

# **Modelling, optimisation, and debottlenecking of a pharmaceutical production process utilising a batch process simulator**

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## **ABSTRACT**

Computer Aided Process Design (CAPD) and simulation tools have been successfully used in the bulk chemical industry since the early 1960s. However, the use of these tools had only occurred in the biochemical-related manufacturing industry throughout the past decade. Process simulation is useful during process development, process commercialisation, process design and optimisation. There are different types of commercial simulators available in the market based on their specialisation in either continuous, batch or semi-batch processes. The main objective of this work is to model, optimise and debottleneck a pharmaceutical production process with SuperPro Designer 5.0, a batch process simulator. A case study is modelled based on the operating condition from a local pharmaceutical plant for the production of an anti-allergic cream. Two alternatives were proposed for process debottlenecking due to the increase of the product demand in the market. Process simulation is utilised to evaluate these alternatives. The base case process consists of 6 working stations while the newly proposed alternatives comprise of 5 and 6 working stations respectively. Throughput analysis was carried out for the base case and two newly proposed strategies. Economic analysis is also performed on each case to determine the annual production output. The second proposed scheme with a higher cost benefit ratio (CBR) of 2.06 is found to be a better alternative compared to the first proposed scheme with a CBR of 1.67.

**Keywords:** Pharmaceutical production, batch processing, modelling and optimisation, throughput analysis, debottlenecking.

## **1.0 INTRODUCTION**

Computer Aided Process Design (CAPD) and simulation tools have been widely used in the chemical process industries and it have become standard tools in process development, design and optimisation (Westerberg *et al.*, 1979, Turton *et al.*, 1998). However these tools have only emerged in the biochemical-related manufacturing in the past decade (Ernst *et al.*, 1997; Shanklin *et al.*, 2001).

Process simulators are mainly used to evaluate the “what if” scenarios and to optimise integrated processes. This can be applied in several stages during the commercialisation process. Once process ideas are conceived, process simulators are used for project screening and selection based on economic analysis or other critical process requirement. A computer model of overall process is very important to provide a reference and an evaluation framework that can show the effects of process changes. It can facilitate the transfer of process technology as well as to facilitate design. This pinpoints the cost-sensitive areas especially for integrated processes. Experiments conducted on the simulator with alternative process setups and operating conditions allow a company to reduce costly and time consuming laboratory and pilot plant efforts. When process development nears completion on the pilot level, simulation tools are used to systematically design and optimise the large scale process for the commercialisation of products. A good process simulator can facilitate the transfer of process technology as well as to facilitate design. It can be used to estimate the required capital investment of the process. Via the use of a computer model, it helps the transfer of process to the existing manufacturing sites in the most cost-effectiveness way. In large scale batch manufacturing, process simulations are primarily used for process scheduling, debottlenecking and on-going process optimisation. It is capable of tracking equipment use for overlapping batches and to identify process bottleneck (Petrides, Koulouris and Siletti, 2002).

## **2.0 SIMULATION AND OPTIMISATION ON BATCH PROCESSES**

Batch processes normally contain several units that are designed to be started and stopped frequently (Douglas, 1988). Usually, a batch or several batches of raw material are prepared in the first step or the beginning of the operation. Then, the batches prepared in the

first step are delivered to the second step where further operations are carried out, and so on. A batch process is operated in a series of “step” in sequence. Batch processes offer the ease of changing from the production of one product to another where multiple products are produced with variably sized orders (Manganaro, 2002; Seider *et al.*, 2004). In this instant, pharmaceutical manufacturing processes are normally carried out in batch operation mode. Other industries that operate processes under batch mode include specialty chemicals, biotechnology, food, consumer product and mineral processing.

The commercial batch process simulator SuperPro Designer V5.0 is used in this work. SuperPro Designer can handle continuous and batch processes and a combination of both. The main method that SuperPro performs its simulations is through *unit procedures* where a set of operations that take place sequentially in a piece of equipment. The concept of unit procedures enables the user to model batch processes in greater detail. In SuperPro Designer, unit procedure is represented by a single equipment-looking icon on the simulation flowsheet. Multiple procedures can also share the same equipment item as long as their cycle times do not overlap. Scheduling and execution of each unit procedure as well as operations are clearly displayed on Gantt chart and equipment utilisation chart.

A problem of particular interest on any manufacturing plant is that of process debottlenecking, which is the identification and removal of obstacles in the attempt to increase the plant throughput. A good tool to be used to identify batch process bottlenecks is via throughput analysis, i.e. the dependence of 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 a product between the batch size and the number of batches executed annually, as shown in Equation 1 (Koulouris, Calandranis and Petrides, 2000), as follow:

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

However, since the number of batches is inversely proportional to the plant cycle time, the plant throughput becomes proportional to:

$$\text{Plant throughput} \propto \frac{\text{Batch throughput}}{\text{Number of batches}} \quad (2)$$

The scheduling bottleneck is the piece of equipment that has the longest total occupancy time. This is the piece of equipment that determines the *effective batch time* (time between batch starts) and consequently the maximum number of batches per year. The equipment size bottleneck can be identified by considering the capacity and time utilisation of each equipment item. Equipment capacity utilisation for a unit procedure is calculated by selecting the maximum capacity utilisation among all operations of that procedure as in Equation 3 (Koulouris, Calandranis and Petrides, 2000):

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

The equipment uptime is represented by the percentage of plant operating time that a certain piece of equipment is occupied. For plants operating in batch mode, equipment uptime can be defined as in Equation 4:

$$\text{Equipment uptime} = \frac{\text{total time equipment utilised per batch}}{\text{plant cycle time}} \quad (4)$$

Equipment items of this type usually operate at 100% capacity utilisation and changes in their throughput amount only affect their uptime. A resource bottleneck happens when the resources become size throughput and time scheduling bottlenecks such as when their average or instantaneous demand exceeds their average or instantaneous capacity, respectively. Ability to identify and remove equipment and resource bottlenecks that create obstacles in a manufacturing process will increase plant throughput and fulfil customer orders in time.

By using the “what if” scenario, the process can be optimised during development stage through the use of the simulation tool, providing the minimal risk to the products along with significant time and cost benefit. Cost benefit ratio (CBR) are among the criteria that are used to evaluate the appropriate alternatives (Blank and Tarquin, 2003). As the name suggest, the CBR method of analysis is based on the ratio of the benefits to the cost associated with the

particular project. The first step in CBR analysis is to determine which of the elements are benefits, disbenefits and cost. For the case of batch process debottlenecking, CBR value can be defined as Equation 5:

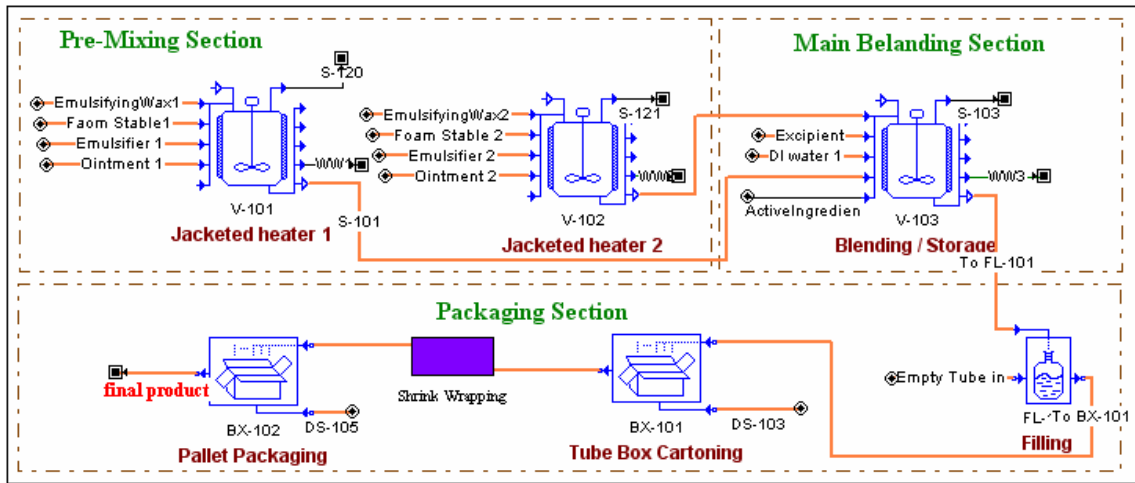
$$\text{CBR} = \frac{\text{Revenue of the alternatives} - \text{revenue of current process}}{\text{Operating cost} + \text{investment cost} - \text{operating cost of current process}} \quad (5)$$

### 3.0 CASE STUDY – PHARMACEUTICAL PRODUCTION

A pharmaceutical production of an anti-allergic cream is used to demonstrate the batch modelling, optimisation and debottlenecking methodology. Figure 1 shows the base case flowsheet modelled based on the operation condition of a local pharmaceutical plant. Customer demand for the products is expected to rise to 100% of the current production capacity in the near future. Hence, it is necessary to analyse the current production facilities to cater for increased production.

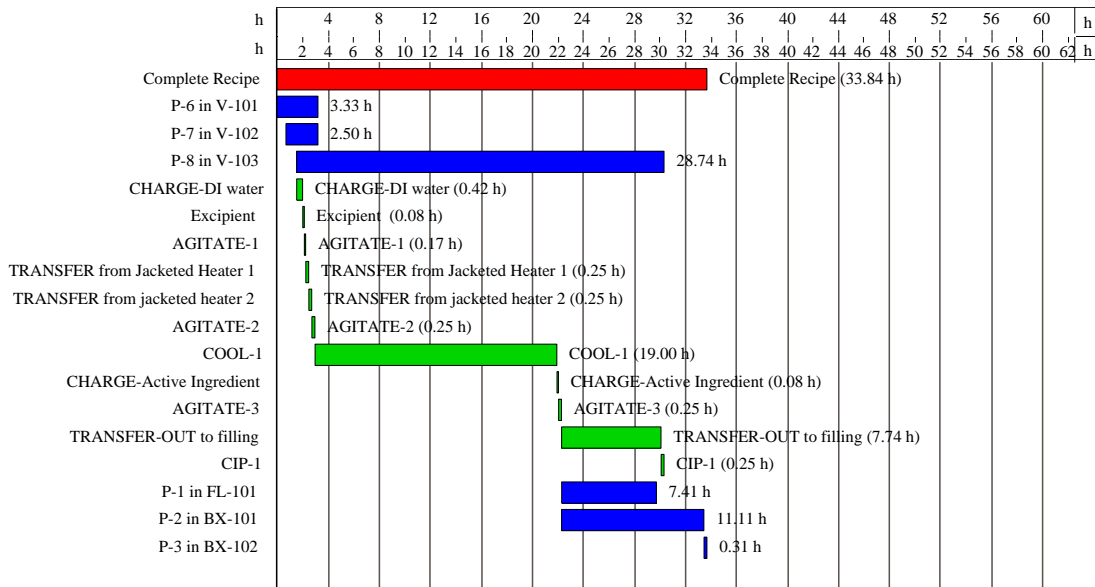
In the base case process, there are six major processing steps which consist of melting, blending, filling, cartoning, packaging (shrink wrapping) and shipment packaging. Fifty two operation weeks (with 5 working days a week and 8 hours a day) is taken as the basis of this work. Due to the capacity limitation of heated vessel, raw material is divided into 2 sub-mix batches for pre-mixing. Two batches of emulsifying wax and foam stable are independently heated in the jacketed heater V-101 and V-102 to approximately 100°C before the emulsifier and ointment are added. The emulsifier and ointment are originally in wax form and need to be melted for uniform mixing.

On the other hand, Deionised (DI) water is heated in a heater before transferring into the blending tank, V-103. Excipient 3 is next added into the hot DI water, followed by agitation for 10 minutes. The mixture in the jacketed heater V-101 and V-102 are then transferred into V-103. Again, the mixtures of all ingredients in V-103 are blended for 15 minutes in order to obtain uniform composition. The mixture is then left in dispensing room to cooled to room temperature, before the active ingredient is finally added. This cooling procedure took approximately 19 hours. When active ingredient of the anti-allergic cream is added, the products are blended for 15 minutes to get uniform composition.



**Figure 1: Base case simulation flowsheet for the production of anti-allergic cream**

The blended product is next transferred to filler FL-101 where it is filled into the tubes of 15g each. The speed of the current filling machine is 30 tubes per minute. The operation then proceeds to manual cartoning packaging where 20 tubes of anti-allergic cream are packed per minute by each operator. The final products in the carton boxes are packed into 144 tubes per shipment before they are sent to the warehouse. Approximately 5 sealed boxes are packed per minute. The Gantt chart for the complete operation is shown in Figure 2.



**Figure 2: Operation Gantt chart for the base case study**

From the base case simulation results, the batch time is calculated as 33.84 hours, equivalent to a production of 72 batches of anti-allergic annually with 13,333 tubes produced per batch. Owing to the rising market demand of this product, options for increasing plant throughput are needed. Figure 3 displays the capacity, time and combined utilisation of all the procedures/equipments pairs in the base case. The blending tank V-103 which has the highest combined utilisation of 75.5% is identified as the process scheduling bottleneck. This mainly due to its cooling operation that consumes 19 hours. Hence, debottlenecking strategies will be focused on this unit procedure in order to increase the plant throughput.

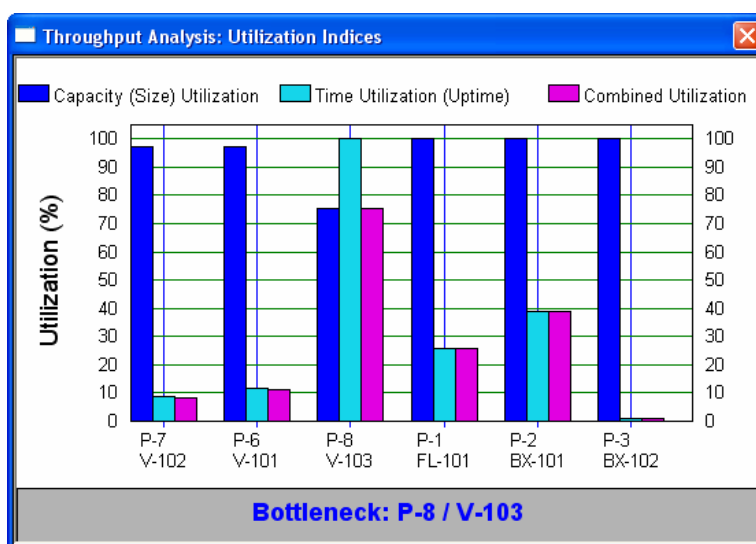
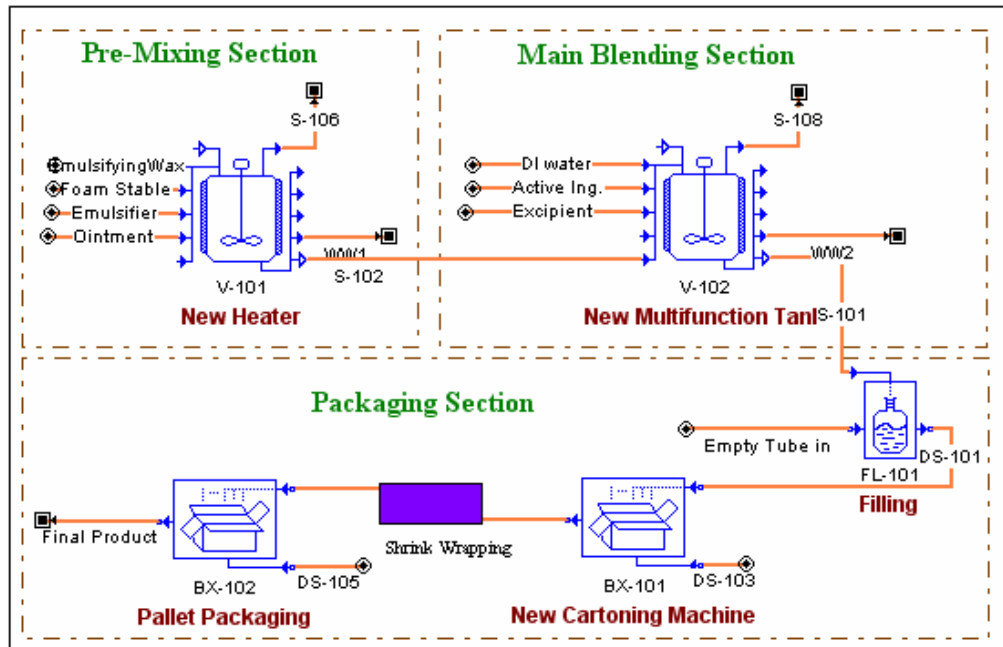


Figure 3: Capacity, time and combined utilisation chart for the base case study

#### 4.0 DEBOTTLENECKING STRATEGIES

Two debottlenecking strategies are proposed, i.e. alternative 1 and 2. The flowsheet for alternative 1 is shown in Figure 4. As shown, the two independent pre-mixing vessels (V-101 and V-102 in Figure 1) are now replaced by a 70 L jacketed heater (V-101 in Figure 1). This enables the melting and heating process of the raw materials to be carried out in a single jacketed heater, which avoids the time consuming and labour intensive procedures as before. A multifunctional blending tank with a cooling system is also introduced to shorten the cooling time of the cream from the current 19 hours to 1 hour with a constant cooling rate of 1°C per minute. Chilled water is used as the cooling agent to cool the mixture from 87°C to

the room temperature. In addition, an automatic cartoning machine with a line speed of 60 tubes per minutes is introduced. The equipment investment cost is estimated at USD 1.5M. From the simulation result, the annual throughput has increased to 202 batches which is almost triple of the base case. The batch time decreased to 10.28 hours from the original of 33.84 hours. The CBR value is calculated using Equation 5 to be 1.67.

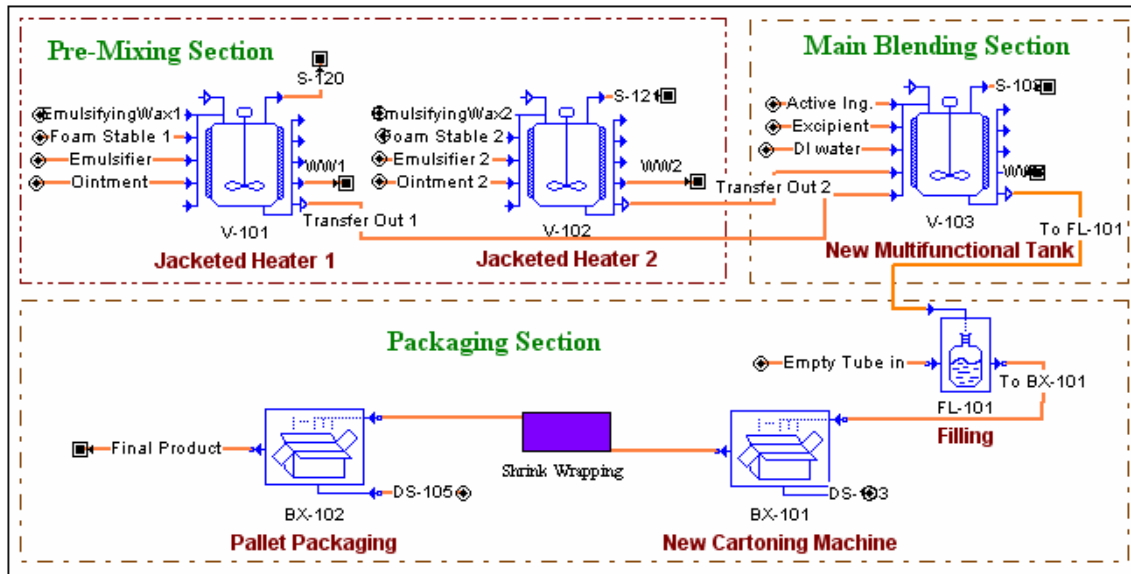


**Figure 4: Process flowsheet of alternative 1**

The second debottlenecking alternative is shown in Figure 5 where the existing jacketed heater V-101 and V-102 are retained. A new multifunctional blending tank and automatic cartoning machine with line speed of 60 tubes per minute are introduced. The estimated cost of investment is approximately USD0.9M. Simulation results shows that the annual throughput for this alternative is 195 batches with a batch time of 11.44 hours. This corresponds to an increase of productivity for more that 270% compared to the base case. Although the annual productivity of the second debottlenecking alternative is lower than that of the first alternative, it is a more preferable option as it has a higher CBR ratio of 2.06, compared to the first option at 1.67. Table 1 shows a summary of the economic comparison on the base case study, alternatives 1 and 2.

**Table 1: Economic comparison of the base case and debottlenecking alternatives 1 and 2**

Scenario	No. of jacketed heater (Volume)	Packaging (tube / minute)	Annual batches	Annual Throughput (tubes)	Cost of investment (USD)	Annual Operating cost (USD)	Annual Revenue, (USD)	Unit Production cost, USD/tube	CBR
Base case	2 (35L)	20	72	959,976	-	1,437,631	4,001,400	1.50	-
1	1 (70L)	60	202	2,693,266	1,500,000	4,245,318	11,224,467	1.58	1.67
2	2 (35L)	60	195	2,599,936	900,000	3,847,157	10,835,500	1.48	2.06



**Figure 5: Process flowsheet of alternative 2**

## 5.0 CONCLUSION

Computer-aided process design (CAPD) and simulation tools are useful in various stages of the engineering activities. In this work, it is shown that process simulator can be used to identify the cost effective process debottlenecking strategies for a pharmaceutical production. Economic analysis is used as the main criteria to identify the best debottlenecking alternative to increase plant throughput.

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