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This article describes the use of a batch process simulator in the modelling and debottlenecking of an anti-allergic cream production line at an existing pharmaceutical facility.

Debottlenecking of a Batch Pharmaceutical Cream Production

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Introduction

Computer Aided Process Design (CAPD) and simulation tools have been widely used in the bulk and petrochemical industries since the early 1960s. It involves the use of computers to perform steady-state heat and mass balancing as well as sizing and costing calculations for a process.[1] However, the use of these CAPD and simulation tools has only emerged in pharmaceutical manufacturing in the past decade.[2-8] Compared to the readily available process simulators in the bulk and petrochemical industries, there are only a limited number of simulators available for pharmaceutical process modelling. This situation is mainly due to the uncommon unit operations and the batch operation nature of pharmaceutical processing. Due to its relatively new emergence, more work needs to be done in this sector.

Due to the increasing customer demand of the anti-allergic cream product, the pharmaceutical facility management team was looking for alternative expansion schemes to increase the current production rate as the production capacity was limited by the current operating condition and equipment setup. Hence, a debottlenecking study is needed for an increase in production. In addition, the debottlenecking study will assist the management team in future expansion plans.

Background Theory

In order to increase production throughput, process bottlenecks that limit the current production need to be identified. Bottlenecks are process limitations that are related to either equipment or resources (e.g., demand for various utilities, labor, and raw material). Hence, *process debottlenecking* can be defined as the identification and removal of obstacles in the attempt to increase the plant throughput.[5] In batch manufacturing, two types of process bottlenecks can be categorized. These are the equipment capacity-related *size* bottleneck (an equipment that is limited in size) as well as the *scheduling* bottleneck (due to the long occupancy of a piece of equipment during a process).

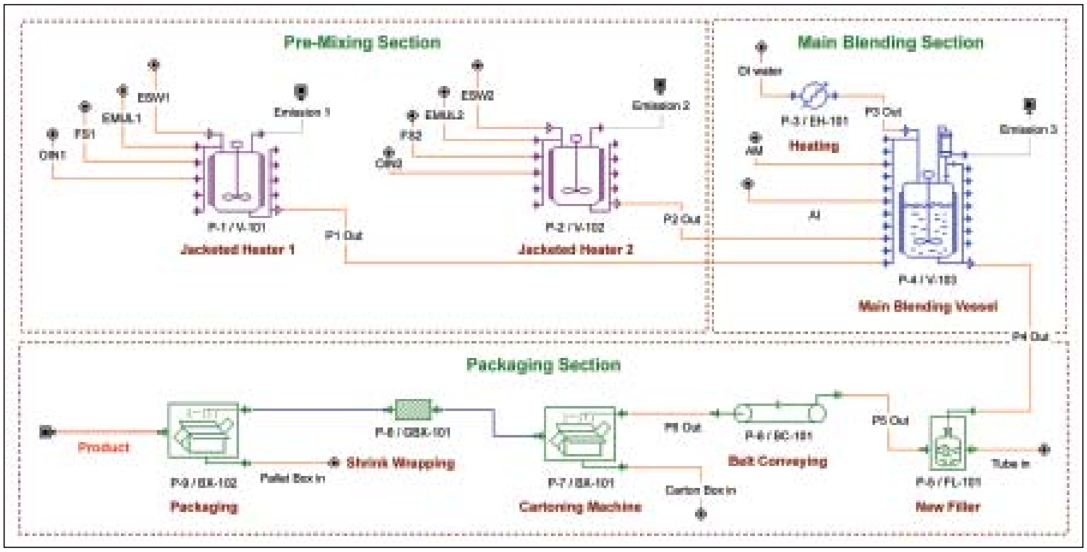


Figure 1. Base case simulation flowsheet for the production of anti-allergic cream.

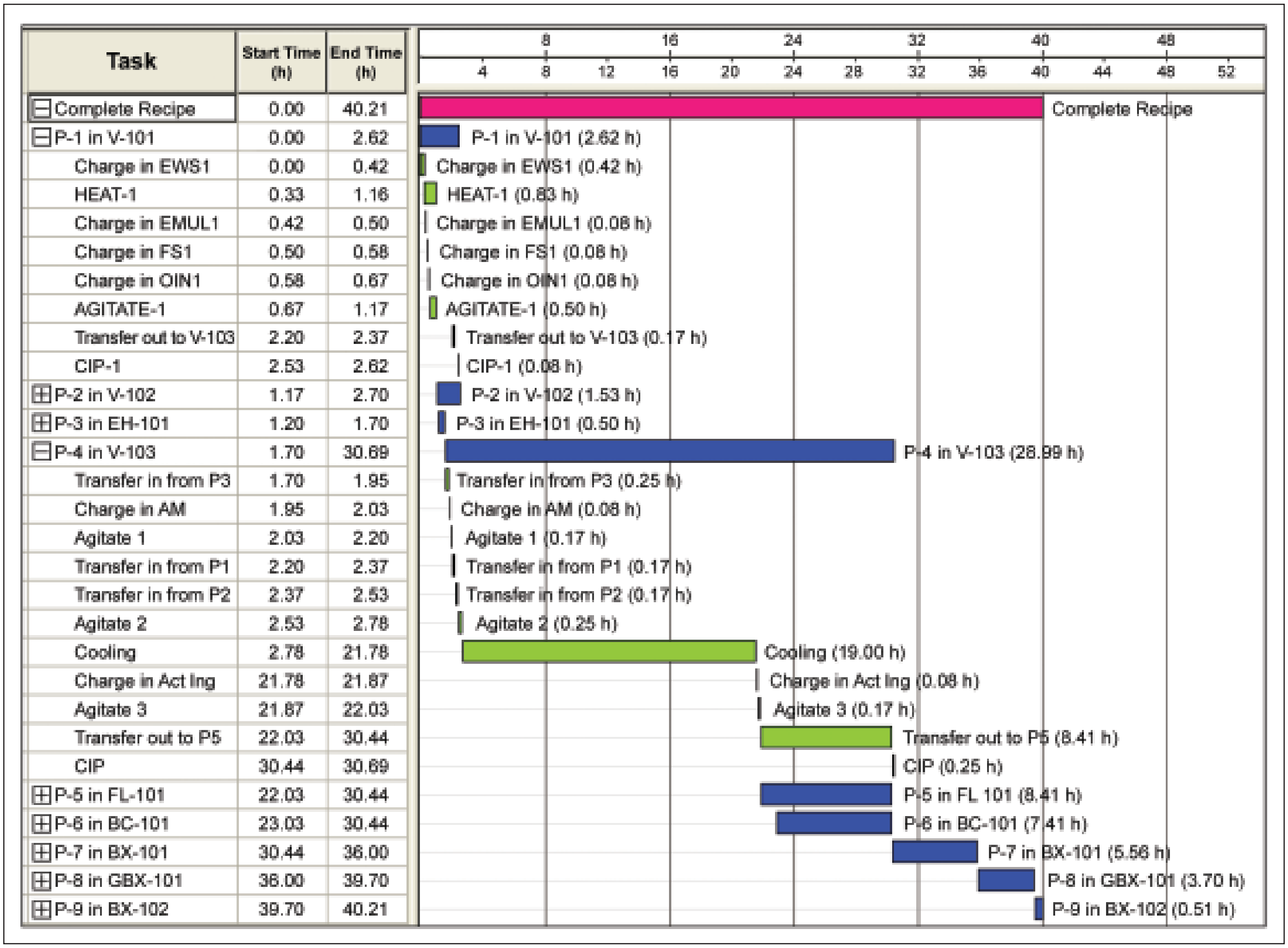
The ability to identify and remove process bottlenecks that create obstacles in a manufacturing process will increase plant throughput and fulfill customer needs.

A good tool to identify batch process bottleneck is via a throughput analysis study. Throughput analysis measures the equipment utilization in a batch process with two variables, i.e., the *capacity utilization* and *equipment uptime.*[5-6] Capacity utilization is defined as the percentage of the current operating load of a piece of equipment (e.g., vessel volume for a reactor or filtering area of a filter) relative to its maximum load. For instance, a vessel with 100% capacity utilization means that its current content has reached its maximum level.

Equipment uptime measures the effectiveness of a piece of equipment that is utilized in time. It is given as the percentage of the equipment utilization time over the plant cycle time. For example, a reactor that operates for five hours within a plant with a cycle time of 10 hours has an uptime of 50%. The product of equipment capacity utilization and its uptime defines the *combined utilization* of the respective equipment.[5-6]

In an ideal situation, a plant should have all equipment running at 100% combined utilization to achieve maximum production. However, this is often not the case. All process equipment will normally feature different utilization. The ability to raise utilization of the equipment will help in raising process throughput. The processing step with the highest combined utilization is normally identified as the first candidate for process debottlenecking. Simulation tools that are capable of tracking capacity utilization and equipment uptime can facilitate the identification of process bottlenecks and the development of the scenarios for process debottlenecking. By using the "what if" scenario, process alternatives can be simulated via the use of simulation tools to reveal potential candidates for the debottlenecking study.

The Cost Benefit Ratio (CBR) is among the criteria that can be used to evaluate the economic performance of debottlenecking alternatives. As the name suggests, CBR is a measure based on the ratio of benefits obtained for a given expansion cost.[9] The first step in CBR analysis is to determine the beneficial elements, disbenefits, and expansion cost for a project. For the case of pharmaceutical process debottlenecking, CBR formulation can be defined as shown in the following equation:



Task	Start Time (h)	End Time (h)
⊟Complete Recipe	0.00	40.21
⊟P-1 in V-101	0.00	2.62
Charge in EWS1	0.00	0.42
HEAT-1	0.33	1.16
Charge in EMUL1	0.42	0.50
Charge in FS1	0.50	0.58
Charge in OIN1	0.58	0.67
AGITATE-1	0.67	1.17
Transfer out to V-103	2.20	2.37
CIP-1	2.53	2.62
⊞P-2 in V-102	1.17	2.70
⊞P-3 in EH-101	1.20	1.70
⊟P-4 in V-103	1.70	30.69
Transfer in from P3	1.70	1.95
Charge in AM	1.95	2.03
Agitate 1	2.03	2.20
Transfer in from P1	2.20	2.37
Transfer in from P2	2.37	2.53
Agitate 2	2.53	2.78
Cooling	2.78	21.78
Charge in Act Ing	21.78	21.87
Agitate 3	21.87	22.03
Transfer out to P5	22.03	30.44
CIP	30.44	30.69
⊞P-5 in FL-101	22.03	30.44
⊞P-6 in BC-101	23.03	30.44
⊞P-7 in BX-101	30.44	36.00
⊞P-8 in GBX-101	36.00	39.70
⊞P-9 in BX-102	39.70	40.21

Figure 2. Operation Gantt Chart for the base case simulation.

$$\text{CBR} = \frac{\begin{matrix}\text{Revenue of} \\ \text{alternative}\end{matrix} - \begin{matrix}\text{Revenue of} \\ \text{current} \\ \text{operation}\end{matrix}}{\begin{matrix}\text{Investment} \\ \text{cost of} \\ \text{alternative}\end{matrix} + \begin{matrix}\text{Operating} \\ \text{cost of} \\ \text{alternative}\end{matrix} - \begin{matrix}\text{Operating} \\ \text{cost of} \\ \text{current} \\ \text{operations}\end{matrix}} \quad (1)$$

Model Development – Antiallergic Cream Production

Figure 1 shows the base case simulation flowsheet for the production of anti-allergic cream modelled in a process simulator.[10] The base case simulation model was developed to reflect the actual operating condition in the existing pharmaceutical manufacturing facility that is operated in batch processing mode. This modelling environment, involves the modelling of a few *operations* that take place sequentially in a single *unit procedure*.[10] For instance, the Jacketed Heater procedure P-1 in the Pre-Mixing section - *Figure 1* was used to model the sequential operations of raw material charges, material heating (for melting purpose), agitation processes, as well as product discharge. All these individual operations took place in the single vessel of V-101. The modelling of these single operations is described next.

In the base case process, there are nine major processing steps in three different sub-sections. This includes raw material melting in the Pre-Mixing Section, deionized (DI) water heating, and material blending in the Main Blending Section, as well as filling, conveying, cartoning, shrink wrapping, and shipment packaging in the Packaging sections. Due to the capacity limitation of the pre-mixing vessel, the raw material is divided into two sub-mix batches in the Pre-Mixing Section. Two batches of Emulsifying Wax (ESW) and Foam Stabilizer (FS) are independently heated in the heating procedures P-1 (carried out in Jacketed Heater V-101) and P-2 (in Jacketed Heater V-102) to approximately 100ºC before the emulsifier (EMUL) and ointment (OIN) are added. The emulsifier and ointment are originally in wax form and need to be melted for uniform mixing. All raw materials are charged at room temperature.

DI water is heated in the electric heater EH-101 (procedure P-3) before being transferred into the Main Blending Tank, V-103 (P-4) in the Main Blending Section. An Antimicrobial Agent (AM) 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 is then transferred into V-103. The mixture of all ingredients in V-103 is blended once more for 15 minutes in order to produce a uniform composition. The mixture is then left in an air-conditioned dispensing room to be naturally cooled to room temperature. This cooling operation took approximately 19 hours to accomplish due to the slow rate of natural cooling. Upon the completion of the cooling operation, the Active Ingredient (AI) of the anti-allergic cream is finally added. The products are once again blended for 15 minutes to obtain uniform composition before the product mixture is sent to the Packaging Section.

Upon the completion of the Main Blending Procedure, the blended product is next transferred to Filler P-5/FL-101 in the Packaging Section where it is filled into the tubes of 15 g each. The existing filling machine is operated at a speed of 30 tubes/min. The tubes are then sent to the cartoning packaging procedure P-7 (using a belt conveyer P-6/BC-101) where the anti-allergic cream in tubes are packed manually by two operators into the tube cartons, each at a speed of 20 cartons/min. Next, 12 cartons of anti-allergic cream are packed into one wrapper in the Shrink Wrapper (P-8/GBX-101) with a speed of five wrappers/min. Finally, six wrappers are packed into each of the pallet boxes in Packing Machine P-9/BX-102 (equivalent to 72 tubes/pallet box) before they are sent to the warehouse. Approximately six sealed pallet boxes are packed per minute by the operator manually.

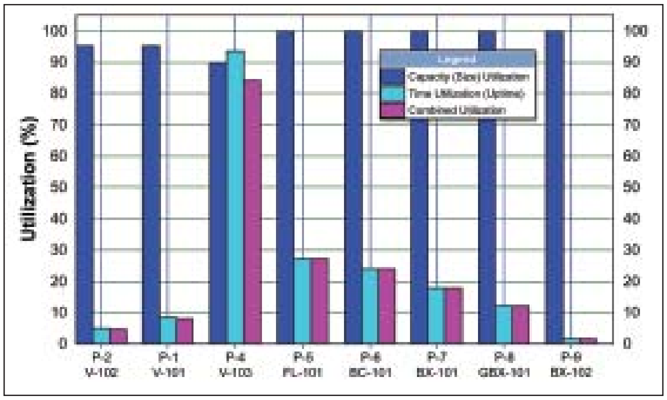


Figure 3. Capacity, time and combined utilization for unit procedures in base case simulation.

As the manufacturing process is carried out in a batch operation mode, efforts have been made to document the scheduling details of each processing step. The Operation Gantt Chart for the complete recipe of a single batch operation is shown in Figure 2. It also should be noted that the process time for certain operations are dependant upon other operations of other procedure (e.g., transfer-out operation in P-4 is set equal to the filling duration of P-5). Hence, the duration of this *slave* operation is set to follow to the duration of the *master* operation using the Master-Slave Relationship function.[10] The customer demand for this anti-allergic cream product is expected to rise another 150% of the current production capacity in upcoming years. However, the process is currently running at its maximum capacity and any attempt to increase production is not possible due to the process bottleneck. This calls for a systematic procedure to analyze the current production facilities and next to debottleneck the process. Apart from debottlenecking the current production, the debottlenecking study also will develop solutions for future expansion.

Bottleneck Identification Strategies

In the current operation, the annual operating time for the anti-allergic cream manufacturing is taken as 2080 hours, which is based on 52 operation weeks, five days a week and eight hours operation per day. From the base case simulation, a complete batch of pharmaceutical cream production is found to have a process batch time of 40.2 hrs and a *minimum*

Economic Parameters	Base Case	Scheme 1	Scheme 2	Scheme 3	Scheme 4	Scheme 5
Batch Production (tubes/batch)	13,333	13,333	13,333	13,333	13,333	13,333
Plant Batch Time (hour)	40.2	41.7	26.2	23.3	27.7	24.8
Minimum Cycle Time (hour)	29.0	21.6	15.0	12.0	9.9	7.6
Number of Batches/year	66	87	121	147	173	215
Annual Production (tube/yr)	880,000	1,160,000	1,613,300	1,960,000	2,306,600	2,866,600
Cost of Investment ($)	-	10,000	255,000	555,000	265,000	565,000
Annual Operating Cost ($)	947,200	1,310,000	1,432,700	1,536,000	2,167,200	2,393,500
Unit Production Cost ($/tube)	2.30	1.13	0.89	0.78	0.94	0.83
Annual Revenue ($)	2,200,000	2,900,000	4,033,000	4,900,000	5,766,700	7,166,700
Gross Margin	57.0	54.9	64.5	68.7	62.7	66.6
Cost Benefit Ratio (CBR)	-	1.88	2.47	2.36	2.40	2.47

Table A. Throughput and economic evaluation of base case study and various debottlenecking schemes.

cycle time of 29 hrs - *Figure 2*. The minimum cycle time of the process is defined as the minimum time possible between the start of two consecutive batches. It is equal to the longest occupation time among all pieces of equipment involved in this process.[10] In the case of anti-allergic cream manufacturing; the minimum cycle time corresponds to the prolonged cooling operation in the Main Blending procedure P-4. With an interval of two hours for tank cleaning between batches, this sets the plant annual production at 66 batches. The throughput of the base case is summarized in Table A (column 2). The simplest option to increase the process throughput by increasing daily operating duration is determined to be uneconomical due to the high operating cost in hiring additional staff. This leads us to explore the use of combined utilization concept as has been discussed earlier.

Figure 3 displays the capacity, time, and combined utilization of all the procedure/equipment pairs in the base case simulation. As shown, the Main Blending Procedure P-4 (V-103) with an equipment capacity utilization of 89.9% and the equipment uptime of 93.6% has a much higher combined utilization percentage of 84.1% as compared to other procedures. The high equipment uptime of this procedure is mainly due to the long cooling operation (19 hours) and Transfer-Out operation (8.4 hours). This also makes P-4/V-103 the scheduling bottleneck of the process, i.e., process with longest operating duration (see Operation Gantt Chart in Figure 2). Note that certain procedures (e.g. Filler P5/FL-101, Belt Conveyer P-6/BC-101, etc.) are not considered as size bottlenecks even though they have 100% size utilization, as the operation speed of this equipment can be adjusted according to the operational needs.[5]

After identifying the Main Blending Procedure P-4 (V-103) as the first process bottlenecking candidate, debottlenecking strategies will next be focused on reducing either the size or time utilization of this procedure/equipment. However, since there are two pre-mixing tanks that serve as the mixture preparation proceeding to P-4/V-103, any attempt of changing a larger Main Blending vessel will lead to the replacement of the two pre-mixing tanks V-101 and V-102. This has been determined by the management team to be an infeasible option at the present moment. Hence, debottlenecking options will only focus on the reduction of equipment uptime of P-4/V-103. This is described in the next section.

Debottlenecking Schemes

After identifying the candidate for process debottlenecking, the feasibility of various debottlenecking schemes were evaluated. Five debottlenecking schemes were analyzed in which all schemes were applied focusing on reducing the equipment uptime of P-4/V-103 as the process time bottleneck.

Alternative Debottlenecking Schemes

Figure 4 shows the simulation flowsheet for debottlenecking Scheme 1. As shown, a new intermediate tank V-104 is installed after the Main Blending vessel. The main rationale underlying this scheme is to reduce the equipment uptime of Main Blending vessel (P-4/V-103), by spending a minimal investment cost of US $10,000 (purchase cost for V-104). By adding the intermediate tank V-104, the two subsequent procedures P-4/V-103 and P-5/FL-101 are disconnected. The Transfer-Out operation in P-4/V-103 is no longer constrained by the slow filling operation in Filler P-5/FL-101. Upon the completion on the blending operations in P-4/V-103, the product mixture is transferred into the newly added V-104 for temporary storage while waiting for the filling operation to complete. The main blending procedure can then be carried out for a subsequent operation. Simulation results showed that the annual production for this scheme has increased to 87 batches due to the reduction of minimum cycle time that limits the number of annual production from 29 hrs (in the base case simulation) to 21.6 hrs (shown in the third column in Table A). This corresponds to an increase of annual production rate of 32%, but is insufficient to fulfill the projected customer demand.

Scheme 2 for process debottlenecking is shown in Figure 5. It focuses on the reduction of cooling operation of P-4/V-103 instead. A multifunctional blending tank with a cooling system (purchase cost of US $255,000) is installed to replace the main blending tank. This reduces the cooling time of the product mixture from the current 19 hours to five hours.

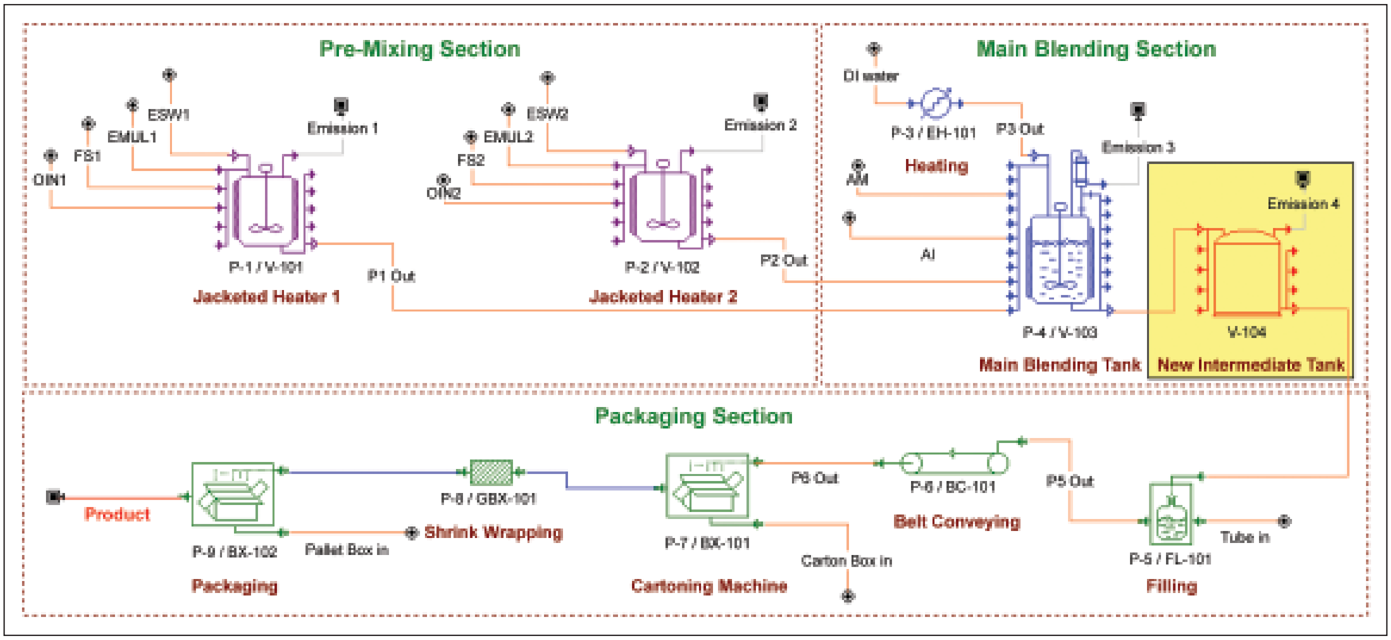


Figure 4. Debottlenecking Scheme 1 with the installation of an intermediate tank.

Chilled water is used as cooling agent to cool the mixture from 85ºC to room temperature. This leads to the reduction of minimum cycle time to 15 hrs. Hence, an increase of 83.3% is achieved for annual production as compared to the base case, i.e., from 66 to 121 batches (fourth column in Table C). From Table B, it is shown that even although P-4/V-103 remains as the overall process bottleneck, its combined utilization value has actually been reduced from 84.2% in the base case simulation to 79.3%, due to the reduction of its uptime. On the other hand, combined utilization of other unit procedures have increased significantly. This leads to an overall increase of process throughput. Further debottlenecking can only be achieved if the long duration of the Transfer-out operation in P-4/V-103 (to filler P-5/FL-101) can be reduced.

Figure 6 shows the simulation flowsheet of Scheme 3 that explores the reduction of P-4/V-103 uptime from a different perspective. As the Transfer-Out duration of P-4/V-103 is dependent upon the filling rate in P-5/FL-10, one alternative to reduce the duration of Transfer-Out operation in P-4/V-103 is to install a high speed filler to shorten the filling duration in P-5/FL-10, and hence the Transfer-out duration in P-4/V-103. As shown in Figure 6, a new filler (50 tubes/min; purchase cost of $300,000) is installed in addition to the new multifunctional blending tank in Scheme 2 to accelerate the filling rate. Simulation results showed that with the reduction of Transfer-out duration in P-4/V-103, combined utilization values of P-4/V-103, P-5/FL-101 and P-6/BC-101 have been reduced slightly, while other unit procedures increase in their combined utilization values - *Table B*. The net result is the reduction of minimum cycle time to 12 hrs and an increase annual production rate of 147 batches, i.e., 122.7% compared to the base case (fifth column in Table A).

Another debottlenecking alternative focusing on reducing the overall uptime of P-4/V-103 is presented in Scheme 4 - *Figure 7*. Instead of installing a new filling machine as in Scheme 3, an intermediate storage tank (V-104; purchase cost of US $10,000) is added in addition to the installation of a new Blending Tank (P-4/V-103). This scheme exhibits the same characteristics as the combination of Scheme 1 and Scheme 2. Simulation results showed that the annual production for this scheme is 173 batches with a minimum cycle time reduced to 9.9 hrs (sixth column in Table A). This corresponds to an increase of annual production rate of 162%, fulfilling the future market demand. It also should be noted

Equipment Tag		Procedure Name	Base Case	Scheme 1	Scheme 2	Scheme 3	Scheme 4	Scheme 5
V-102	P-2	Jacketed Heater 2	4.71	6.19	8.59	10.41	12.26	16.00
V-101	P-1	Jacketed Heater 1	8.04	10.56	14.66	17.76	20.92	27.30
V-103	P-4	Main Blending Tank	84.12	82.30	79.34	77.11	57.27	79.13
FL-101	P-5	Filler	27.13	35.65	49.48	38.81	70.61	56.81
BC-101	P-6	Belt Conveyor	23.90	31.41	43.60	31.68	62.21	46.38
BX-101	P-7	Manual Cartoning	17.93	23.56	32.70	39.60	46.66	57.97
GBX-101	P-8	Shrink Wrapping	11.95	15.70	21.80	26.40	31.10	38.65
BX-102	P-9	Manual Pallet Packaging	1.66	2.18	3.03	3.67	4.32	5.37

Table B. Combined utilization for different debottlenecking schemes.

Raw Material	Symbol	Price ($/kg)	Unit/Batch	Cost/Batch ($)	Annual Cost ($)	% Contribution
Emulsifier	EMUL	15.50	30.00 kg	465.00	30,690.00	11.15
Emulsifying Wax	ESW	5.05	3.60 kg	18.18	1,200.00	0.44
Foam Stable	FS	3.00	14.40 kg	43.20	2,851.00	1.04
Antimicrobial Agent	AM	4.00	0.24 kg	0.96	63.00	0.02
Active Ingredient	AI	650.00	2.00 kg	1,300.00	85,800.00	31.17
Emulsifying Ointment	OIN	15.00	12.00 kg	180.00	11,880.00	4.32
Deionized Water	DI water	0.50	137.76 kg	68.88	4,546.00	1.65
Water	Water	0.03	69.63 kg	2.09	138.00	0.05
Tube	Tube	0.10	13,333.00	1,333.30	88,000.00	31.97
Carton Box	Small box	0.05	13,333.00	666.65	44,000.00	15.98
Pallet Box	Big box	0.50	185.00	92.50	6,110.00	2.22
TOTAL COST				**3,635.44**	**239,939.06**	**100.00**

Table C. Cost of raw material for base case simulation.

that after the installation of intermediate storage tank V-101, filler P-5/FL-101 has became the unit procedure with the highest combined utilization value. As shown in Table B, all unit procedures experienced an increase in their combined utilization values except that of P-4/V103. This is consistent with the finding of Koulouris *et al,*[5] where new bottleneck equipment will emerge after the current bottleneck is overcome. Debottlenecking efforts are stopped at this scheme as the debottlenecking objective is reached, i.e., achieving the 150% increase in production as compared to current production. However, to cater for future expansion plan as requested by the management team, the replacement of a new P-5/FL-101 is studied in the next debottlenecking scheme.

Figure 8 shows the simulation flowsheet for Scheme 5, which includes filler P-5/FL-101 for debottlenecking. With the presence of the additional intermediate tank and the high speed filling machine, the production increases to 215 batches per annum, i.e., an increase of 225% with minimum cycle time reduced to 7.6 hr (seventh column in Table C). The capital investment needed in this scheme is calculated as the summary of individual equipment in the previous schemes, i.e. $565,000.

All the proposed debottlenecking schemes have demonstrated significant improvement on the annual production throughput. This is mainly due to the reduction of minimum cycle time associated with main blending tank procedures. As previously mentioned, Scheme 4 serves as the debottlenecking scheme for current increase of production; while Scheme 5 with the highest process throughput is reserved for future expansion plans.

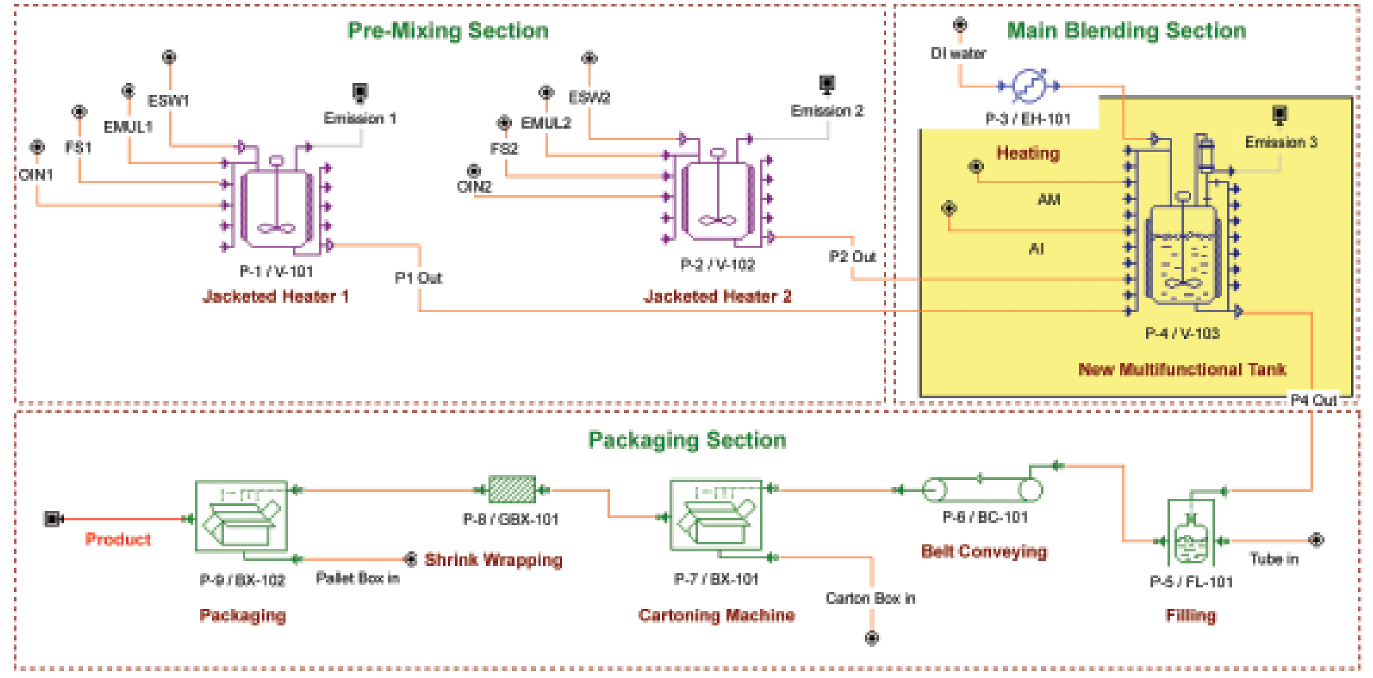


Figure 5. Debottlenecking Scheme 2 with the installation of new multifunctional blending tank.

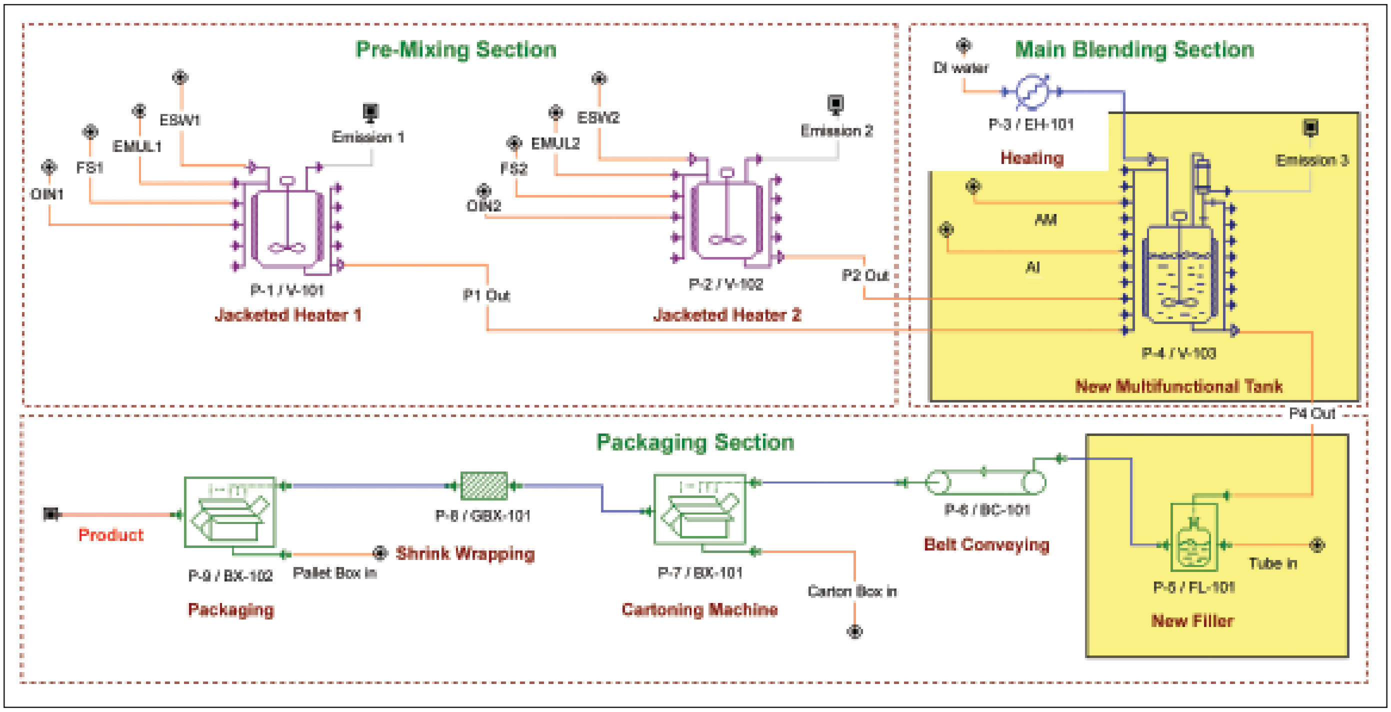


Figure 6. Debottlenecking Scheme 3 with the installation of new multifunctional blending tank and new filler.

Economic Evaluation

Preliminary economic evaluations are next carried out for the base case simulation and each of the debottlenecking schemes. This is done via the economic evaluation function of the simulation software.[10] In order to regenerate a realistic cost estimate, raw material costs and equipment purchase costs are obtained from local industrial suppliers. Table C shows the cost of the raw material for the production of anti-allergic cream and their contribution to the overall production cost in the base case simulation. The active ingredient for the anti-allergic cream and the tube (where 15 g of cream is filled) dominate the raw material cost, each contributing 31% of the overall production cost. Note that the distribution of raw material costs remains the same for all schemes as shown in Table C, only differing by total annual cost for each scheme due to the different annual throughput.

The economic evaluation comparing the various debottlenecking schemes with respect to the base case study is shown in Table A. The Cost Benefit Ratio (CBR) is used as a tool in comparing the alternative schemes. As shown, except for Scheme 1, all other debottlenecking schemes are having similar CBR values with Scheme 2 and Scheme 5

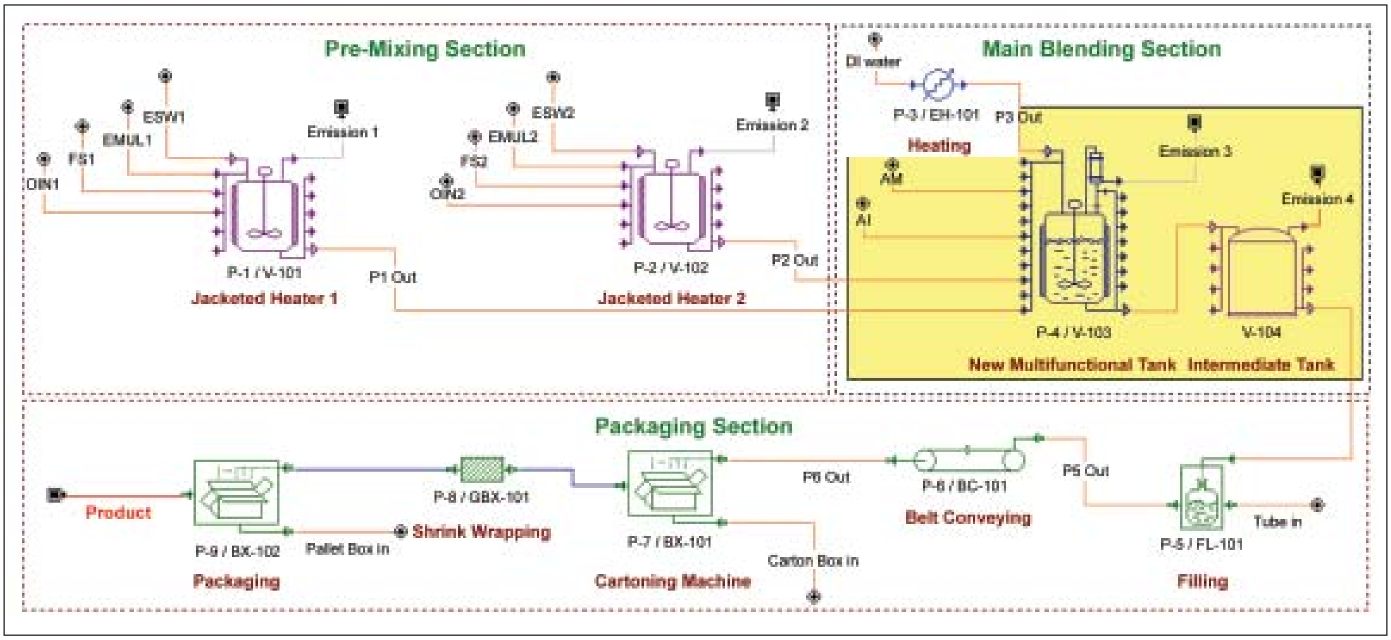


Figure 7. Debottlenecking Scheme 4 with the installation of intermediate tank and new multifunctional blending tank.

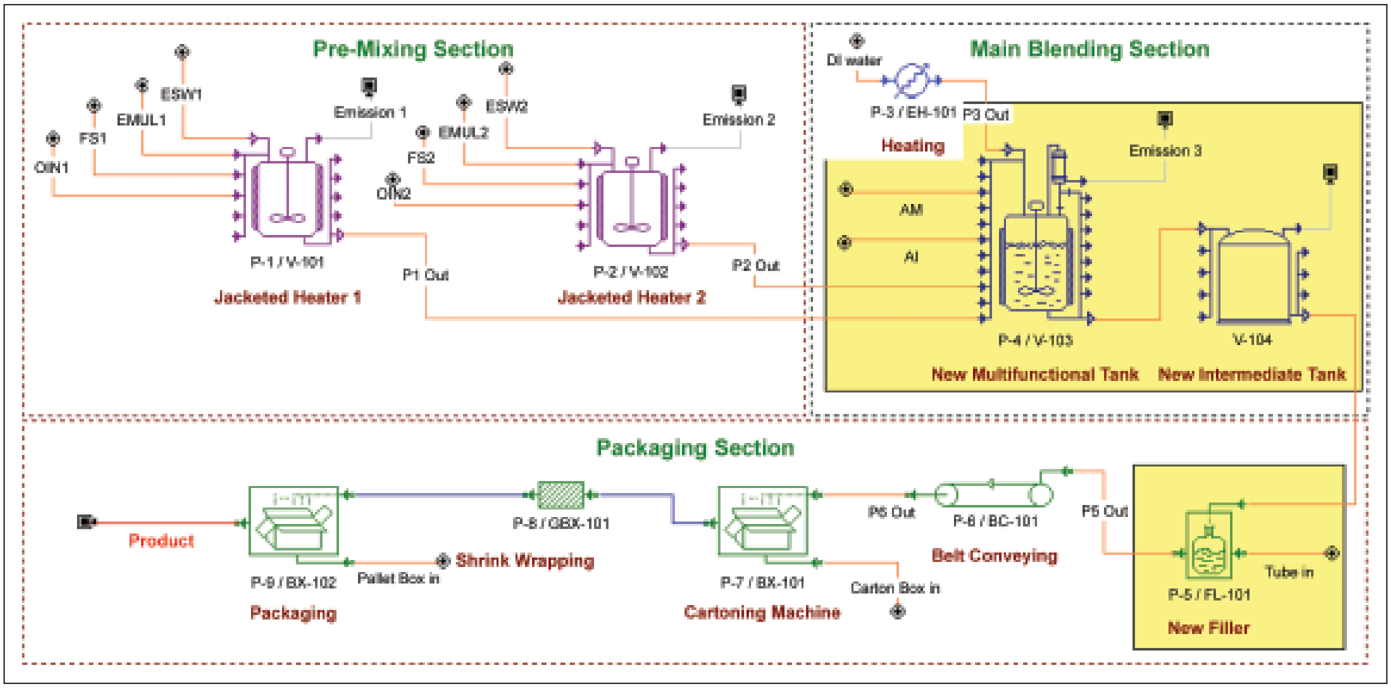


Figure 8. Debottlenecking Scheme 5 for future plant expansion.

having the highest value of 2.47. This indicates that except for Scheme 1 all debottlenecking schemes have equal value for investment.

In the previous debottlenecking section, it is shown that Scheme 4 was selected to be the debottlenecking scheme due to its fulfillment to future customer demand, i.e., by producing more than 150% of the current production. On the other hand, Scheme 5 that has been identified to be the future debottlenecking scheme also shows a promising CBR value of 2.47.

Conclusion

In this work, Computer-Aided Process Design (CAPD) and simulation tools are used in the systematic identification of the process bottleneck and a debottlenecking study. An operational pharmaceutical case study of anti-allergic cream production is used to demonstrate the effectiveness of the tools. The base case and four debottlenecking schemes are simulated using SuperPro Designer. The annual process throughput is increased significantly with the reduction of equipment uptime of the process time bottleneck. The study produced a debottlenecking scheme that achieves the current production needs, with a scheme that will cater for a future expansion plan.

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