# Simulation Tool for Teaching Multivariate Experimental Design on Paracetamol Syrup Formulation

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**Abstract**

Computer simulation is one of effective tools for instructors to illustrate effects of experimental design in its entire complexity since the students can be exposed to a large variety of experimental designs within a relative short period of time. In this study, the syrup formulation of paracetamol was used as a model topic. The program written as a Visual Basic module within Microsoft Access™ was used to simulate the formulation behavior. The 23 forth-year pharmacy students in Faculty of Pharmaceutical Sciences, Prince of Songkhla University used this program to have direct experience in 'EXPERIMENTAL DESIGN' topic. The efficiency of the generated computer simulation program on the students' learning was determined by the evaluation of the satisfaction of the students using a questionnaire. The results suggested that this tool was useful and satisfactory for the students' self-studying.

***Key Words***: Computer simulation; Multivariate experimental design; Syrup formulation

**Introduction**

Computer simulation could be used as computer-assisted learning tool. It had been used in studying many topics in pharmaceutical fields such as pharmaceutical industry management (Nelson and Gagnon, 1975), pharmaceutical formulations (Mezei et al., 1990), pharmacokinetics (Hayton and Collins, 1991), pharmacotherapy (Chiholm et al., 1996) and pharmaceutical calculation (Ramanathan et al., 1997). Recently, we used the simulation for laboratory practice in analyzing accelerated stability test data for pharmacy students of the Faculty of Pharmaceutical Sciences, Prince of Songkhla University, and found that the results were satisfactory (Wongpoowarak and Boonme, 2005). In this study, we used a computer simulation program for practicing experimental design of multivariate problems using paracetamol syrup as a model. This program was written in Visual Basic language within Microsoft Access™ to compute the effect of cosolvent amounts (polyethylene glycol 4000 or PEG 4000, propylene glycol, sorbitol solution, and glycerin) on the syrup properties, i.e. solubility, taste and price according to the actual published result (Worakul et al., 2002).

Noises were added in order to mimic the real-world behavior of the simulation results.

The aim of this study was to evaluate the efficiency of the generated computer simulation program on the students' learning.

## Methods

### Description of computer simulation program

Microsoft Access™ was selected as a platform for software development in this study. Microsoft Excel™ was avoided for its random number would change automatically for every new entry of new input, while Microsoft Access™ is well-behave in this respect. The most important thing to consider is that it could be run directly without further installation in most Microsoft Windows™ environment.

The program was written in Visual Basic language in Microsoft Access™, according to the formulation behavior described previously (Worakul et al., 2002). Briefly, the physicochemical behavior of the syrup formulation under the influence of various cosolvents (PEG 4000, propylene glycol, sorbitol solution, and glycerin) was described by a published regression analysis. When the amounts of each cosolvent were given, the theoretical values of solubility, taste and price of the formulations could be calculated. In this study, the noises with normal distribution property around zero-mean were added to the generated data in order to mimic the actual situation. This normal distribution noise was generated by Derenzo's approximation (Derenzo, 1977). The arbitrary standard deviations were used in the cases of solubility and taste. The actual standard deviation of solubility prediction with the empirical regression in the previous publication was 47 mg/50 ml (Worakul et al., 2002), but we used 70 mg/50 ml in the simulation process in order to enhance the noise effect. The 0.6 unit standard deviation of taste in the simulation was, however, purely arbitrary. This noise effect required duplication or triplication measurements in order to avoid spurious conclusion. Since the price of chemicals was constant, no normal distribution

noise was added. The generated noise was normally distributed around zero with the assigned standard deviation. This simulated solubility and taste would be slightly different from the theoretical results, but by repeating this process indefinitely, the average of simulated values would be equal to the theoretical solubility as well as taste and their standard deviation would be 70 and 0.6 arbitrary units as intended for solubility values and taste scores, respectively. The information of simulation program used was described in the Appendix. The simulated data were generated automatically and reported on the spreadsheet in the same screen of Microsoft Access™.

Paracetamol is used in the symptomatic management of pain and fever. Its dosage forms are tablet, capsule, syrup, elixir, suspension, and suppository (Reynolds, 1993). For pediatric patients, the syrup form is most suitable due to the ease of adjusting dose and swallowing. Since the water solubility of paracetamol is low, cosolvents should be added to increase the solubility of the drug in an aqueous medium. Amounts of each cosolvent influence the solubility of the drug. In addition, the taste and price of the product will be affected. The paracetamol syrup formulation is a good example for learning experimental design for multivariate situation, especially under with condition constraint. In this study, the system was designed to be four-variable problem. The four variables were amounts of each cosolvent, i.e. PEG 4000, propylene glycol, sorbitol solution, and glycerin.

### Studying of the students

The 23 forth-year pharmacy students of the Faculty of Pharmaceutical Sciences, Prince of Songkhla University who had studied in tract of Pharmaceutical Technology were attended the lecture of 'EXPERIMENTAL DESIGN' topic in the course of "580-461 Research Methodology in Pharmaceutical Technology". In this lecture, the students had been introduced about the concept of the well-know multivariate designs, for example, full and half factorial design, central composite design,

stochastic design such as genetic algorithm. Subsequently, they were assigned to plan an experimental design for paracetamol syrup formulation with R&D budget constraint. They could design their own experiment and observe (with simulation tool) for values of solubility, taste and price to determine the best formulation of paracetamol syrup. Afterward, they could see and prove that the obtained result was good enough. In this study, they were allowed to use only 40 simulations to achieve the best result for 4-variables experimental design. Therefore, they had to plan their experimental design carefully according to the limitation.
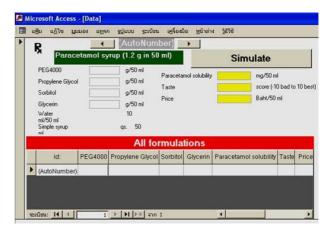
### Evaluation of satisfaction of the students

All students were received a questionnaire asking about the degree of their satisfaction in studying with the computer simulation program. The questionnaire was five-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).
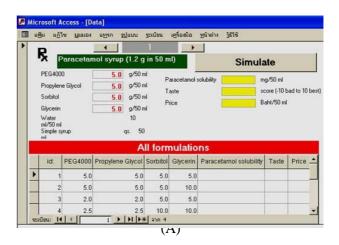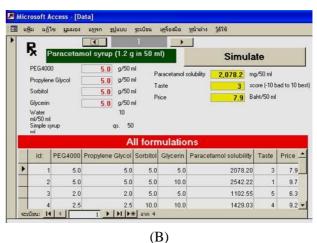
### Results and Discussion
#### Computer simulation program

Figure 1 shows the screen of the Microsoft Access™ simulation program that the user found when commencing the program. After the designed protocol was filled as illustrated in Figure 2(A), the simulated values of solubility, taste and price at the assigned amounts of each cosolvent were shown in the same screen as presented in Figure 2(B) after the simulation button was clicked. The students had to plan the experimental design cautiously to investigate the appropriate amounts of each cosolvent providing the best formulation. A sufficient solubility for therapeutic purposes of paracetamol was 1.2 g/50 ml. The margin of safety for the solubility was set arbitrarily at 1.3 g/50 ml to ensure that all paracetamol in the formulation was dissolved even in stressed condition. However, the predicted values of solubility and taste would fluctuate due to the noise effect of the stochastic nature of the simulation. Certain experimental design may lead to spurious conclusion

due to pure chance, especially the design without duplication such as simplex method. The student could verify this effect in later assignment.



**Figure 1** The screen of Microsoft Access™ computer simulation.



(A)



(B)

**Figure 2** The designed formulation (A) and generated data after simulation (B) obtaining in Microsoft Access™.

**Learning of the students**

The students learned as teamwork and each team could freely use any design available in the textbooks, journals and internet to achieve the optimal result within the assigned condition constraint (i.e., not exceed 40 formulations). The data from their reports show that all students reviewed the literatures about the suitable range of each cosovent concentration in syrup formulation before designing their experiments. There were various strategies that the student used in this study.

For example, one team used central composite design with duplication to determine the effects of each cosolvent on values of solubility, taste and price in order to assess the important of each variable.

Another team performed a few preliminary (simulated) studies to observe the effect of each variable. Afterward, they fixed two variables to constant values and the four-variable problem became two-variable problem in which they could use multi-level full factorial design in the next stage. They planed to use the rest available formulations for final confirmation.

Another team used four-variable central composite design in the first stage and using genetic algorithm in the second stage in adaptive learning process.

Another team ignored an unimportant variable initially since they purposed that the taste of propylene glycol is very poor. Hence, the four-variable problem became three-variable problem; therefore they could use central composite design for three-variables.

The results from students' reports show that all teams understood the principle of experimental design and could apply to determine the suitable formulation of paracetamol syrup. They could learn by themselves that there were more than one design models that could provide the robust result. In addition, they could verify their finding with more simulations as needed. However, since interpretation of certain experimental design requires sophisticated statistical technique, they

may not be able to interpret the results appropriately in that case.

**Evaluation of satisfaction of the students**

Total 23 questionnaires were answered and returned from the 23 students. The number of each answer for each question was presented in Table 1.

The results showed that the method of learning was medium-to-high satisfactory since the majority of the students answered at satisfaction level 3-4 for all questions. The majority of the students thought that the learning method was interesting, useful, and helped them to understand the subject of experimental design much deeper than only lecture-only or literature assignment-only. Computer simulation experiments offered possibility to understand the complexity of experimental design within a relative short period of time. Only 1 of 23 students did not answer the question number 3 but most students thought that computer simulation can be applied to use in studying of other topics. The software program of computer simulation using in this study was easy to apply for all students.

**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 difficult task in teaching experimental design was how the instructors could manage to provide critical skill to the students in Experimental Design topic. The instructors could teach them various designs and they could memorize various designs. But they might fail to use it properly because they never had direct experience in actual design. This software let them test their idea. They could just simulate and then see and prove that their design was good enough.

To realize the full potential of the software, the students need more time in data analysis practice,

**Table 1**   The number of the answers on the questionnaires about the opinion of 23students on the studying with the computer simulation program.

| No. | Question | Satisfaction level* | | | | | |
|---|---|---|---|---|---|---|---|
| | | 5 | 4 | 3 | 2 | 1 | 0 |
| 1 | The computer simulation was interesting. | 7 | 12 | 4 | 0 | 0 | 0 |
| 2 | The studying with computer simulation affected the student to understand the subject in a relative short period of time. | 3 | 12 | 8 | 0 | 0 | 0 |
| 3 | The computer simulation was able to be applied to use in studying of other topics. | 4 | 12 | 6 | 0 | 0 | 1 |
| 4 | Using computer simulation in this study provided the student to understand the subject of "Experimental Design". | 1 | 11 | 11 | 0 | 0 | 0 |
| 5 | Listening to the lecture in this study provided the student to understand the subject of "Experimental Design". | 0 | 5 | 16 | 1 | 1 | 0 |
| 6 | Searching information by your own in this study provided the student to understand the subject of "Experimental Design". | 2 | 9 | 10 | 2 | 0 | 0 |
| 7 | The software program of computer simulation using in this study was easy to apply. | 8 | 12 | 3 | 0 | 0 | 0 |
| 8 | Using computer simulation supported the student to understand the subject of "Experimental Design" more than only listening to the lecture. | 7 | 13 | 3 | 0 | 0 | 0 |

**Note:** *Score: 5 = excellence, 4 = good, 3 = fair, 2 = poor, 1 = very poor, 0 = no answer or missing data.

which could not be available in the semester of this study. However, this software provided the opportunity for the students to integrate their knowledge in proactive manner for solving problem at hand. Although this software was not a complete CAI (Computer-Assisted Instruction) suite in itself, it could be act as a self- assessment tool for what the students learned. The students could learn by themselves that there were more than one design models that could provide the robust result. In addition, they could verify their finding with the same simulation tool as needed. However, since interpretation of certain experimental design requires sophisticated statistical technique, they may not be able to interpret the results appropriately. But this tool could also be used as a general tool for training critical skill in research design for graduated

studies. This tool will be very useful with proper teaching of statistical analysis technique. We proposed that this software could also be used as a concise tool for teaching research methodology topic in post-graduated course study.

### References
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## Appendix

The whole software in Microsft Access™ platform could be constructed easily. It needs one Table call "DATA" as defined below (see Table Section). Only one SQL command (see SQL section below) is needed in order to simulate the result. It requires Module content as shown below (see Visual Basic Section)

## Table Section:

Table name: "DATA"

The data structure was shown below.

Id (autonumber)

PEG4000 (single-precision number; expressed as g/50 mL)

Propylene Glycol (single-precision number; expressed as mL/50 mL)

Sorbitol (single-precision number; expressed as mL/50 mL)

Glycerin (single-precision number; expressed as mL/50 mL)

Paracetamol solubility (single-precision number; expressed as mg/50 mL)

Taste (single-precision number; expressed as a scale between 10 and -10 approximately)

Price (single-precision number; expressed as Baht/ 50 mL)

After the user defines the cosolvent values, the query was invoked to compute "Paracetamol solubility", "Taste", "Price". The query would call the Visual Basic module automatically.

## SQL Section (content in a single Query to be executed in simulation process):

UPDATE Data SET Data.[Paracetamol solubility] = SimSolubility([Data]![PEG4000], [Data]![Propylene Glycol], [Data]![Sorbitol], [Data]![Glycerin]), Data.Price = SimPrice([Data]![PEG4000],[Data]![Propylene Glycol],[Data]![Sorbitol],[Data]![Glycerin]), Data.Taste = SimTaste([Data]![PEG4000], [Data]! [Propylene Glycol], [Data]![Sorbitol],[Data]![Glycerin])
WHERE (((Data.[Paracetamol solubility]) Is Null) AND ((Data.Price) Is Null) AND ((Data.Taste) Is Null));

## Visual Basic section:

'Copy and paste this section to a new created Module
Option Compare Database

'A is g of PEG4000 in 50 ml preparation
'B is ml of PG in 50 ml preparation
'C is ml of Sorbitol in 50 ml preparation
'D is ml of Glycerin in 50 ml preparation

'User defined constant (change values here)
Const TastePEG4000 = -0.5, TastePG = -3,
    TasteSorbitol = 0.6, TasteGlycerin = 0.6,
    TasteSyrup = 1
Const PricePEG4000 = 0.12, PricePG = 0.49,
    PriceSorbitol = 0.21, PriceGlycerin = 0.39
Const PriceSyrup = 0.04, PriceAcetaminophen
    = 1.2*0.89

Function Price(PEG4000, PG, Sorbitol, Glycerin)
    A = PEG4000
    B = PG
    C = Sorbitol
    D = Glycerin

'simulation shows that min 2.7 max 10.1 for all possible 'combination of cosolvents used within 0-7.2 %
Price = PriceAcetaminophen + PricePEG4000*A
        + PricePG*B + PriceSorbitol*C
Price = Price + PriceGlycerin*D
        + PriceSyrup*(40 - A - B - C - D)
End Function

Function Taste(PEG4000, PG, Sorbitol, Glycerin)
    A = PEG4000
    B = PG
    C = Sorbitol
    D = Glycerin
    Taste = TastePEG4000*A + TastePG*B
            + TasteSorbitol*C + TasteGlycerin*D
    Taste = Taste + TasteSyrup*(40 - A - B - C - D)
End Function

Function Solubility(PEG4000, PG, Sorbitol, Glycerin)
    'Best case of data fitting is obtained for solubility.

Rem PEG4000.  PG.  SORBITOL.  GLYCERIN.
solubility.   [Calculated]

Rem 2.02 2 2 2     1047.7 [ 1040.1 ]
Rem 6.06 2 2 6     2282.4 [ 2166.913 ]
Rem 2.05 6 2 6     1488.3 [ 1484.794 ]
Rem 6.02 6 2 2     2287.4 [ 2270.122 ]
Rem 2.03 2 6 6     1189.5 [ 1178.781 ]
Rem 6 2 6 2     1741.7 [ 1802.363 ]
Rem 2.02 6 6 2     1255.9 [ 1238.189 ]
Rem 6 6 6 6     2383 [ 2365.717 ]
Rem 7.2 4 4 4     2204.4 [ 2235.474 ]
Rem .8 4 4 4     1150.3 [ 1164.833 ]
Rem 4.07 4 4 4     1675.4 [ 1639.093 ]
Rem 4.04 4 4 4     1681.4 [ 1630.956 ]
Rem 4.01 7.2 4 4     1814.2 [ 1883.806 ]
Rem 4.02 .8 4 4     1346.5 [ 1400.433 ]
Rem 4.01 4 7.2 4     1590.9 [ 1568.584 ]
Rem 4.01 4 .8 4     1627.1 [ 1679.007 ]
Rem 4.02 4 4 7.2     1772.9 [ 1812.722 ]
Rem 4.01 4 4 .8     1492.3 [ 1455.232 ]

Rem ****** Best Model of solubility.
'N  Mean.Err Mean.Sq.Err Adj.R2 F(7,10) p-value
'18 6.57E+01 3.71E+03 0.97769 105.62 <
 0.00001

P1 = 6.779647     'SE  8.812277E-02
P2 = -0.126402     'SE  6.668624E-02
P3 = 0.05168648     'SE  6.086049E-03
P4 = -0.005538856     'SE  6.085679E-03
P5 = 0.03916023     'SE  6.081619E-03
P6 = -0.00007934417     'SE  5.305214E-05
P7 = 0.07475764     'SE  1.855178E-02
P8 = -0.006262458     'SE  1.531221E-03

x = PEG4000
y = PG
z = Sorbitol
u = Glycerin
Solubility = Exp(P1 + P2*x + P3*y + P4*z + P5*u
    + P6*x*y*z*u + P7*x ^ 2 + P8*x ^3)
End Function

Function NormalDistribution(xbar, sd) As Double

    'Adapted from Log-and-trigonometric formula
    'from C.D.Daykin, T.Pentik,,inen, M.Pesonen
    'Practical Risk Theory for Actuaries
    'Chapman & Hall, 1994; London
    'Appendix F, p 469
    'This routine generate N(0,1) in pairs; x1 and x2
    'x1=(COS(2*Pi*r2))*SQR(-2*LOG(r1))
    'x2=(SIN(2*Pi*r2))*SQR(-2*LOG(r2))

    Do
    r1 = Rnd(Timer)
    r2 = Rnd(Timer)
    Loop Until r1 > 0
    x1 = (Cos(2*Pi*r2))*Sqr(-2*Log(r1))
    If Rnd(Timer) > 0.5 Then
        NormalDistribution = xbar + x1*sd
    Else
        NormalDistribution = xbar - x1*sd
    End If
End Function

Function SimSolubility(PEG4000, PG, Sorbitol,
    Glycerin)
    SimSolubility = NormalDistribution (Solubility
        (PEG4000, PG, Sorbitol,
        Glycerin), 70)
End Function

Function SimTaste(PEG4000, PG, Sorbitol, Glycerin)
    x = NormalDistribution(Taste(PEG4000, PG,
        Sorbitol, Glycerin), 3) / 5
    SimTaste = CInt(x)
End Function

Function SimPrice(PEG4000, PG, Sorbitol, Glycerin)
    SimPrice = Price(PEG4000, PG, Sorbitol,
        Glycerin)
End Function