The Scheduling of Anti-Retroviral Drugs Production Line

S. Bositthipichet
Production Department at the Government Pharmaceutical Organization, Bangkok, Thailand
Email: mayso_rx@hotmail.com)

S. Prombanpong and T. Somboonwiwat
Dept. of Industrial Engineering Faculty of Engineering King Mongkut's University of Technology Thonburi KMUTT
Email: {suksan.pro, tuanjai.som}@gmail.com

***Abstract*—The Government Pharmaceutical Organization (GPO), a state enterprise under the Ministry of Public Health is one of the pharmaceutical manufacturers in Thailand. The GPO produces various different dosage forms of medical products such as solid, semi-solid, liquid and injection dosage form. A nowadays solid dosage form which is the main product type is confronted with backorder problem. Anti-Retroviral (ARV) drugs also face with this problem. The ARV production line can be divided into 4 stages, mixing, compression, coating and packing. Each process is designed as a job shop environment. The production of ARV drug is considered complex and must comply with regulations such as GMP/PICs in order to prevent contamination between drugs and quality of drugs. Thus, sequencing and assigning the task is tedious but crucial. This paper aims to develop a mathematical model for a job shop scheduling problem with sequence dependent setup times. The developed model utilizes a binary linear programming technique whose objective is to minimize a maximum completion time of all the jobs.**

***Index Terms*—pharmaceutical industry, scheduling, sequencing, job shop**

I. Introduction

The pharmaceutical industry manufactures medical products that are vital to the health of patients. Medical products not only must be due to specifications, quality, efficacy and safety, but also the economy [1]. The pharmaceutical industry must have a competitive edge to survive, which means that the industry must cut down time to market and deliver a fast response to customers [2].

The goal of the pharmaceutical industry has been to efficiently respond to ever changing customer demand but at the same time maximize utilization. Relatively simple production planning and scheduling is not optimized to increase complexity of these processes. Scheduling is one of the most important issues in the planning and operation of production system [3], [4]. There are few research studies on this topic [5], [6]. Almost all of pharmaceutical industry, scheduling has been performed by manual without any optimization tool [7].

Manuscript received May 10, 2014; revised July 16, 2014.

This paper considers the job shop scheduling with setup times dependent on a single machine. The job shop scheduling problem has attracted attention of many researchers. This problem becomes complicated when set up time is taken into account. Setup operations are normally dependent upon the preceding operating [8]. As an example, Corwin and Esogbue presented a dynamic programming approach to solve a two machine scheduling problem with the objective of minimizing the make-span [9]. Sun *et al*. developed a Lagrangian relaxation approach to solve a single machine scheduling problem with release dates, due dates and sequence dependent setup times [10]. Asgeirsson et al. investigates the automation of a manual production scheduling process at a pharmaceutical company, by using mixed integer optimization and a simple greedy algorithm [2].

The job-shop scheduling problem (JSSP) is a common problem in the manufacturing industry. A classical JSSP is a combination of N jobs and M machines. Each job consists of a set of operation that has to be processed on a set of known machines, and has a known processing time. A schedule is a complete set of operations, required by a job, to be performed on different machines, in a given order. In addition, the process may need to satisfy other constraints. The total time between the start of the first operation and the end of the last operation is termed as makespan. Makespan minimization is widely used as an objective in solving JSSPs. [11]-[17]. A feasible schedule contains no conflicts such as (i) no more than one operation of any job can be executed simultaneously and (ii) no machine can process more than one operation at the same time. The schedules are generated on the basis of predefined sequence of machines and the given order of job operations.

The JSSP is widely acknowledged as one of the most difficult NP-complete problem [18]-[20] which is also well known for its practical applications in many manufacturing industries. Wong *et al*.[21] propose a genetic algorithm to schedule spreading cutting and sewing operations in an apparel manufacture. Lundgren *et al*.[22] solve the programming problem in an oil refinery company using mixed integer programming.

It can be seen that scheduling problem is complex since there are several factors involved; therefore, the

doi: 10.12720/jomb.4.3.244-249

mathematical model is the most effective tool to obtain the optimal solution. This paper also employed a binary integer programming approach and will be described next.

II. Methodology

A. Problem Description

The Government Pharmaceutical Organization (GPO) is the main generic drugs manufacturer in Thailand and provides many essential drugs used in the government and private hospitals and health care centers. Its main product is in tablet dosage form. The Process flow of tablet production is quite simple. The first process is a dispensing of raw materials from the Dispensing center. Then the weighted raw material will be transferred to the production line which is divided into 4 stages i.e. mixing, compression, coating and packing respectively as shown in Fig. 1. Note that each processing step must follow GMP /PICs (Good Manufacturing Product/Pharmaceutical Inspection Co-operation Scheme) guidelines.

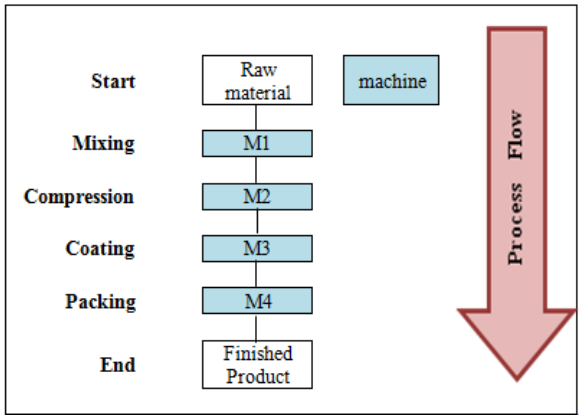


Figure 1. Process flow in a tablet production line

Due to ever increasing of the customer demand GPO has faced with backorder problems and must strive to meet the quantity and delivery date required. Thus, production scheduling must be efficient to counteract the problem. However, there are several factors involved in the scheduling task. Each production stage is operated in a batch mode and the products may be produced in large lot called campaigns. Due to the fact that there are several products needed to produce to suit customer demand, changing production batch type is unavoidable. The production line must be cleaned up to avoid cross contamination and cleaning time is time consuming. In addition, the pharmaceutical product has a limited holding time. For example, the product must be processed to the next processing stage no later than a specified holding time. For more complicated problem, a certain tablet can be processed by only specified machine and this will restrict the scheduling task. Thus, the research issue is the sequence of product in the processing batch at each stage. The mathematical model will be formulated to solve the problem and will be described next.

B. Mathematical Model

As mentioned earlier, the mathematical model is of crucial importance and must be developed to formulate the problem. The objective function is to minimize of a maximum completion time of all of jobs which is a function of ending time and setup time in the last stage. The model can be shown as follows.

Let define indices, parameters and decision variables

Indices

i, i' item of products ; i, i' = 1, 2, 3,…I
j batch ; j = 1, 2, 3,…J
k sequence; k = 1, 2, 3,…K
l processing stage ; l = 1, 2, 3,…L

Parameters

P_{ijkl} processing time of the item i batch jth at sequence kth on processing stage l

S_{ijkl} setup time of the item i batch jth at sequence kth onprocessing stage l

H_{ijkl} holding time of the item i batch jth at sequence kth on processing stage l

St_{ijkl} starting time of the item i batch jth at sequence kth on processing stage l

E_{ijkl} ending time of the item i batch jth at sequence kth on processing stage l

C_{ijkl} completion time of the item i batch jth at sequence kth on processing stage l

Decision variables

X_{ijkl} 1 ; if item i batch jth is assigned at sequence kth on processing stage l
0 ; otherwise

$Y_{ii'kl}$ 1; if the product assignment is changed product i to product i' at sequence kth on processing stage l
0 ; otherwise

Dependent variables

C_{ijmax} completion time of the item i batch jth at the last sequence on the final processing stage

Objective function

Minimize Z = Minimize C_{ijmax}

Where the maximum of completion (C_{ijmax}) is

$$C_{ijmax} = E_{ijKL} + (Y_{ii'KL} \times S_{ijKL}) \forall i, \forall j \qquad (1)$$

Constraints

1) This constraint ensures that the starting time of the item i batch jth at the first sequence on the first processing stage is zero.

$$St_{ij11} = 0 \qquad \forall i, \forall j \qquad (2)$$

2) This constraint describes that the starting time of the item i in the batch jth of the first sequence on processing stage l equals to the sum of ending time of the item i in the batch jth of the first sequence on the previous processing stage.

$$St_{ijl1} = E_{ij1(l-1)} \quad \forall i, \forall j, \text{l= 2,3,…L} \qquad (3)$$

3) This constraint defines that the starting time of the item i in the batch jth of the sequence kth on the first processing stage is the maximum between completion time of the item i in the batch jth of the previous sequence kth on the first processing stage and the completion time of the item i in the batch jth of the previous sequence kth on the second processing stage minus by the processing time of

the item i on the second stage and the holding time of the item i in the batch j[th] of the previous sequence k[th] on the first stage.

$$St_{ijk1} = \max\left[C_{ij(k-1)1}, \{C_{ij(k-1)2} - \left(P_{ijk2} \times X_{ijk2}\right) - H_{ij(k-1)1}\}\right] \quad (4)$$

$$\forall i, \forall j, \text{k} = 2, 3, \ldots \text{K}$$

4) This constraint defines that the starting time of the item i of the batch j[th] in sequence k[th] on the second processing stage is the maximum between the completion time of the item i of the batch j[th] in the previous sequence k[th] on the second processing stage and the finishing time of the item i of the batch j[th] in the same sequence k[th] on the first processing stage, and completion time of the item i of the batch j[th] in the previous sequence k[th] on the third processing stage minus the processing time of the item i on the third processing stage and holding time of the item i in the batch j[th] of the previous sequence k[th] on the second processing stage.

$$St_{ijk2} = \max\left[C_{ij(k-1)2}, E_{ijk1}, \{C_{ij(k-1)3} - \left(P_{ijk3} \times X_{ijk3}\right) - H_{ij(k-1)2}\}\right] \quad (5)$$

$$\forall i, \forall j, \text{k} = 2, 3, \ldots \text{K}$$

5) The constraint defines that the starting time of the item i of the batch j[th] in sequence k[th] on the processing stage l is a maximum between the completion time of the item i of the batch j[th] in the previous sequence k[th] on the processing stage l and the ending time of the item i of the batch j[th] in the same sequence k[th] on the previous processing stage.

$$St_{ijkl} = \max\left[C_{ij(k-1)l}, E_{ijk(l-1)}\right] \forall i, \forall j, \text{k} = 2, 3..\text{K}, \quad \text{l} = 3, \ldots \text{L} \quad (6)$$

6) This constraint defines the ending time of the item i of the batch j[th] in sequence k[th] on the processing stage l equals to the summation of the starting time of the item i of the batch j[th] in sequence k[th] on the processing stage l and the processing time of the item i of the batch j[th] in sequence k[th] on the processing stage l.

$$E_{ijkl} = St_{ijkl} + \left(P_{ijkl} \times X_{ijkl}\right) \ \forall i, \forall j, \forall k, \forall l \quad (7)$$

7) This constraint defines that the completion time of the item i of the batch j[th] in sequence k[th] on the processing stage l equals to the summation of the ending time of the item i of the batch j[th] in sequence k[th] on the processing stage l and changing time from item i to item i' in sequence k[th] on the processing stage l.

$$C_{ijkl} = E_{ijkl} + \left(S_{ijkl} \times Y_{ii'kl}\right) \ \forall i, \forall j, \forall k, \text{L}=1,2..\text{L}-1 \quad (8)$$

8) This constraint ensures that the only one item and one batch can be produced in sequence k on the processing stage l.

$$\sum_{i=1}^{I} \sum_{\text{j}=1}^{J} X_{\text{ijkl}} = 1 \quad \forall k, \forall l \quad (9)$$

9) This constraint ensures that only item i of batch j[th] on the processing stage l can be assigned only one time.

$$\sum_{\text{k}=1}^{\text{K}} X_{\text{ijkl}} = 1 \forall i, \forall j, \forall l \quad (10)$$

10) This constraint defines that all decision variables are binary integer.

$$X_{ijkl}, Y_{ii'kl} \in \{0,1\} \quad (11)$$

Once the mathematical model is formulated, it will be verified by several cases using Excel solver software to check model validity and to obtain the result.

III. Result

In this section a numerical exampledemonstrates the application of this model. The mathematical model is applied to a case study to generate decision for the scheduling of ARV drugs manufacturing over one week. The test example is simplified for demonstration purpose. The data of one week demand is shown in Table I. The product is consecutively processed into four processing stages, and each processing stage is equipped with one machine. There are four products (A, B, C, and D) needed to be produced. According to GMP and PIC/S standard, only one type and one batch of product can be produced on any machine at a time to prevent cross contamination among products. In addition, setup (cleanup) of machine between production batch is a must.The processing time, setup time and maximum holding time are tabulated in Table II-Table IV respectively. Note that the maximum holding time is the allowance time that the product must be processed to the next processing stage.

TABLE I. Weekly Demand

item	A	B	C	D
No. of lots	3	6	2	2

TABLE II. Processing Time of the Product (hr)

Stage	Product			
	A	B	C	D
1	2	2	2	2
2	14	5	8	8
3	10	7	7	7
4	4	2	2	2

TABLE III. Clean Up Time of the Product (hr)

Stage	Product			
	A	B	C	D
1	2	3	2.5	2.5
2	10	12	10	11
3	7	10	7	8
4	2	3	2	3

The problem is solved using Excel Solver software. The optimal schedule is shown in Table V-Table VII respectively. Gantt chart is shown in Fig. 2 and Fig. 3. These figures show the assignment of product at each

processing stage. The completion time of all jobs obtained from this optimization model is 155 hours.

TABLE IV. MAXIMUM HOLDING TIME OF THE PRODUCT (HR)

Stage	Product			
	A	B	C	D
1	120	48	120	120
2	360	72	360	360
3	0	0	0	0
4	0	0	0	0

TABLE V. RESULT OF SCHEDULING OVER ONE WEEK

Stage	Sequence			
	1	2	3	4
1	B	B	B	B
2	B	B	B	B
3	B	B	B	B
4	B	B	B	B

TABLE VI. RESULT OF SCHEDULING OVER ONE WEEK (CONT.)

Stage	Sequence			
	5	6	7	8
1	B	B	C	C
2	B	B	C	C
3	B	B	C	C
4	B	B	C	C

TABLE VII. RESULT OF SCHEDULING OVER ONE WEEK (CONT.)

Stage	Sequence				
	9	10	11	12	13
1	A	A	A	D	D
2	A	A	A	D	D
3	A	A	A	D	D
4	A	A	A	D	D

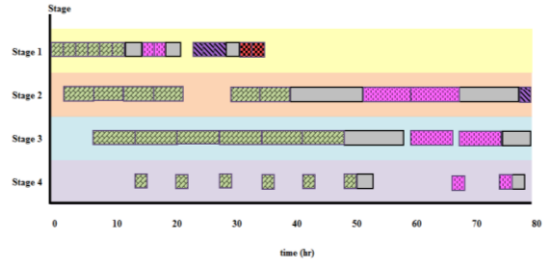
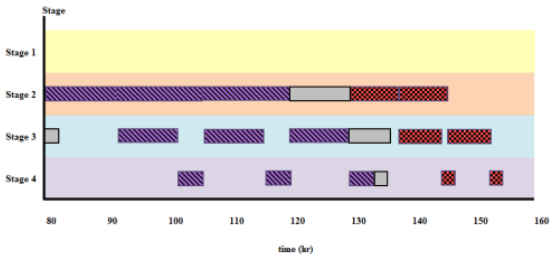


Figure 2. Gantt chart of the optimal solution



Figue 3. Gantt chart of the optimal solution (cont.)

When we get the result from optimization of mathematical model, we should improve it for real work. Due to ARV section works one shift (10 hours) in mixing (stage 1) and packing (stage 4) processes and two shifts (20 hours) in tableting (stage 2) and coating (stage 3) processes, the improvement of scheduling must follow available real time. Also, maximum completion time in the last stage from improvement equals mathematical model as shown in Fig. 4 and Fig. 5.

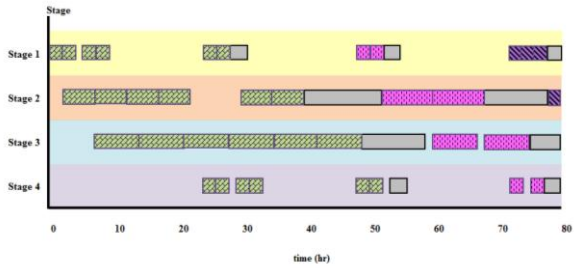


Figure 4. Gantt chart of the optimal solution that improve for real time

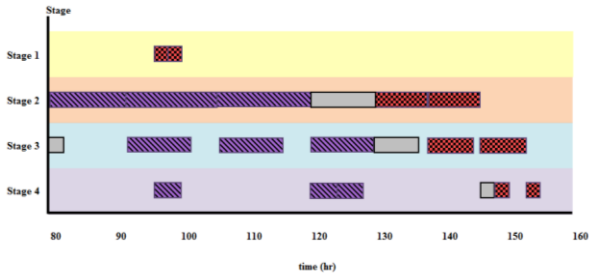


Figure 5. Gantt chart of the optimal solution that improve for real time(cont.)

After that, we use this mathematical model for expanding the one-month case study. The data of one month demand is shown in Table VIII. There are five products (E, F, G, H and I) needed to be produced according to GMP and PIC/S standard. In addition, setup (cleanup) of machine between production batch is a must. The processing time, setup time and maximum holding time are tabulated in Table IX-Table XI respectively. Note that the maximum holding time is the allowance time that the product must be processed to the next processing stage.

TABLE VIII. WEEKLY DEMAND

item	E	F	G	H	I
No. of lots	6	13	8	26	29

TABLE IX. PROCESSING TIME OF THE PRODUCT (HR)

Stage	Product				
	E	F	G	H	I
1	4	2	2	2	2
2	7	14	3.5	8.5	5
3	0	10	2.5	7	7
4	0	4	2	2	2

The problem is solved using Excel Solver software. The optimal schedule is shown in Table XII. The completion time of all jobs obtained from this optimization model is 622 hours.

TABLE X. CLEAN UP TIME OF THE PRODUCT (HR)

Stage	Product				
	E	F	G	H	I
1	5	3.5	3.5	3.5	5
2	12	10	10	10	12
3	0	7	7	7	10
4	0	2	2	2	3

TABLE XI. MAXIMUM HOLDING TIME OF THE PRODUCT (HR)

Stage	Product				
	E	F	G	H	I
1	120	120	120	120	48
2	0	360	360	360	72
3	0	0	0	0	0
4	0	0	0	0	0

TABLE XII. RESULT OF SCHEDULING OVER ONE WEEK

Stage	Sequence				
	1-29	30-42	43-68	69-76	77-82
1	I	F	H	G	E
2	I	F	H	G	E
3	I	F	H	G	E
4	I	F	H	G	E

IV. CONCLUSION

This research paper shows an attempt to apply an industrial engineering technique in pharmaceutical production. It is shown that the optimization technique is one of the potential and useful methods for problem solving. The job shop scheduling with dependent setup time is studied. The machine setup is a vital process so as to decrease the risk of cross-contamination which may lead to adverse drug effects in patients.

The problem is formulated as a binary integer programming to minimize the total make-span to alleviate the backorder problem. The resultshows that not only the total make-span can be reduced withbetter scheduling, but also cost reduction from fewer regular and overtime hours. The processing time that is reduced from the scheduling can be used to produce more products.

ACKNOWLEDGMENT

We would like to thank Government Pharmaceutical Organization for the financial support of this research and ARV drugs section for the support data.

REFERENCES

[1] A. Sodsangaroonngam, C. Soontravanich, and C. Khompatraporn, "Optimal sequence-dependent job scheduling of packing process with multiple non-identical machines in tablet production," in *Proc. Applied Mechanics and Materials*, Switzerland, 2014, pp. 1046-1050.

[2] E. I. Asgeirsson, G. S. Axelsdottir, and H. Stefansson, "Automating a manual production scheduling process at a pharmaceutical company," in *Proc. IEEE, Computation Intelligence in Production and Logistics System*, Paris, 2011, pp. 1-8.

[3] *Theory of Scheduling,* 1st ed., Dover Publications Inc., Mineola, N.Y., 2003, pp. 2-6, 22-49.

[4] J. Ung San, "A comparative study of two-phase heuristic approaches to general job shop scheduling problem," in *Proc. IEMS*, 2008, pp. 84-92.

[5] H. Stefansson, N. Shah, and P. Jensson, "Multiscale planning and scheduling in the secondary pharmaceutical industry," in *Proc. AIChE Journal*, pp. 4133-4149, 2006.

[6] M. RezaAmin-Naseri and M. Alibeheshti, "Hybrid flow shop scheduling with parallel batching," *Int. J. Production Economic*, pp. 185–196, 2009.

[7] S. Chaoleam, T. Somboonwiwat, and S. Prombanpong, "The production planning of pharmaceutical production under multi variables," presented at the IEEE, Thailand, December 10-13, 2013.

[8] H. Stefansson, S. Sigmarsdottir, P. Jensson, and N. Shah, "Discrete and continuous time representations and mathematical models for large production scheduling problems: A case study from the pharmaceutical industry," *European Journal of Operational Research*, pp.383-392, 2011.

[9] B. D. Corwin and A. O. Esogbue, "Two machine flow shop scheduling problems with sequence dependent set up times," in *Proc. A Dynamic Programming Approach, Naval Research Logistics*, 1974, pp. 515-524.

[10] X. Q. Sun, J. S. Noble, and C. M. Kein, "Single-machine scheduling with sequence dependent set up to minimize total weighted squared tardiness," in *Proc. IIE Transactions*, 1999, pp. 113-124.

[11] J. Adams, E. Balas, and D. Zawack, "The shifting bottleneck procedure for job shop scheduling," *Management Science*, vol. 34, pp.391-401, 1988.

[12] S. Binato, W. Hery, D. Loewenstern, and M. Resende, "A GRASP for Job Shop Scheduling," *Kluwer Academic Publishers*, 2000.

[13] F. D. Croce, R. Tadei, and G. Volta, "A genertic algorithm for the job shop problem," *Computer Operation Research*, vol. 22, pp. 15-24, 1995.

[14] R. Nakano and T. Yamada, "Conventional genertic algorithm for job shop problem," in *Proc. Fourth Int. Conf. on Genertic Algorithms*, Morgan Kaufimann, San Mateo, California, 1991, pp. 474-479.

[15] T. Yamada, "Studies on metaheuristics for jobshop and flowshop scheduling problem," in *Department of Applied Mathematics and Physics*, Doctor of Informatics Kyoto, Japan, Kyoto University, 2003, pp. 120.

[16] T. Yamada and R. Nakano. "Genetic algorithms for job-shop schedule problem," in *Modern Heuristics for Decision Support*, UNICOM Seminar, London, 1997, pp. 67-81.

[17] W. Wang and P. Brunn, "An effective genetic algorithm for job shop scheduling," in *Proc. Instruction of Mechanical Engineers. Part B, Engineer Manufacture*, vol. 214, 2000, pp. 293-300.

[18] M. R. Garey, D. S. Johnson, and R. Sethi, "The complexity of flowshop and jobshop Scheduling," *Mathematics of Operations Research*, vol. 1, pp. 117-129, 1976.

[19] J. K. Lenstra and A. H. G. RinnooyKan, "Computaional complexity of discrete optimization problems," *Rotterdam, Annals of Discrete Mathematics*, vol. 4, pp. 121-140, 1979.

[20] M. R. Garey and D. S. Johnson, *Computers and intractability: A guide of the theory of NP-completeness,* San Francisco: W. H. Freeman, 1979.

[21] W. K. Wong, C. K. Chan, and W. H. Ip, "A hybrid flowshop scheduling model for apparel manufacture," *International Journal of Clothing Science and Technology*, vol. 13, pp. 115-131, 2001.

[22] M. Gothe-Lundgren, T. Lundgren, and J. Persson, "An optimization model for refinery production scheduleing," *International Journal of Production Economics*, vol. 78, pp. 255-270, 2002.

Miss Sopin Bositthipichet is currently working in the production department at Government Pharmaceutical Organization Thailand. She graduated in the Faculty of Pharmacy at Chulalongkorn University and pursued her higher education in the area of Manufacturing and System Engineering at King Mongkut's University of Technology Thonburi (KMUTT). Her research interest is in the area of production planning and scheduling.

Prof. Dr. Suksan Prombanpongis currently working at King Mongkut's University of Technology Thonburi (KMUTT). He received Fulbright scholarship to pursue his master and doctoral degree at The Ohio State University (OSU) U.S.A. After graduation he worked at National University of Singapore for three years. Now he is a lecturer in the department of Industrial Engineering at KMUTT. He also holds a position of DEPUTY DIRECTOR for the Institute for Scientific and Technological Research and Services and a head of Continuing Education Center at KMUTT. His research interest is in the area of manufacturing applications, production planning and control, optimization, logistic and supply chain and green industrial.

Prof. Dr. Tuanjai Somboonwiwatis an Associate Professor in the Industrial Management section, Department of Production Engineering Faculty of Engineering,King Mongkut's University of Technology Thonburi**,** Thailand. She received her M.Eng. in Industrial Engineering from Chulalongkhorn University, Thailand and Ph.D. in Industrial Engineering from Corvallis, Oregon State University, USA. Her research interests include green supply chain and logistics, business process and applications of operations research.

