Evaluation of Pharmaceutical Production Expansion Plan via Batch Process Simulation

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INTRODUCTION

Computer Aided Process Design (CAPD) and simulation tools have been widely used in chemical process industries and have become standard tools for process development, design and optimisation [8, 11]. However, this tool is still relatively new to bio-related manufacturing, which are commonly operated in batch mode [1, 4, 5, 6, 7, 10].

In this work, the SuperPro Designer® v6.0 (Intelligen, 2005), a commercial batch process simulation tool is used to evaluate the economical viability of a pharmaceutical production expansion plan. A case study is presented where five proposed alternatives are evaluated. An economic analysis is performed to determine the most economically attractive alternative.

BACKGROUND THEORY

A batch process is operated in a series of operation steps in a specific sequence, also known as a recipe, and offers the ease of changing these operation steps for the production of multiple products with variable sized orders. Typical processes that are operated in batch mode include pharmaceutical, specialty chemicals, biotechnology, food, consumer products and mineral processes. Due to the uncommon unit operations and the nature of batch operations, modelling and optimisation work has remained rare in these areas.

In this work, a batch process simulation tool, SuperPro Designer® v6.0 (Intelligen, 2005), is used to model and evaluate a pharmaceutical production expansion plan. In SuperPro Designer, batch processes are modelled through unit procedures, where a series of operations take place sequentially in a piece of equipment.

A problem of particular interest in any manufacturing plant is that of process debottlenecking, which is the identification and removal of obstacles in the attempt to increase plant throughput (Koulouris et al., 2000). A good tool to be used to identify batch process bottlenecks is throughput analysis, i.e. the dependence on equipment capacity utilisation and occupancy time on batch size. Simulation tools that are capable of tracking equipment time and capacity utilisation can facilitate the identification of potential bottlenecks and the development of alternative scenarios for process debottlenecking. The total annual throughput of a batch plant is given as the product between the batch size and the number of batches executed annually [3]:

$$\text{Annual throughput} = \text{Batch size} \times \text{Number of batches} \quad (1)$$

Hence, to increase annual throughput of a batch process, we can either increase the batch size or the number of batches. However, the two variables are not independent. With number of batches being inversely proportional to the batch cycle time, Equation 1 takes its new form [3]:

$$\text{Annual throughput} \propto \frac{\text{Batch size}}{\text{Batch cycle time}} \quad (2)$$

Equipment bottlenecks for a batch process can be identified by considering the capacity and time utilisation of each procedure. Equipment capacity utilisation for a unit procedure is defined by the percentage of capacity utilisation among all operations of that procedure [3]:

$$\text{Equipment capacity utilisation} = \frac{\text{Actual capacity}}{\text{Maximum capacity}} \times 100\% \quad (3)$$

The scheduling bottleneck is the piece of equipment that has the longest occupancy time. This is the equipment that determines the minimum recipe cycle time (minimum time between the start of two consecutive batches) and consequently the maximum number of batches per year. The equipment uptime is represented by the percentage of plant operating time that a certain piece of equipment is occupied, as given in Equation 4:

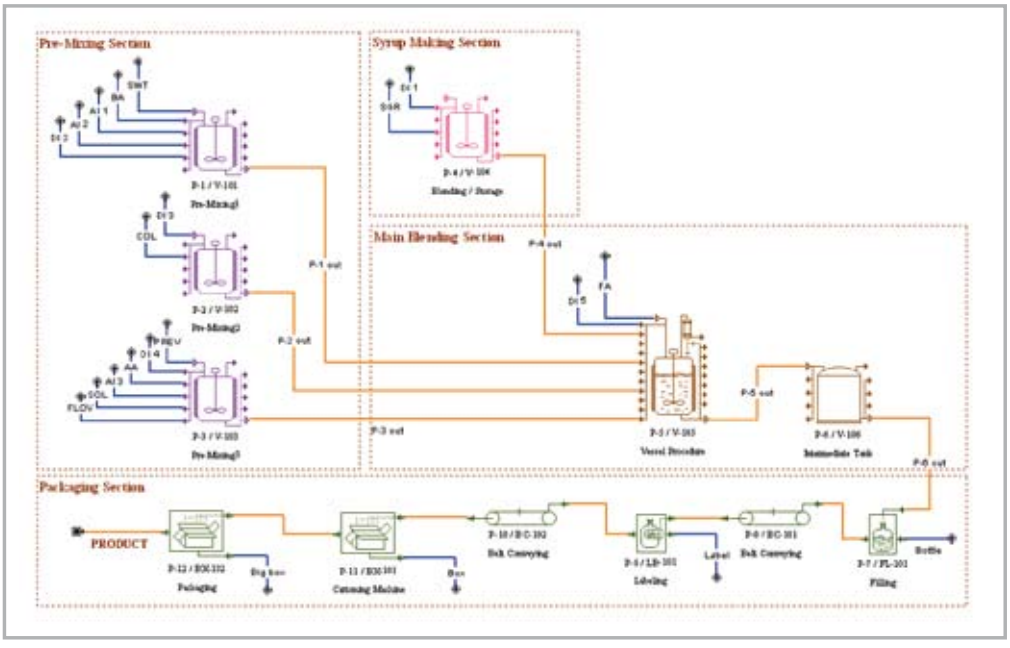
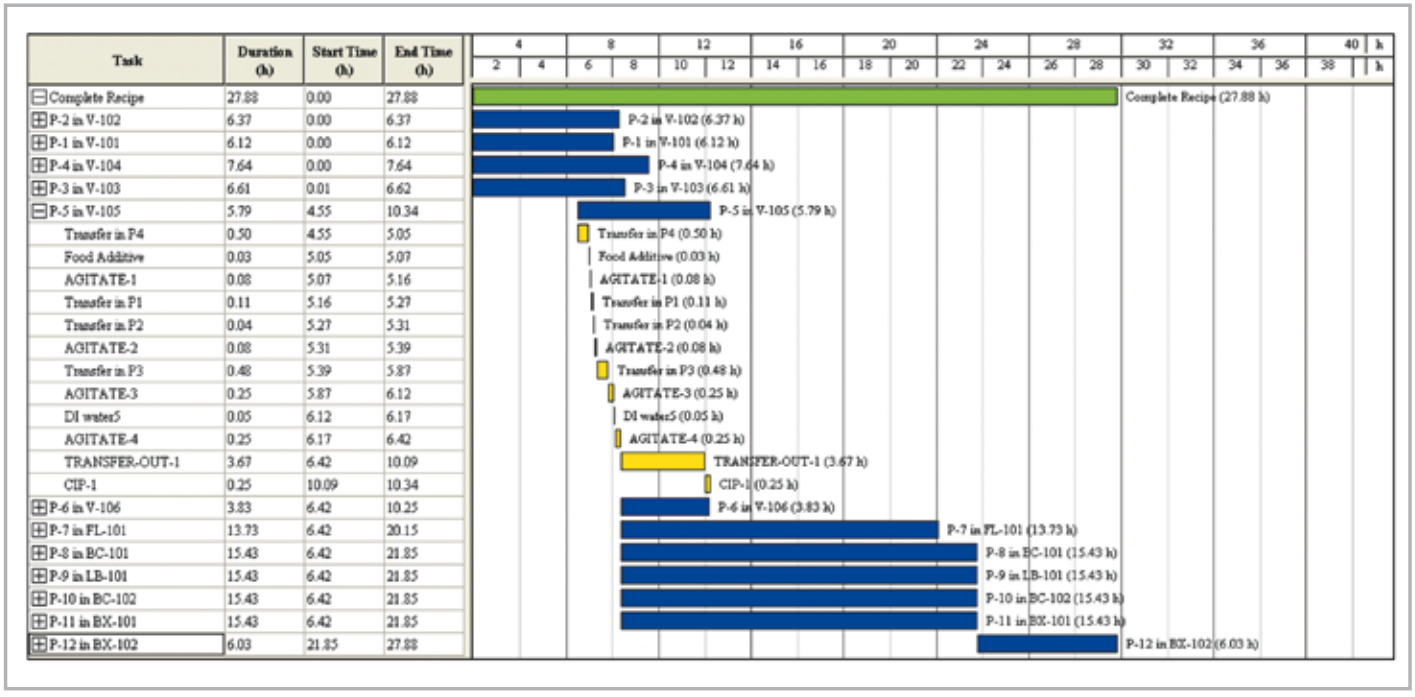


Figure 1: Base case simulation flowsheet for the production of LIQMED



Task	Duration (h)	Start Time (h)	End Time (h)
Complete Recipe	27.88	0.00	27.88
P-2 in V-102	6.37	0.00	6.37
P-1 in V-101	6.12	0.00	6.12
P-4 in V-104	7.64	0.00	7.64
P-3 in V-103	6.61	0.01	6.62
P-5 in V-105	5.79	4.55	10.34
Transfer in P4	0.50	4.55	5.05
Food Additive	0.03	5.05	5.07
AGITATE-1	0.08	5.07	5.16
Transfer in P1	0.11	5.16	5.27
Transfer in P2	0.04	5.27	5.31
AGITATE-2	0.08	5.31	5.39
Transfer in P3	0.48	5.39	5.87
AGITATE-3	0.25	5.87	6.12
DI water5	0.05	6.12	6.17
AGITATE-4	0.25	6.17	6.42
TRANSFER-OUT-1	3.67	6.42	10.09
CIP-1	0.25	10.09	10.34
P-6 in V-106	3.83	6.42	10.25
P-7 in FL-101	13.73	6.42	20.15
P-8 in BC-101	15.43	6.42	21.85
P-9 in LB-101	15.43	6.42	21.85
P-10 in BC-102	15.43	6.42	21.85
P-11 in BX-101	15.43	6.42	21.85
P-12 in BX-102	6.03	21.85	27.88

Figure 2: The operation gantt chart for the base case simulation

$$\text{Equipment uptime} = \frac{\text{Total time equipment is utilised per batch}}{\text{Plant cycle time}} \quad (4)$$

The product of equipment capacity utilisation and its uptime defines the combined utilisation of the respective equipment. The processing step with the highest combined utilisation is normally identified as the first candidate for process debottlenecking [3]. The ability to identify and remove process bottlenecks will increase plant throughput and fulfil customer orders in time. In considering a debottlenecking work, economic criterion such as cost benefit ratio (CBR) is used to evaluate the appropriate debottlenecking alternatives. As the name suggest, CBR is based on the ratio of the benefits to the cost associated with the particular project (Blank and Tarquin, 2003). Higher CBR means a project has higher revenue for a given amount of cost (operating and investment). For the case of production expansion, CBR can be defined in Equation 5:

$$\text{CBR} = \frac{\begin{array}{c}\text{Revenue of the alternative}\\ \text{Revenue of current process}\end{array}}{\begin{array}{c}\text{Operating cost of the alternatives}\\ \text{Operating cost of current process}\\ \text{Additional annualised capitalcost}\end{array}} \quad (5)$$

PRODUCTION EXPANSION EXAMPLE – ORAL LIQUID MEDICINE MANUFACTURING

A production expansion case on pharmaceutical manufacturing is illustrated here. Figure 1 shows the base case simulation flowsheet for the production of oral liquid medicine (LIQMED) developed in SuperPro Designer. Various production expansion alternatives are evaluated using the developed model aiming to increase at least another 120% based on current production rate.

The annual operating time for the base case model is taken as 4160 hours, i.e. 52 operation weeks per annum, five working days a week and 16 hours a day (two shifts of eight hours each). The manufacturing process consists of 12 major processing equipment, i.e. three pre-mixing tanks, syrup blending tank, main blending tank, an intermediate tank, filler, belt conveyors (two units), labeller, cartoning machine and packaging (shrink wrapping) machines. As shown in Figure 1, these processing equipments are allocated in four sections, i.e. pre-mixing section, syrup making section, main blending section and packaging section. The batch throughput for this production is 2000 litre, with the final product being packed into 90ml bottles. Thirteen ingredients are used to produce LIQMED.

In the first pre-mixing procedure P-1 (carried out in vessel V-101), the charging of raw material sweetener (SWT), brewing agent (BA), active ingredient (AI1, AI2) and deionised (DI) water take place sequentially. Upon the completion of raw material charges, agitation is carried out to ensure uniform mixing. In pre-mixing tank procedure P-2 (vessel V-102), DI water is heated to 95°C, before the highly viscous colouring agent (COL) is melted in the hot DI water. The mixture is then agitated to form a homogenous mixture. In pre-mixing procedure P-3 (V-103), the mixing of preservative (PREV), DI water, anaesthetic agent (AA), active ingredient (AI3), solvent (SOL) and flavouring agent (FLOV) takes place in tank V-103. Note that the operation in the V-103 will only start when the heating operation of the DI water in V-102 commences(due to limited manpower).

The syrup making procedure (P-4) takes place in a 4000 litre blending tank (V-104). The syrup ingredients (DI water and sugar, SGR) are mixed together, followed by an agitation of three hours to ensure good mixing. A total amount of 1400 litre syrup is made in each batch. The syrup is then transferred into P-5/V-105

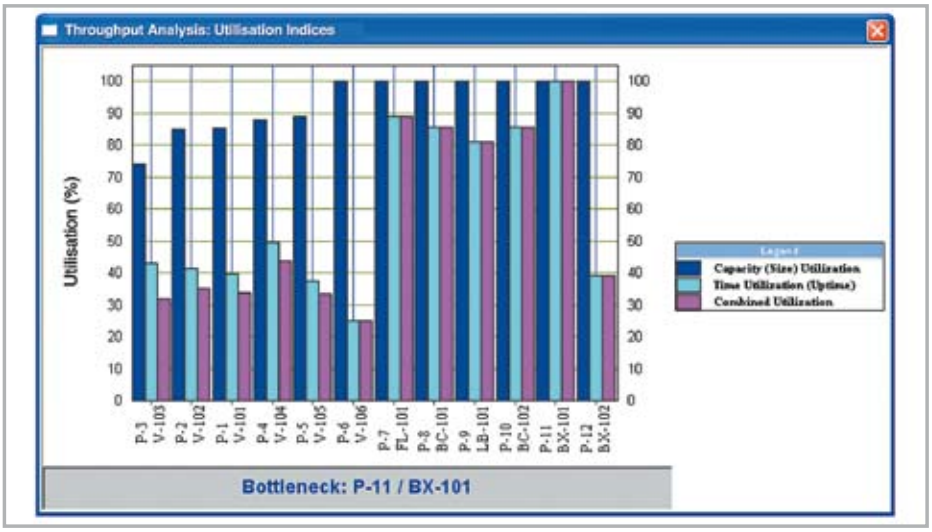


Figure 3: Throughput analysis chart for base case simulation

upon the completion of the various operations in P-4.

The main blending procedure (P-5) takes place in V-105. Upon the completion of syrup transfer from P-4/V-104, the LIQMED ingredient, i.e. food additive (FA) is charged into P-5/V-105. This is followed by the mixture transfer from V-101, V-102 and V-103 and DI water charge. Agitation is carried out during these mixture transfers to ensure uniform composition of the resulting mixture. The addition of DI water is to adjust the final mixture volume to 2000 litre. Upon the completion of these operations, the mixture in vessel V-105 is transferred into an intermediate tank, P-6/V-106 in which it serves as the feed to the packaging procedures in the downstream manufacturing. Vessel cleaning (CIP) is carried out in all pre-mixing and main blending tanks after the transfer-out operations are completed.

Prior to the start of packaging procedures, a setup time of 30 minutes is needed to clean up the Filling machine (P-7/FL-101). In the base case flowsheet, the Filling machine (P-7/FL-101), Labeller (P-9/LB-101) and Cartoning Machine (P-11/BX-101) are operated at the speed of 28, 30 and 24 bottles/min respectively. Finally, 72 bottles of LIQMED products are packed together in a shrink wrapper in the packaging machine (BX-102) and sent to the warehouse. Belt conveyors (P-8/BC-101 and P-10/BC-102) are used to transfer products in the packaging section. Figure 2 shows the Operation Gantt Chart for the case study.

EVALUATION OF PRODUCTION EXPANSION SCHEMES

Figure 3 shows the Throughput Analysis Chart for the base case model. As shown, almost all processing units in the packaging section have relatively high combined utilisation. Hence, to expand production in meeting customer demand (at least

Table 1: Equipment supplies by each of the five alternative suppliers

Equipment Supplier	Alternative 1	Alternative 2	Alternative 3	Alternative 4	Alternative 5
Processing Speed	80 bpm	35 bpm	77 bpm	80 bpm	70 bpm
Bottled Unscramble			X		X
Bottle Cleaner	X	X	X	X	X
Filler	X	X	X	X	X
Capping			X	X	
Cup Placing			X		
Labeller		X	X	X	X
Cartoning Machine	X	X	X	X	X
Over Wrapping			X		
Total Cost of Investment, US$	**808,500**	**427,000**	**1,188,580**	**1,746,765**	**3,881,072**

Note: bpm = bottle per minute

Table 2: Economic comparison of the base case study and debottlenecking strategy

	Minimum cycle time (h)	No. of Annual Batches	Annual Entities (bpm)	Cost per Unit ($)	Revenue ($)	Operating Cost ($)	Annualised Investment Cost ($)	CBR
Base case	15.43	268	5,955,496	0.61	9,925,927	3,651,381	–	nil
Alternative 1	15.43	268	5,955,496	0.65	9,925,927	3,881,303	213,280	0.000
Alternative 2	11.08	374	8,311,028	0.67		5,584,156	112,642	1.919
Alternative 3	6.61	627	12,933,194	0.61		8,441,404	313,544	2.605
Alternative 4	6.61	627	12,933,194	0.62		8,570,567	460,792	2.471
Alternative 5	6.61	627	12,933,194	0.66		9,249,803	1,023,817 7	2.008

Table 3: Overall process data for alternative 3

Equipment cost (US$)	
Bottle Unscramble, Bottle Cleaner and new Filter	712,895
Capping, Cup Placing and Labeller	118, 885
Cartoning Machine Packer	237, 905
Over Wrapping Machine Packer	118, 895
Annual throughput (boxes/year)	193, 518
Plant batch time (h)	17.26

additional 120% of increment is needed), these process bottlenecks need to be overcome.

In order to cater for production expansion, five debottlenecking alternatives proposed by different equipment suppliers are evaluated. Each alternative consists of different equipment package (of different processing speed) with different investment cost (Table 1), and hence re-simulation is needed. Capital cost is assumed to be paid back over five years, with an interest rate of 10%. Table 2 shows the summary for the base case simulation and the various debottlenecking alternatives. As shown, Alternatives 3–5 exceed the production increase of 120%. Among these alternatives, Alternative 3 (Figure 4) is determined to have the highest CBR value of 2.605 due to its moderate investment cost and high revenue generated (due to the increase of number of batches). Table 3 shows the major equipment cost distribution for Alternative 3.

CONCLUSION

CAPD and simulation tools are utilised to evaluate different production expansion alternatives for the pharmaceutical manufacturing of an oral liquid medicine. With access to a process simulator that performs repetitive calculations within a short period of time, the decision making process can be done more accurately and effectively. Among the evaluated strategies, Alternative 3 is determined to have the highest CBR and, hence, is selected as the expansion alternative for the pharmaceutical production. ■

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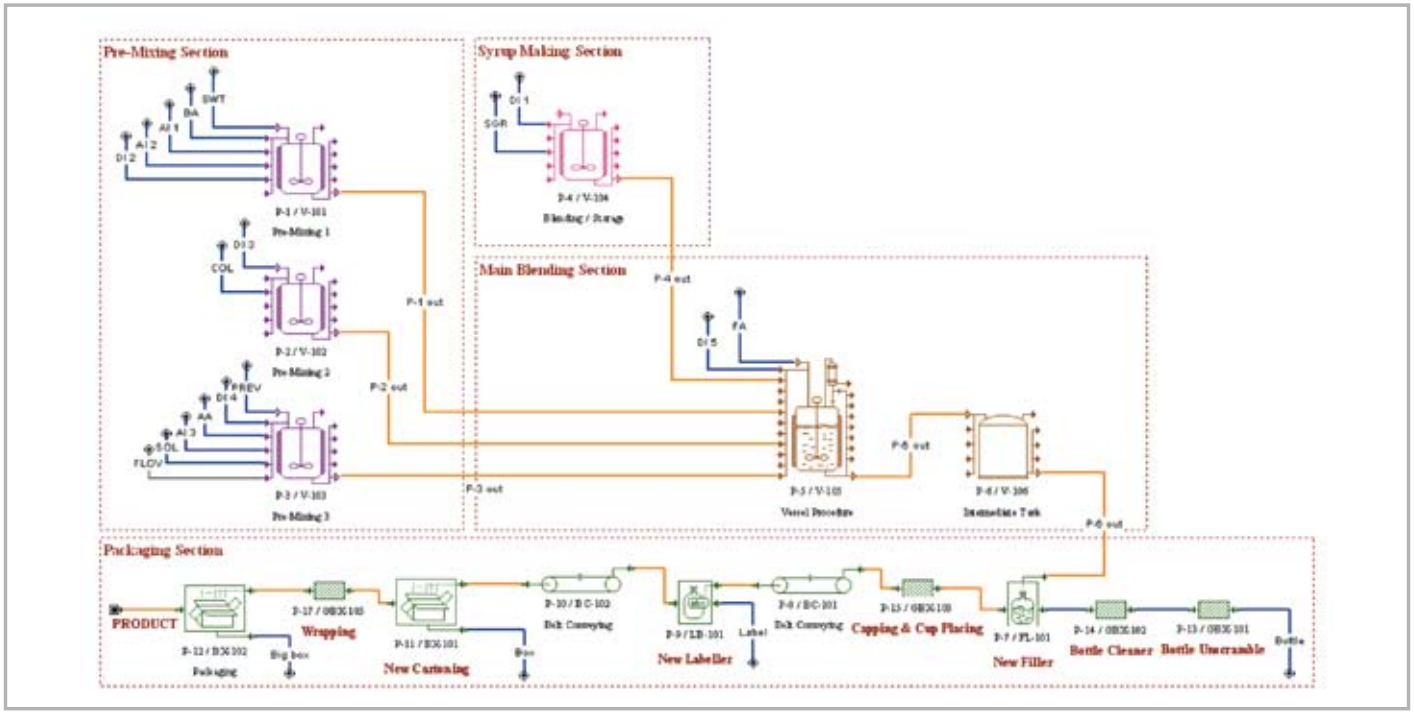

Figure 4: Simulation flowsheet for alternative 3