was reached in an early stage, which is followed by the long tail. This was also verified by the failure rate in Figure 4(b), since there was an abrupt increase in the failure rate during the time less than 1,000 h, which is the reflection of failure of the strips within the time period. It was found that the failure rate showed an IFR (increasing failure rate) mode as shown in Figure 4(b), which indicated that the degradation of the strips developed as the stress conditions (temperature and humidity) were getting severe and the failure of the strips caused by the degradation was drastically progressed within 3,000 h.

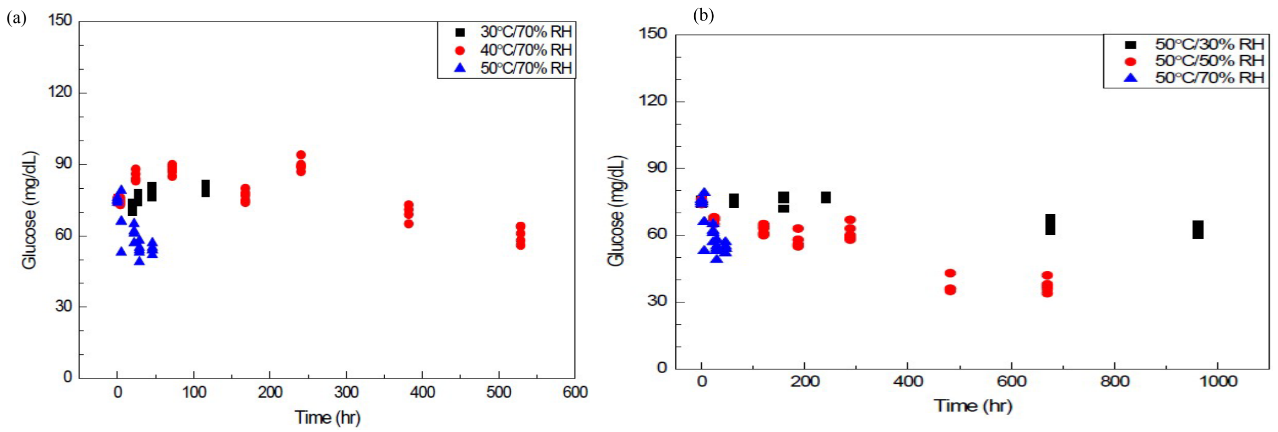

Figure 1: Scatter diagram of strips under different stress conditions: (a) Temperature and (b) Humidity.

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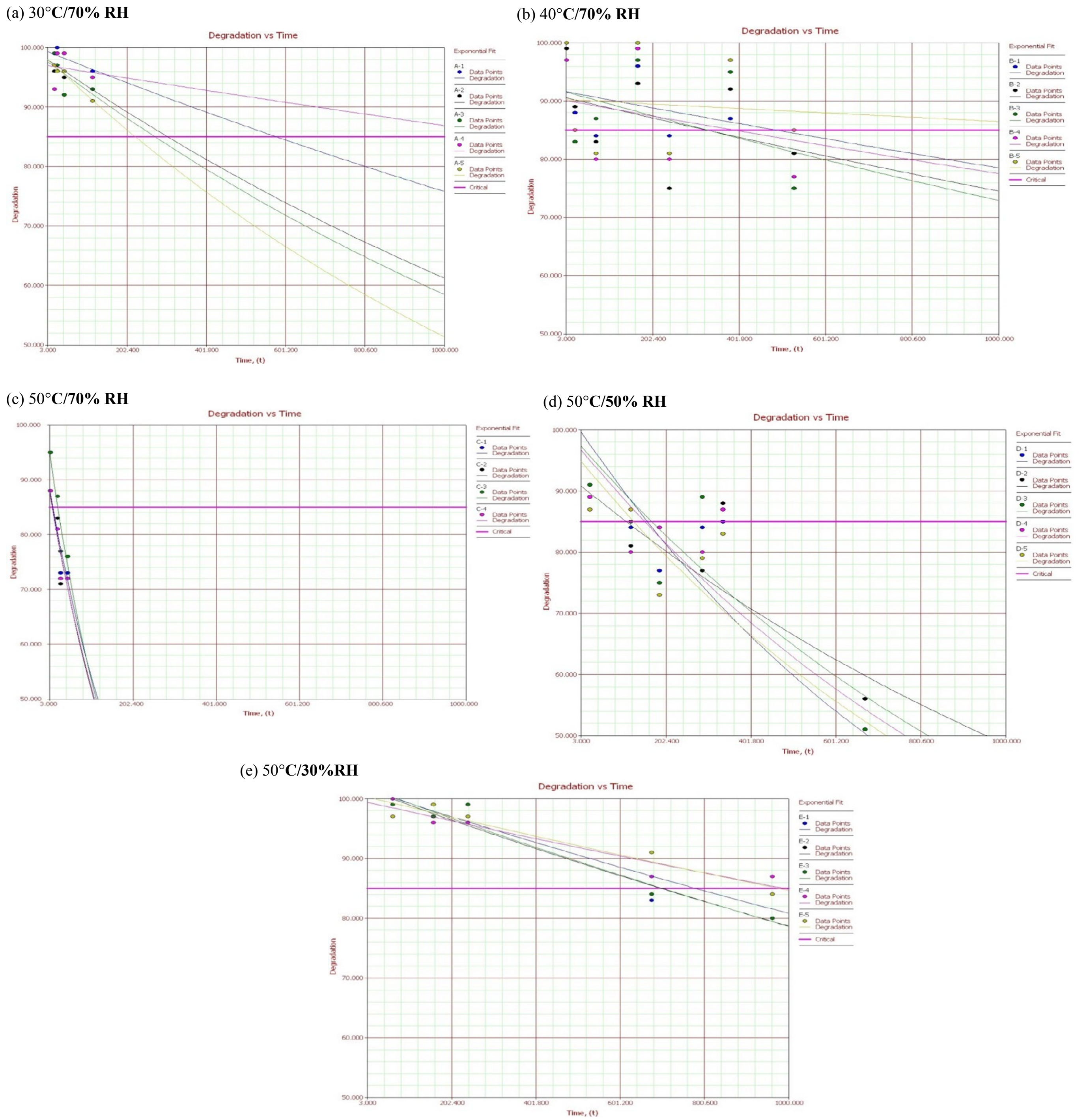

Figure 2: Degradation pattern under different stress conditions.

The lifetime prediction was made by adopting a modified Eyring Eq. Model (1) for Life-Stress relationship.

$$L(V,U) = A \cdot e^{\left(\frac{\phi}{V}+\frac{b}{U}\right)} \quad (1)$$

- φ, *b*: Parameters to be determined

- A: Constant

- V: Temperature (in absolute units)

- U: Relative Humidity (decimal or percentage)

Using the model equation, the B_{10} lifetime mean lifetime was estimated to be 505 h (lower limit) with confidence level=90% as shown in Table 2. The life predicted in the present study was relatively short, which was due to the experimental conditions because the strips were completely exposed to the stress conditions rather than kept in the closed vials as is the actual storage condition in the field.

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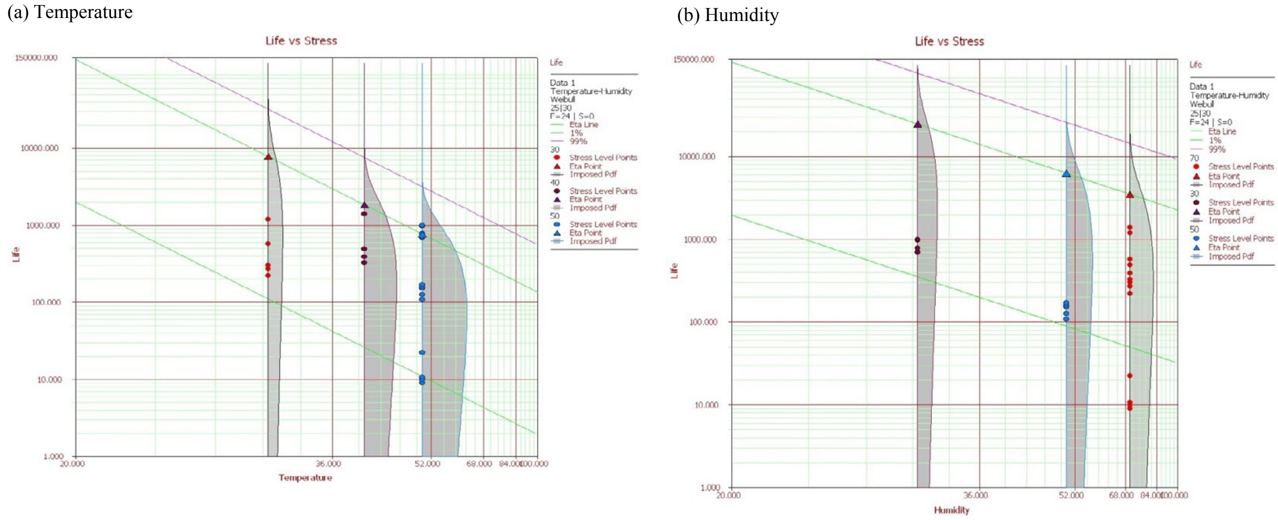


Figure 3: Life-Stress under different stress condition: (a) temperature and (b) humidity.

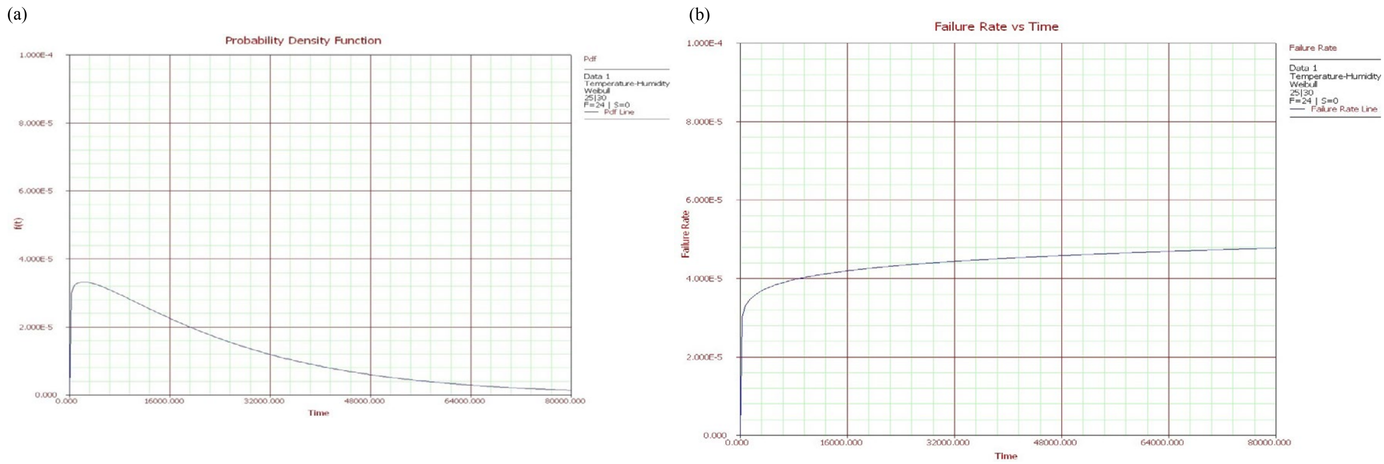


Figure 4: Lifetime behavior of strips: (a) Probability density function vs. time and (b) Failure rate *vs.* time

Temp (°C)	Humi (% RH)	B_{10} Life (CL=90%, lower limit)
25	30	505 h

Table 2: Prediction of lifetime.

The acceleration factors (AF) were calculated for each accelerated conditions from the Stress-Life relationship by setting 25°C/30% RH as the actual field condition for use.

$$AF = \frac{L_{use}}{L_{accelerated}} = \frac{Ae^{\left(\frac{\varphi}{V_u}+\frac{b}{U_u}\right)}}{Ae^{\left(\frac{\varphi}{V_A}+\frac{b}{UA}\right)}} = e^{\varphi\left(\frac{1}{V_u}-\frac{1}{V_A}\right)+b\left(\frac{1}{U_u}-\frac{1}{U_A}\right)} \quad (2)$$

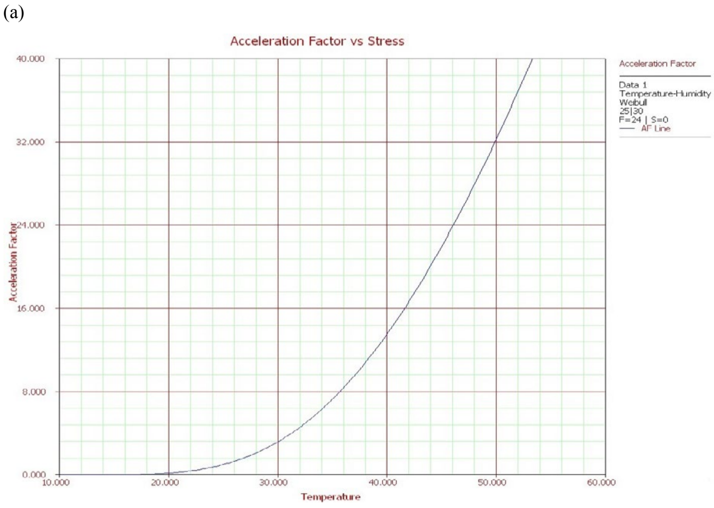
- L_{USE}: the life at use stress level
- $L_{accelerated}$: the life at the accelerated stress level
- V_u: use temperature level
- V_A: accelerated temperature level
- U_u: use humidity level
- U_A: accelerated humidity level

The effect of stress conditions on the accelerating factor (AF) were shown in Figure 5. Comparing the pattern of Figures 5(a) and 5(b), it could be seen that the temperature is a more efficient stress factor than humidity since the acceleration factor was increasing more drastically as the temperature increased. However, it should be noted that it was not recommended to go over the temperature shown in the Figure 5(a), i.e., 50°C, since the acceleration would not hold in a practical situation in the field, which could be due to the nature of biomaterials used in the strips (e.g. glucose oxidase).

Finally, the activation energies were estimated for the stress conditions used in the present study as shown in Table 3.

Conclusion

The stability of test strips of diagnostic devices were evaluated



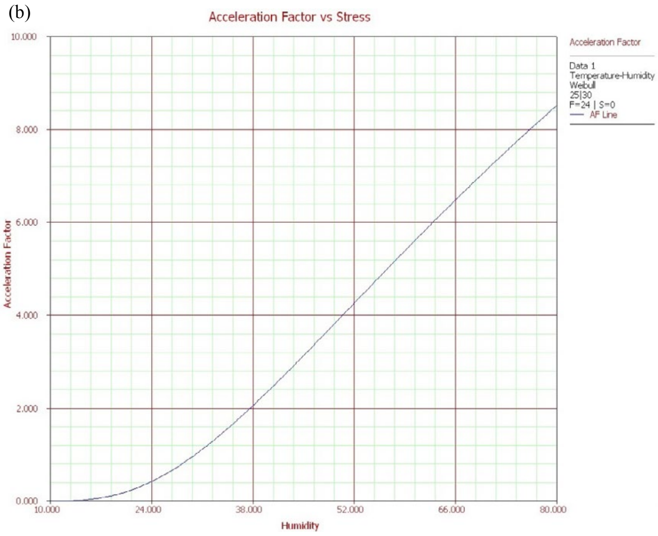


Figure 5: Effect of stress on acceleration factor: (a) Temperature and (b) Humidity.

Ea (eV)	Stress		Life distribution	Accelerated model	Shape parameter (β)
	Temp (°C)	Humi (% RH)			
0.0139	30	70	Weibull	Arrhenius	0.8293
	40				
	50				
0.0111	50	30	Weibull	Eyring	2.1882
		50			
		70			
0.0150	30-50	30-70	Weibull	T-H	1.0808

Table 3: Activation energy estimated from different accelerated models and shape parameters.

under 5 different accelerated conditions of Temp/Humi, for which the lifetime was assessed using commercial POCT products. The failure time of the test strips was determined to be the time when the concentration at the time of the measurement was out of the range of ± 15% of the initial concentration value, by following the degradation pattern in the exponential fashion.

The lifetime prediction was made by adopting a modified Eyring Eq. Model for Stress-Life relationship, and the B_{10} lifetime (with CL=90%) was estimated to be 505 h (lower limit).

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