



Computer Simulation for Studying Effects of Laboratory Design on Results of Accelerated Stability Test

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Abstract

Computer simulation is one of effective tools for instructors to illustrate effects of laboratory design in its entire complexity since the students can be exposed to a large variety of results of laboratory design within a relative short period of time. In this study, the accelerated stability study of a hypothetical drug was used as a model topic. The program of computer simulation for studying effects of laboratory design on results of accelerated stability test was created with Microsoft Access™. The fourth year pharmacy students of the Faculty of Pharmaceutical Sciences, Prince of Songkhla University used this program for studying 'KINETICS AND DRUG STABILITY' topic. Satisfaction of the students on the instruction using this computer simulation program was evaluated using a questionnaire. The results suggested that this learning method was useful and satisfactory.

Keywords : Computer simulation, Laboratory design, Accelerated stability test

Introduction

In recent years, student-center learning attracts great attention in Thailand. Computer simulation is one of such methods. Many reports presented that computer simulation had been used in studying many topics in pharmaceutical fields such as pharmaceutical industry management (1), pharmacokinetics (2), pharmacotherapy (3), pharmaceutical calculation (4), and pharmaceutical formulations (5). The majority of the students who studied using the computer programs thought that the programs had been useful in learning. We demonstrate here a computer simulation program for studying effects of laboratory design on the results of accelerated stability test. The implementation concept is straightforward and the software could be easily constructed in Microsoft Excel™. However, we implemented in Microsoft Access™ in order to hide calculation from user's attention. The fourth year pharmacy students of the Faculty of Pharmaceutical Sciences, Prince of Songkhla University were assigned to learn the effects of laboratory design on the results of accelerated stability test in the course of "Pharmaceutical Technology IV". The satisfaction of the students on learning with the program was also investigated.

Description of computer simulation program

The program of computer simulation for studying effects of laboratory design on results of accelerated stability test was created with Microsoft Access™. In the program, the parameters in the Arrhenius equation, i.e., collision factor (A) and activation energy/gas constant (E_a/R), of a hypothetical drug were fixed and assigned as reference standards. In this stage the theoretical value of shelf-life ($t_{90\%}$) could be known. After the laboratory protocol (including initial concentration of drug in a solution, temperature, sampling time, and precision of analytical instrument) was given, the software generated simulated data according to the designed laboratory protocol. The noises with normal distribution property

were added to the generated data in order to mimic the actual situation. This normal distribution noise was generated by Derenzo's approximation (6). For example, the student chose Ultraviolet-Visible Light (UV) Spectrophotometer as an assay method, the % coefficient of variation (%C.V.) of measurement was estimated to be 1% for this instrument. At theoretical concentration of 20 arbitrary units, %C.V. at 1% is equivalent to standard deviation of 0.2 arbitrary units in this case. Noise was generated and added to the theoretical concentration to make a simulated concentration. The generated noise was normally distributed around zero with the assigned standard deviation. This simulated concentration would be slightly different from the theoretical concentration, but by repeating this process indefinitely, the average of simulated values would be equal to the theoretical concentration and their standard deviation would be 0.2 arbitrary unit as intended. The simulated data were generated automatically and reported in Microsoft Excel™ file format.

The process described above could also be developed and tested in Microsoft Excel™. The user may assign their own Arrhenius parameters, %CV of measurement, sampling time, initial concentration, and temperature in order to know the theoretical rate constant for conversion to theoretical concentration the assigned sampling time. The normal distribution noise could be added with the function NORMINV

$$=NORMINV(RAND(), [\text{theoretical_value}],$$
$$[\text{standard_deviation_of_measurement}])$$

This function, NORMINV, was used to validate the Derenzo approximation algorithm implemented in the software run on Microsoft Access™. By running 10,000 calculations for zero mean and a unit standard deviation, the $NORMINV(\text{rand}(), 0, 1)$ provided a sets of data with a mean of 0.00396 and a standard deviation of 1.0044 which is not statistically different from the assigned value (t-test; $p > 0.1$). While the Derenzo approximation provide a mean of -0.01371 and a standard deviation of 0.999263, which is also not statistically different from the assigned value (t-test; $p > 0.1$).

The result shows that the noise-generator works properly regardless of the software platform.

However, we prefer the Microsoft Access™ for it is easier to make the computation process invisible to the user's attention, and the user could control recalculation to be made manually only when needed.

The students could use this simulated data to answer their own specific research question. They analyzed their own data and used the calculated Arrhenius constants to predict a shelf-life of a product. A good research design would provide a shelf-life that was similar to the theoretical prediction. By assigning constraint such as the amount of project funding, the students could design a laboratory protocol that was cost effective yet powerful enough to prove that the protocol was robust.

A hypothetical drug was assumed to degrade via first order rate kinetics. Two equations were used to predict the rate constant of the decomposition of the drug at room temperature (25°C) which was first order rate equation and Arrhenius equation as shown in Eq. 1 and Eq. 2, respectively.

$$C = C_0 e^{-kt} \quad (\text{Eq. 1})$$

$$k = A e^{-E_a / RT} \quad (\text{Eq. 2})$$

In these equations, C is a concentration of the drug at time t; C_0 is the initial concentration of the drug; k is the rate constant of the first order rate reaction; E_a is the energy of activation; R is the gas constant; and T is the absolute temperature. When the values of k at various T were found, the theoretical value of k at room temperature was able to be predicted and used to calculate the theoretical shelf-life ($t_{90\%}$) from Eq. 3 (7).

$$t_{90\%} = \frac{\ln(100 / 90)}{k} \quad (\text{Eq. 3})$$

Effects of initial drug concentration, temperature, sampling time, and type of analytical equipment on the precision of the results were included in the simulation program. The assumptions were assigned as default values. The user could change these values as needed.

1. The values of A and E_a/R were assigned at 100000 min^{-1} and 6000 Kelvin , respectively.

2. When High Pressure Liquid Chromatography (HPLC) technique was used in analysis process, %CV was assumed to be 0.5%. When UV spectrophotometer was used in analysis process, %CV was 1.0%.

3. The budget was not more than 10,000 Bahts when calculated following these assumptions.

Incubator : 50 Bahts/incubator/day (Not more than 10 samples/incubator).

Analytical cost : 50 Bahts/sample for UV and the analytical time was 15 min/sample, 250 Bahts/sample for HPLC and took 10 min/sample.

Personnel cost : 400 Bahts/day.

The sole purpose for this part is to keep all designs by the students to be within reasonable financial constraints. It is not intended to be a part in the simulation process.

Evaluation of satisfaction of the students

All students attended Pharmaceutical Technology IV class were received a questionnaire asking about the degree of their satisfaction in studying with the computer program. The questionnaire was 5-choice of satisfaction level with the statement, i.e. excellence (score = 5), good (score = 4), fair (score = 3), poor (score = 2), and very poor (score = 1).

Results and discussion

Figure 1 shows an example of spreadsheet in Microsoft Access™ simulation program. After the designed protocol was filled, the generated concentration-time profiles at the assigned temperature were reported in a Microsoft Excel™ file as presented in Figure 2. The students analyzed data to obtain the kinetics rate constant at the assigned temperatures using the first order rate equation (Eq. 1), the obtained k were extrapolated with the Arrhenius equation (Eq. 2) to the k at room temperature (25°C). Finally, shelf-life of the hypothetical drug was calculated using Eq. 3. If a good protocol was set, the obtained shelf-life would be similar to the theoretical shelf-life. After the class, the students discussed about how to design the laboratory plan that should provide robust result at reasonable cost. If they found that their designed protocol was not good enough, they could set a new one and proved again using the program.

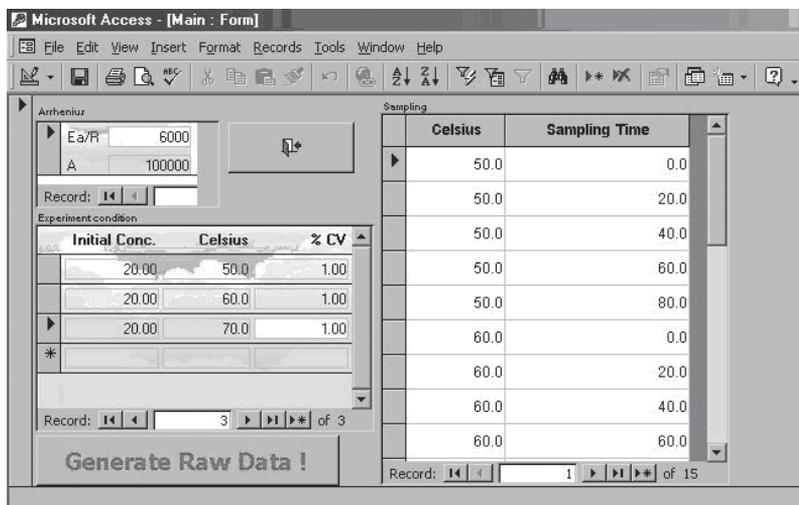


Fig. 1 An example of Microsoft Access™ computer simulation.

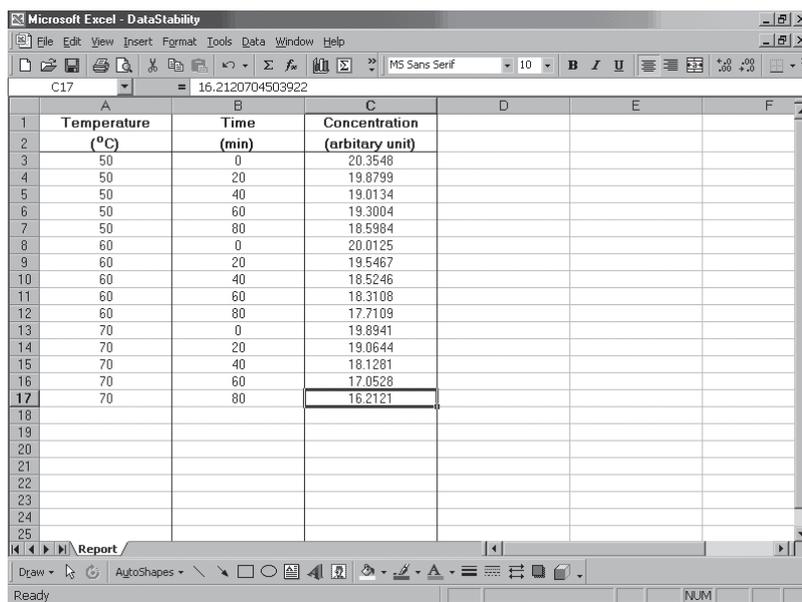


Fig. 2 Generated data obtaining in Microsoft Excel™ calculated according to the designed protocol in Figure 1.

Total 81 questionnaires (75.25%) were answered and returned from 108 students. The percentage of each answer for each question presented in Table 1.

Table 1 The percentage of the answers on the questionnaires about the opinion of students on the studying with the computer simulation program (N=81).

No.	Question	Satisfaction level*				
		(5)	(4)	(3)	(2)	(1)
1.	The amounts of computers were enough for studying.	1.31	2.63	35.53	44.74	15.79
2.	The computer simulation was interesting.	13.16	51.32	32.89	2.63	0.00
3.	The student had a role in this studying.	17.11	44.74	32.89	5.26	0.00
4.	The student studied in teamwork.	15.79	56.58	26.32	1.31	0.00
5.	The student approached to the understanding of the effects of laboratory design.	2.63	47.37	42.11	7.89	0.00
6.	The student satisfied on studying with computer simulation.	7.89	47.37	39.47	5.26	0.00
7.	The studying with computer simulation was useful.	9.21	65.79	22.37	1.31	1.31
8.	The studying with computer simulation helped the student to understand the subject in a relative short period of time.	10.53	46.05	39.47	3.95	0.00

Note: *Score: 5 = excellence, 4 = good, 3 = fair, 2 = poor, 1 = very poor.

The results showed that the method of learning was satisfactory. The majority of the students thought that the learning method was useful, helped them to study by themselves, and reduce the time of studying. Computer simulation experiments offered possibility to understand the complexity of laboratory design in short period of time. However, the available amounts of computers should be increased.

Conclusions

Studying requires a proactive approach by both the instructors and the students. Developing new tools such as computer simulations enables the instructors to provide students new avenues to study. The students not only develop their knowledge but also develop their ability to study by themselves. The results suggested that the proposed simulation program for accelerated stability test was a successful studying tool.

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