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COMMUNICATION

Optimization in Development of Acetaminophen Syrup Formulation

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ABSTRACT

Formulation of acetaminophen syrup could be developed by an optimization technique to reduce the time and cost of study. Cosolvents were used in the formulation because of the low solubility of acetaminophen in water. They were composed of polyethylene glycol 4000, propylene glycol, sorbitol solution, and glycerin. Their effects on the solubility of acetaminophen and the pH of formulations were investigated. Effects on taste and price were calculated based on their properties. Simulation study of the effect of cosolvents upon the formulation scores was performed, using an algorithm based upon a simulated annealing concept to achieve the global optima and heuristic optimization concept to accelerate convergence. The program written as a Visual Basic module within Microsoft Access 97 was used to simulate and assess the optimal cosolvent amounts to achieve the most desirable formulations automatically according to the specified criteria. Formulators could customize the optimal formulation according to their needs and cost constraints by redefining the desirable outcomes in the source code of the program.

Key Words: *Acetaminophen; Formulation; Optimization; Syrup*

INTRODUCTION

Acetaminophen is used in the symptomatic management of pain and fever. Its dosage forms are tablet, capsule, syrup, elixir, suspension, and suppository (1). For pediatric patients, the syrup form is most suitable. It is easy to adjust dose and swallow. Since the solubility of acetaminophen in water is low, cosolvents should be added to increase the solubility of the drug in an aqueous

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medium (2,3). Suitable amounts of each cosolvent affect the solubility of the drug. In addition, they affect the taste and price of the product. The optimizations of formulations and processing of pharmaceutical or cosmetic products, such as tablet, granule, pellet, and shampoo, are well documented (4–7). It is also applicable in developing acetaminophen syrup formulation to reduce the time and cost of formulation study.

The purpose of this study was to develop adaptive acetaminophen syrup formulation by applying an optimization technique, where cosolvents were composed of polyethylene glycol 4000, propylene glycol, sorbitol solution, and glycerin. The formulation should be customizable according to the needs and constraints of the formulator.

MATERIALS AND METHODS

Materials

All the chemicals met USP or BP specifications and were used as received from suppliers, without further purification. Acetaminophen, polyethyleneglycol 4000, propylene glycol, sorbitol solution, and glycerin were purchased from Vidhyasom Co. Ltd. (Bangkok, Thailand). Sucrose, used in the preparation of simple syrup, was the product of Mitrphol Co. Ltd., Thailand.

Methods

Formulation of Acetaminophen Syrup for Determination of the Maximum Drug Solubility

Excess amount of acetaminophen was added to melted polyethylene glycol 4000. Then propylene glycol, sorbitol solution, and glycerin were added according to a central composite design, with quantities listed in Tables 1 and 2, respectively. A 10-mL portion of purified water was added and mixed. The volume of the mixture was adjusted to 50 mL with simple syrup (Syrup USP). Each product was stored for 2 days at ambient temperature (30±2°C) to ensure equilibrium before determining the amount of dissolved acetaminophen.

Determining Drug Solubility

Each acetaminophen syrup was vibrated with a Vortex mixer then filtered through Whatman filter paper no. 1 until the filtrate was clear. A 2-mL portion of filtrate was pipetted and diluted with distilled water to 100 mL. The absorbance of solution was measured at a wavelength of 295 nm using an ultraviolet (UV) spectrophotometer (DU^R 64 Beckman Instruments, Inc., Fullerton, CA, USA). The data was calculated to obtain the drug quantity by comparing with the standard curve and converted to solubility values. The empirical mathematical model describing the relationship between the cosolvent amounts and solubility values was determined by regression analysis from various ad hoc models.

Table 1

Experimental Design[a]

Trial	*A*	*B*	*C*	*D*
1	−1	−1	−1	−1
2	+1	−1	−1	+1
3	−1	+1	−1	+1
4	+1	+1	−1	−1
5	−1	−1	+1	+1
6	+1	−1	+1	−1
7	−1	+1	+1	−1
8	+1	+1	+1	+1
9	+1.6	0	0	0
10	−1.6	0	0	0
11	0	+1.6	0	0
12	0	−1.6	0	0
13	0	0	+1.6	0
14	0	0	−1.6	0
15	0	0	0	+1.6
16	0	0	0	−1.6
17	0	0	0	0
18	0	0	0	0

[a]Independent variables: *A*=amount of polyethylene glycol 4000 in standard unit, *B*=amount of propylene glycol in standard unit, *C*=amount of sorbitol solution in standard unit, *D*=amount of glycerin in standard unit.

pH Determination of Acetaminophen Syrup Formulations

Acetaminophen syrups were formulated similarly to the previous processing method, but the drug concentration of formulas was 1.2 g/50 mL. Then the pH value of each syrup portion was measured by an Orion pH meter, Model SA520.

Table 2

Amounts of Each Cosolvent in 50 mL of Acetaminophen Syrup Computed from Table 1

Trial	Polyethylene Glycol 4000 (g)	Propylene Glycol (mL)	Sorbitol Solution (mL)	Glycerin (mL)
1	2.0	2.0	2.0	2.0
2	6.0	2.0	2.0	6.0
3	2.0	6.0	2.0	6.0
4	6.0	6.0	2.0	2.0
5	2.0	2.0	6.0	6.0
6	6.0	2.0	6.0	2.0
7	2.0	6.0	6.0	2.0
8	6.0	6.0	6.0	6.0
9	7.2	4.0	4.0	4.0
10	0.8	4.0	4.0	4.0
11	4.0	7.2	4.0	4.0
12	4.0	0.8	4.0	4.0
13	4.0	4.0	7.2	4.0
14	4.0	4.0	0.8	4.0
15	4.0	4.0	4.0	7.2
16	4.0	4.0	4.0	0.8
17	4.0	4.0	4.0	4.0
18	4.0	4.0	4.0	4.0

Calculation of Taste

Taste in arbitrary scale (T) of each acetaminophen syrup was calculated by the following equation:

$$T = -0.5A - 3B + 0.6C + 0.6D + (40 - A - B - C - D)$$

where A, B, C, and D were amounts of polyethylene glycol 4000 (g), propylene glycol (mL), sorbitol solution (mL), and glycerin (mL) in 50 mL of acetaminophen syrup, respectively. The taste factors for polyethylene glycol 4000, propylene glycol, sorbitol solution, glycerin, and simple syrup were set arbitrarily according to the formulator taste preference. The taste score was normalized to be in the range of 0 to 1 (see Fig. 1) in order to be used in the optimization process by the following equation:

$$\text{taste score} = \frac{(T - \text{minimum of } T)}{(\text{maximum of } T - \text{minimum of } T)}$$

Under the experimental conditions, the minimum and maximum of T were computed to be approximately 11 and 40, respectively, by simulation analysis.

Calculation of Price

Price (P) of each formulation was calculated based on price (in U.S. cents per 50 mL) of each chemical by the following equation:

$$P = 1.2 \times 0.89 + 0.12A + 0.49B + 0.21C + 0.39D + 0.04(40 - A - B - C - D)$$

where A, B, C, and D were amounts of polyethylene glycol 4000 (g), propylene glycol (mL), sorbitol solution (mL), and glycerin (mL) in 50 mL of acetaminophen syrup, respectively.

The price score was normalized to be in the range of 0 to 1 (see Fig. 1) in order to be used in the optimization process by the following equation:

$$\text{price score} = \frac{1 - (P - \text{minimum of } P)}{(\text{maximum of } P - \text{minimum of } P)}$$

Under the experimental condition, the minimum and maximum of P were found to be approximately 2.7 and 10.1, respectively, by simulation analysis.

Optimization Method

The optimization was performed by simulation analysis in order to maximize the sum of the pre-

Figure 1. Scoring criteria for acetaminophen syrup evaluation (see text for more details).

dicted score calculated above under the experimental conditions. However, zero extrapolation was permitted even though it was outside the experimental condition for two reasons. The first reason was to achieve the simplest formulation by eliminating the unnecessary ingredient. The second reason was that the zero condition was not too far from the experimentation range, the reliability of the prediction should still be acceptable with a low degree polynomial function. The search strategy used was a simulated annealing concept combined with a heuristic optimization concept, as described in the following section and in the Appendix.

RESULTS AND DISCUSSION

The drug solubility data is shown in Table 3. The best model of solubility achieved by regression analysis with empirical models was:

$$\begin{aligned}\text{solubility} = \exp(&6.779647 - 0.126402A \\ &+ 0.05168648B - 0.005538856C \\ &+ 0.03916023D - 0.00007934417ABCD \\ &+ 0.07475764A^2 - 0.00626458A^3)\end{aligned}$$

where A, B, C, and D were amounts of polyethylene glycol 4000 (g), propylene glycol (mL), sorbitol solution (mL), and glycerin (mL) in 50 mL of acetaminophen syrup, respectively. The coefficient of determination (R^2) was 0.97769 and $p < .00001$. The high value of R^2 implied that the solubility prediction should provide a satisfactory result.

From this relationship, it was indicated that: sorbitol solution did not make a meaningful contribution to acetaminophen solubility within the experimentation range; propylene glycol and glycerin exerted a moderate effect on acetaminophen solubility; and polyethylene glycol 4000 was the determining factor in the solubility value.

Table 3

Drug Solubility and pH of Acetaminophen Syrup

Trial	Experiment Drug Solubility Values (mg/50 mL)	Calculated Drug Solubility Values (mg/50 mL)	pH
1	1047.70	1040.10	6.16
2	2282.40	2166.91	6.50
3	1488.30	1484.79	6.58
4	2287.40	2270.12	6.78
5	1189.50	1178.78	6.35
6	1741.70	1802.36	6.32
7	1255.90	1238.19	6.46
8	2383.00	2365.72	6.55
9	2204.40	2235.47	6.56
10	1150.30	1164.83	6.48
11	1814.20	1883.81	6.44
12	1346.50	1400.43	5.99
13	1590.90	1568.58	6.38
14	1627.10	1679.01	6.42
15	1772.90	1812.72	6.43
16	1492.30	1455.23	6.53
17	1675.40	1639.09	6.37
18	1681.40	1630.96	6.35

The calculated drug solubility values from the model were similar to the experimental values. Therefore, this model should be acceptable for simulation study.

A sufficient solubility for therapeutic purposes was 1.2 g/50 mL. The margin of safety for the solubility was set arbitrarily at 1300 mg/50 mL. It was determined that no added benefit could be achieved if the solubility was higher than 1800 mg/50 mL

(also an arbitrary setting). So, the solubility score was adjusted to 1 for solubility at or higher than 1800 mg/50 mL. If solubility was in the range of 1300 to 1800 mg/50 mL, the solubility score was adjusted to be reduced gradually according to the formula (solubility − 1300)/500. If solubility was less than 1300 mg/50 mL, the formulation should be impossible to use, so the solubility score was adjusted to a negative score according to the formula (solubility − 1300)/100 as a penalty function. The score for all possible ranges of solubility was defined in terms of a piecewise function (see Fig. 1). The maximum value of the score would be 1 and the minimum should be $-\infty$.

The pH values of all products were in the range of 6 to 7. Since pH did not fluctuate in this experimentation condition, and it was reported that acetaminophen solution was still stable in this pH range (8), pH was not included in the optimization process.

Calculated taste scores were used for formulation selection, however, the taste of products was not tested by panels since cultural judgement might vary from place to place. The scoring criteria for taste were set arbitrarily in order to achieve a 0–1 range within the experimentation conditions.

Price of products was calculated directly from the purchased price of excipients, not including other facility overheads. The scoring criteria for price were set arbitrarily in order to achieve a 0–1 range within the experimentation conditions.

In simulation analysis, the amount of each cosolvent was randomized in a range similar to the experimental conditions. The scores of solubility, taste, and price were weighted according to the formulator preferences and combined as a total score.

To maximize the total score, various combined ratios of cosolvent amounts were used in the simulation study. Since the relationship between compositions of the formulation and the product score was attainable, it was possible that the hypothetical best formulation could be achieved from computer simulations. Since four cosolvents were used, grid search (all possible combinations) of the cosolvent amount between 0 and 7.2 (g/50 mL or mL/50 mL) with an accuracy of 0.1 requires 73^4 simulations (approximately 3×10^7 simulations). This would achieve a conclusion of one decimal place accuracy for each specified criterion. It was impractical for our purpose. The more efficient search algorithm was unavoidable.

Among various search algorithms, the simplex search might be the most well-known algorithm in optimization processes applied in pharmaceutical product development; however, it might lead to local optima if the initial guess condition is not located properly. A search algorithm that was capable of escaping from local optima was preferable. Among such algorithms, the simulated annealing search algorithm (9,10) was selected for its simplicity and ease of implementation. It could provide the result several orders of magnitude faster than grid search, and was much easier to implement than simplex search. In order to accelerate convergence and ease the programming process, the random-walk strategy according to the heuristic random optimization protocol (11) was used with modification.

In brief, the search parameters were allowed to random-walk from their initial condition in order to find a better condition; the walking length could be adjusted according to previous success. This was a concept of heuristic random optimization (11). The method is very easy to implement, yet achieves a satisfactory convergence. However, it could not escape the local optima at the end of the run. To increase the chance of achieving the global optima, a simulated annealing method was used; in essence, the parameter could escape from the present optima to an unknown region with a probability that depends on the quality of the present optimal condition. This would enable the search to continue until a very satisfactory condition was attained. It could avoid the "success-leads-to-failure" dilemma in the ordinary greedy search, such as in the case of the simplex method (9,10).

Table 4 is a summary of general "acceptable" formulations according to the selected criteria. The optimization of each formulation by simulation study required less than 1 min of computation time.

The suitable cosolvent system was selected by defining the preference scale of taste, price, and solubility. The program selected the best system from the total score (sum of taste score, price score, and solubility score) automatically. These scores were arbitrary in nature. Therefore, it was unavoidable that when changing the preference criteria for these formulations, it would reach a different conclusion.

From Table 4, it was found that propylene glycol and sorbitol solution were not necessary in most formulations. The two most important cosolvents in acetaminophen syrup were polyethylene glycol 4000 and glycerin. This conclusion was drawn

Table 4

Examples of Acetaminophen Syrup Formulations[a]

Ratio of Determination $S:T:P$	Amount of Cosolvents				Total Score	Predicted Solubility (mg/50 mL)	Taste Score	Price[b]
	A (g)	*B* (mL)	*C* (mL)	*D* (mL)				
0:0:6	—[c]	—	—	—	—	—	—	—
0:1:5	—	—	—	—	—	—	—	—
0:2:4	—	—	—	—	—	—	—	—
0:3:3	—	—	—	—	—	—	—	—
0:4:2	—	—	—	—	—	—	—	—
0:5:1	—	—	—	—	—	—	—	—
0:6:0	—	—	—	—	—	—	—	—
1:0:5	7.0	0	0.1	0	5.33	1655	29.4	3.3
1:1:4	6.9	0	0.1	0.1	5.04	1657	29.6	3.3
1:2:3	6.8	0	0.2	0.1	4.76	1650	29.7	3.3
1:3:2	6.6	0	0.1	2.3	4.50	1793	29.1	4.0
1:4:1	6.1	0	0	3	4.33	1778	29.7	4.2
1:5:0	5.2	0.1	0	5.7	4.20	1804	29.6	5.1
2:0:4	6.8	1.3	0.1	0.5	5.29	1798	24.2	4.0
2:1:3	6.8	0.1	0.1	2.1	5.07	1798	28.4	4.0
2:2:2	6.6	0	0.1	2.5	4.85	1812	28.9	4.1
2:3:1	6.3	0	0.4	3.0	4.65	1815	29.1	4.3
2:4:0	5.1	0	0.1	6.9	4.56	1843	29.5	5.5
3:0:3	6.9	1.4	0.1	0.3	5.47	1798	23.8	4.0
3:1:2	6.8	0	0.2	2.2	5.24	1798	28.7	4.0
3:2:1	6.6	0.1	0	2.4	5.05	1802	28.9	4.1
3:3:0	5.5	0	0.1	4.9	4.92	1812	29.5	4.9
4:0:2	7.1	1.5	0	0.2	5.65	1802	23.1	4.0
4:1:1	6.8	0	0.1	2.3	5.43	1805	28.7	4.0
4:2:0	5.1	0	0	6.9	5.28	1856	29.5	5.5
5:0:1	6.9	0.9	0	1.0	5.82	1801	25.5	4.0
5:1:0	5.5	0	0	5.1	5.64	1813	29.6	4.9
6:0:0	5.8	3.1	7.1	4.5	6.00	1983	14.3	7.3

[a]*S*=solubility, *T*=taste, *P*=price, *A*=amount of polyethylene glycol 4000, *B*=amount of propylene glycol, *C*=amount of sorbitol solution, *D*=amount of glycerin.
[b]In U.S. cents per 50 mL.
[c]No preparations conform to such criteria (i.e., insufficient solubility).

from the fact that the major contributions in optimization criteria were based upon local pricing of raw materials and subjective preference in taste of the experimenters.

Acetaminophen syrup formulations proposed in this study were able to use a core formulation. They could be modified by adding preservatives, colors, and flavors for stability and palatability. The program used in this experiment is illustrated in the Appendix. Formulators could use this Appendix as an example for other systems as well.

CONCLUSIONS

By varying formulator preferences in the optimization criteria, the draft formulation could be found by using a simple search technique in the simulation process. This optimization technique could reduce the time and cost of formulation study, since one could easily change the preference criteria to the needs of the patients. This study should be very useful for extemporaneous preparation according to local preferences and

constraints. The source code illustrated in this work could also be adapted to be used in other formulations.

APPENDIX

The following source code was written as a Visual Basic module within a Microsoft Access 97 program. The user must create a new MODULE, type the source code into it, save it with any valid module name, and run it in a debug window by typing **call main** then pressing [Enter] in order to report to a file name "\acetaminophen.txt". The computation time depends on the hardware capability. It takes about 1–2 min for each formulation when computed with a Pentium-166 processor.

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