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Green process development of herbal and/upstream phytochemical products in drug discovery and development cycle

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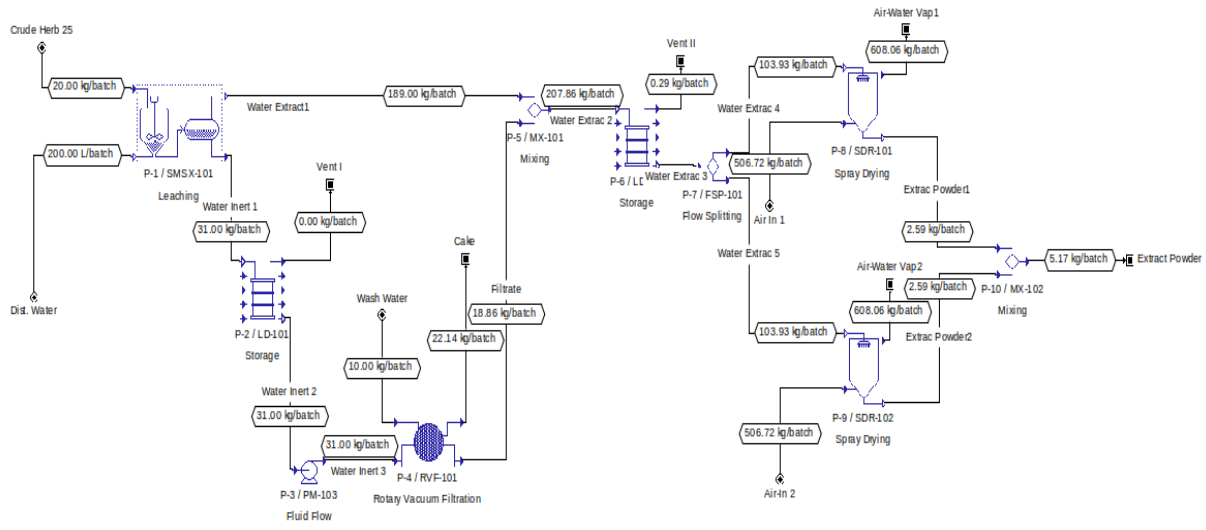
Graphical Abstract



Process Flow Diagram (PFD) of the Base Case Process Model

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Abstract

Herbal, phytochemical, pharmaceutical and related products are produced in batch or/and semi-batch mode. This differs from commodity products that are obtained in large quantities from petroleum, chemical, and petrochemical industries, which operate in continuous mode, as intermediates to other manufacturing firms. Batch and semi-batch processes are always dynamic in nature, and that creates additional challenges in their product and process scheduling, design, and optimization. These processes are best described with batch process simulators that can handle sequencing of events and time-dependency. This study presents the techniques for batch process development, and demonstrates how green process for herbal and/or upstream phytochemical products can be developed through modelling, simulation, and validation before fabrication and commissioning. It examines green process development of a pilot plant for the production of anti-malarial powdered extract from raw Herb 25 (NAFDAC Reg. No: NRN-A7-0155L) as a case study. The process was modelled and simulated with the aid of SuperPro Designer® version 7.0, a batch process simulator and scheduling tool, and validated using existing equipment. It was found that the use of process simulation (PS) and production scheduling tools can facilitate and hasten the green process development for herbal and/or upstream phytochemical products. From the simulation results, the profitability analysis has shown the debottlenecking scheme II process model to have a better return on investment (ROI) of 65.68% and payback time of 1.52 years.

Keywords: Green process development; process synthesis; process scheduling; process design; process optimization; batch process simulator; anti-malarial powdered extracts.

1. Introduction

For almost two decades, Green Chemists, Chemical and Process Engineers have been looking into the practicable ways of implementing the principles of green engineering proposed by Anastas and Zimmerman [1], the Sandestin Declarations [2], and green chemistry proposed by Anastas and Warner [3]. In green process development of herbal and or upstream phytochemical products in drug discovery [4,5] and development cycle [6], Green Chemical and Process Engineers strive hard to avoid the use of toxic substances and the generation of health and environmental hazards throughout the stages of all proposed process and product development life cycles [7]. They have been channelling all their efforts and constraining them toward maximum efficient utilization of harmless substances with the essential materials, while respecting the standard code of ethics for Engineers such as that of the American National Society of Professional Engineers (NSPE), and the general Global Engineering Ethics [7].

Process modelling and simulation is a critical part of process research and development (R&D). It plays an important role in the process synthesis [8], scheduling [9], design [8], optimization [10], operation, and improvement, as well as commercialization of new and existing products. The upstream phytochemical and herbal products are usually produced through batch and semi-continuous mode. This is in contrast to commodity products that are obtained from petroleum, chemical, and petrochemical industries, which deals with large throughputs and employs continuous mode. Batch and semi-

continuous systems are fundamentally recipe-driven processes in their nature and that create additional challenges in their modelling and simulation. Consequently, these processes are best represented by batch process simulators that can handle the allocation of sets of limited resources over time periods to produce one or more products following a batch recipe [10-12].

Computer-aided design (CAD) tools that are utilized in the process simulation of batch and semi-continuous systems could be either based on mathematical software packages (MSP) or process simulators (PS). For instance, MSP such as MATLAB (Mathworks Inc, Massachusetts), MATHCAD (Mathsofts Inc., Cambridge), SPREADSHEET (Microsoft Excel, Microsoft Inc.,), Maple (Maplesoft, Maple Inc., Waterloo), MATHEMATICA can be used to mathematically describe and study the behaviour of the batch or semi-continuous process systems [8,13]. Likewise, these tools have been utilized in the design and optimization of continuous processes of the petroleum, chemical, and petrochemical industries since early 1960s [10-13]. Some of the proven commercial PS for these industries include the following: Aspen Plus® (Aspen Technology, Inc.), Hysys® (Hyprotech, Ltd.), Design II® (WinSim, Inc.), PRO/II® (Simulation Sciences, Inc.), ChemCAD® (Chemstations, Inc.), and Aspen Hysys® (Aspen Technology, Inc.) [11-13]. PS have been designed primarily to model continuous processes and their dynamic behavior for the purposes of process monitoring and control. The first developed batch process simulator was Batches® (Batch Process Technologies, Inc., West Lafayette IN), which was commercialized in the middle of 1980s and later upgraded in 2005. It was employed to model and simulate batch operations using differential equations. In the late 1980s, SuperPro Designer® with its roots as BioPro Designer was initiated at Massachusetts Institute of Technology (MIT) and later became the property of Intelligen Inc., Scotch Plains, NJ in 1991[10]. In the mid and late 1990s, Batch Plus®, which is now renamed Aspen Batch Process Developer® (AspenTech Inc., Burlington, MA) and Batch Design Kit® (Hyprotech, Ltd, Calgary, Alberta) were introduced, respectively [11]. These are recipe-driven simulators that were targeted for batch pharmaceutical processes. SuperPro Designer is a batch process simulator that speeds up modeling, evaluation, optimization, cost analysis, debottlenecking, cycle time reduction, and environmental impact assessment of integrated processes in a wide range of industries [11,14-15]. It was reported that SuperPro Designer had been in used at more than 400 companies and 500 universities around the world, including 18 of the leading 20 pharmaceutical companies and 9 of the top 10 bio-pharmaceutical companies [16]. Recently, the Intelligen Inc. has upgraded the SchedulePro® version 10 to version 11 in December, 2019 (http://www.intelligen.com). The objective of this paper is to describe how green process for herbal and/or upstream phytochemical products can be developed through modeling, simulation, and validation. It examines the green process development of a pilot plant for the production of anti-malarial powdered extracts from raw Herb 25

(NAFDAC Reg. No: NRN-A7-0155L, used anti-malarial drug in the form of tea bags in the Sub Saharan West Africa) as a case study.

2. Materials and methods

In the green process and product development, product was designed based on the active principle of Herb 25 (NAFDAC Reg. No: NRN-A7-0155L) developed by Nuhu. The process synthesis, design, and optimization were carried out through laboratory experimentation, modelling, and simulation using SuperPro Designer® version 7.0, a batch process simulator [17]. In addition, the detailed process equipment design were conducted through a blend of hand computation, design heuristics [11,18-25], and validation of some of the design parameters using existing process equipment. The standard design procedure and detailed steps for the green process development are illustrated in Figures 1 to 4.

2.1. Green process description

The main unit procedures in the product and process design of a pilot plant for the production of anti-malarial powdered extracts from raw Herb 25 are the solid-liquid extraction for the leaching of anti-malarial active ingredients, the filtration operation for the separation of water extract solution from insoluble solid components and the spray drying operation for the separation of water from extracts. Solid-liquid extraction was regarded as the heart of the green process for the production of anti-malarial powdered extracts from raw Herb 25. Three of the 12 principles of green chemistry proposed by Anastas and Warner [3] require prevention of wastes, use of renewable feedstocks, and safer solvents and auxiliaries. Likewise, the second principle of the six principles of the green extraction proposed by Chemat et al. [25] necessitates the use of alternative solvents and mainly water or agro-solvents. Based on these requirements, water was selected over supercritical carbon dioxide, methanol and ethanol as the best green solvent for the extraction of anti-malarial phytochemical compounds. This is because of its unique characteristics such as non-toxicity, non-flammability, odorless, low cost, availability, renewability, and other tunable properties like boiling point, dielectric constant, dipole moment, and Kamlet–Taft solvatochromic parameters [25-30] over all other polar protic, polar aprotic, and non-polar solvents. This research tried to implement most of the 12 principles proposed by Anastas and Zimmerman [1] and the redefined nine principles of green engineering in The Sandestin Declarations [2] in the development.

A batch mode process operation was chosen for the green production of powdered extracts from raw Herb 25. The current process operates at a batch throughput of 20 kg of raw Herb 25, which was supplied by Herbal Point Zaria, Zaria.

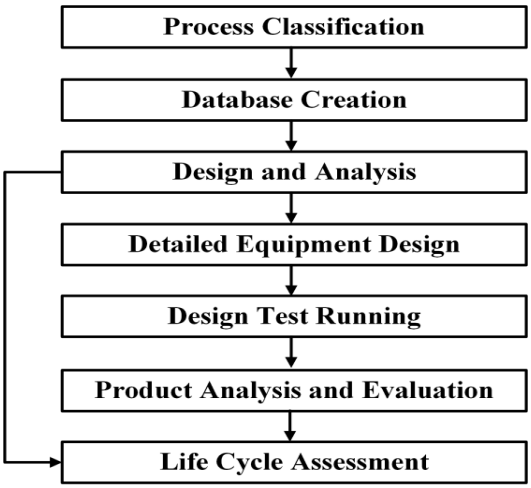

Figure 1. Process design procedure.

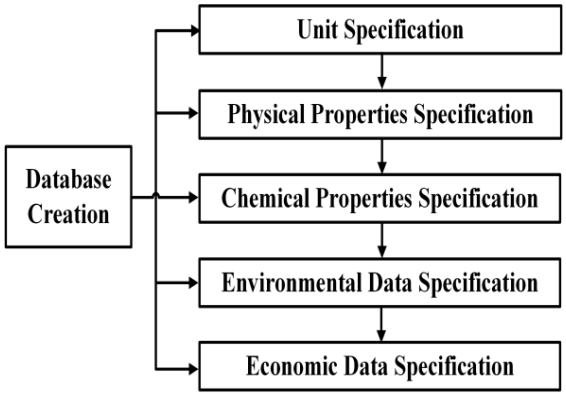

Figure 2. Preliminary database creation step.

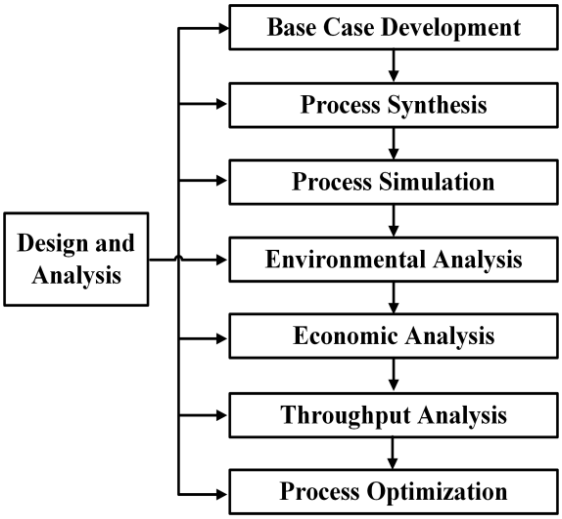

Figure 3. Design and analysis step.

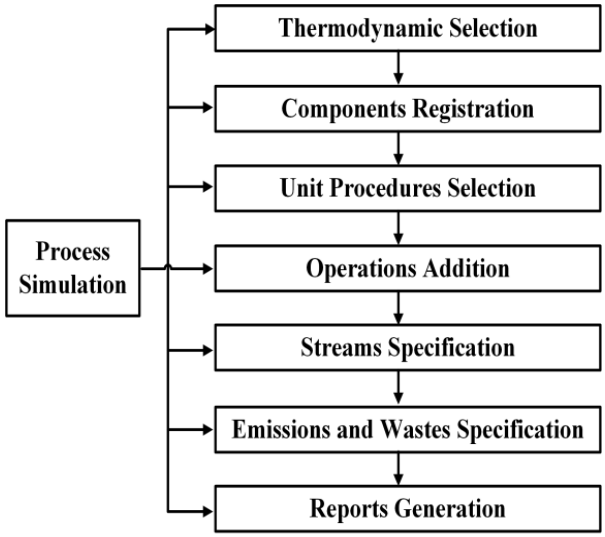

Figure 4. Process simulation step.

In the first unit procedure, the mixer-settler for the leaching operation, raw Herb 25 in powdered form were sent to the mixing vessel so as to leach out the soluble components using distilled water. The solid-liquid ratio was 1 kg to 10 L, at a temperature of 65^{o}C for 15 minutes and the degree of agitation was between 450 rpm and 600 rpm. After completion of the leaching stage, the extracts and the insoluble solids were allowed to settle by gravity in the settler for 30 minutes. The water extract was decanted, mixed in the mixer with the filtrate water extract that was separated from the insoluble solids in the filter and then sent to the storage tank, and later sent for spray drying. Finally, the water extract was sent to the spray dryer operating between air drying temperature of 140^{o}C and 160^{o}C to produce the powdered extracts.

2.2 Database creation

Preliminary database was created for the development of the green process model. The available physical, chemical and economic data of the raw Herb 25, powdered extracts and process were specified in the created simulator database. In the absence of other important user-defined data, laboratory experiments were carried and approximated assumptions were made in the simulator component database.

2.3 Design and analysis

After creation of the database, process design options were synthesized, designed and optimized for the base case process model. A process flow sheet for the base case was formulated as depicted in Figure 5 with the recipe of batch operations in the unit procedures and scheduling basis as shown in Table 1. The material and energy balances for the base case process model were carried. Equipment sizing, costing and profitability analysis for the base case model were carried out. Moreover, the throughput analysis was performed on the base case process model and the process bottleneck was identified according to the following reported techniques [13, 31-33]. Two additional process debottlenecking options (i.e. alternative process schemes) were synthesized, designed, analyzed, and optimized based on the simulation results of the base case process model.

2.4 Detailed equipment design

The detailed process equipment designs were carried out for the chosen debottlenecking alternative process scheme, and their working drawings were drawn using AutoCAD.

2.5 Design test-running

In this stage, some of the process variables and parameters of the designed pilot plant were validated using similar existing equipment under the same specified design conditions to produce powdered extracts prior to fabrication and commissioning of the plant. Practically optimum operating parameters of the pilot design with respect to existing equipment were recorded within the design specifications. The product quality was maintained by increasing the sigma level through identification and monitoring of the root cause of variances in the sequence of operation for the all-unit procedures.

2.6 Product analysis and evaluation

The powdered extracts of Herb 25 were subjected to various analysis and evaluations in order to qualitatively ascertain their constituents present. These include moisture content analysis, melting point determination, thin layer chromatography (TLC), column chromatography (CC), Fourier transform

infrared (FTIR) spectroscopy, microstructure analysis using Scanning electron microscopy (SEM).

3. Results and discussion

3.1 Development of base case process model

Figure 5 shows the process flow diagram (PFD) of the pilot scale for the production of anti-malarial powdered extracts from raw Herb 25, which was the product of process synthesis, scheduling, design, and optimization for the base case process model. Table 1 presents the process scheduling of the base case process model. It was developed to represent the actual operating conditions of the process based on the process description. This involved the modeling of operations that take place sequentially in each unit procedure. For instance, vessel procedure P-1 in Figure 5 was used to model the leaching process that consisted of sequential operations of transferring in 200L of distilled water, heating the distilled water to a temperature of 65^{o}C, charging 20 kg powder of raw Herb 25 into the mixing vessel (i.e. leaching tank), agitating the resulting mixture between 450rpm and 600 rpm, leaching out the active ingredients for 15 minutes. It was also used to allow the inert solids to settle from the water extract in the settler for 30 minutes, discharge the product discharge, and as well as its cleaning in place (CIP) for the preparation of next leaching process cycle. All of these individual operations took place in the vessel of SMSX-101. The trends for modeling the unit procedures were similar but each unit procedure had its own specific sequence of operations except in the case of (P-8/SDR-101) and (P-9/SDR-102) where their procedures were identical. The water extract was decanted from the settler and then sent to the storage tank P-6 (in LD-102) via mixer P-5 (in MX-101) where it mixed with the separated water extract filtrate from insoluble solids in the filtration procedure P-4 (RVF-101). The stored water extract mixture was split into two equal parts in the flow splitter procedure P-7 (FPS-101) and then sent to the twin spray drying procedure (P-8/SDR-101) and (P-9/SDR-102) of equal capacity at a flow rate of 0.01923 L/min. Ambient air was heated at a temperature between 140^{o}C and 160^{o}C before entering the drying chambers of SDR-101 and SDR-102 as the drying medium. Hot air and evaporated water vapor were emitted from the top stream of SDR-101 and SDR-102 at temperature between 80^{o}C and 100 ^{o}C while Herb 25 powdered extract at the bottom stream at temperature of 60^{o}C.

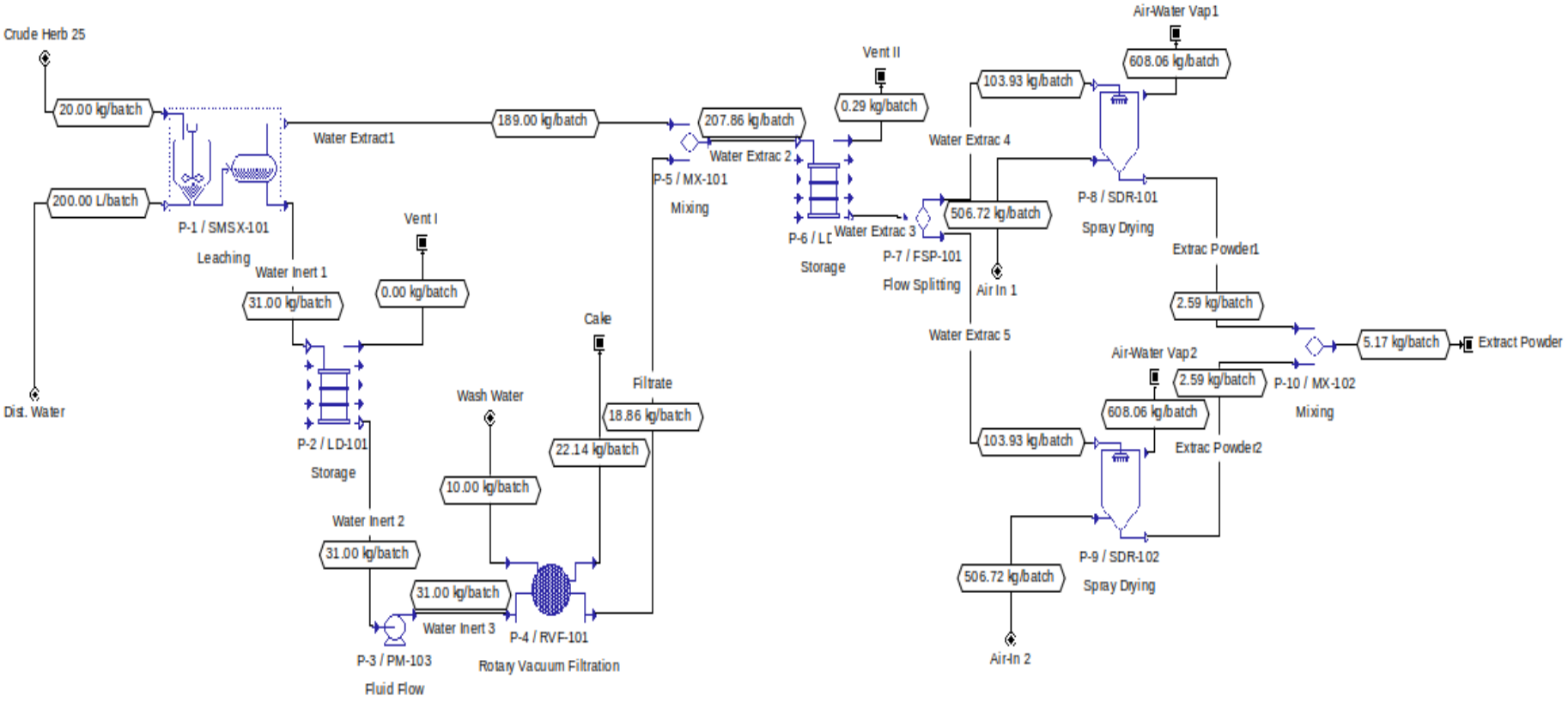

Figure 5. Process flow diagram (PFD) for base case process model.

Table 1. Process scheduling for the base case model.

Procedure	Operation	Setup Time (h)	Process Time (h)	End Time (h)	Start Time (h)
P-1 in SMSX 101	Transfer In-1 Dist. H_2O	-	0.083	0.083	beginning of batch
	Heat-1	-	0.083	0.167	after Transfer In-1 Dist. H_2O
	Charge Raw Herb 25	-	0.083	0.25	after Heat-1
	Agitate-1	-	0.25	0.5	start with Charge raw Herb 25
	Leach-1	-	0.75	1.25	starts with Agitate-1
	Transfer Out-1	-	0.167	1.25	after Leach-1
	Cip-1	-	0.083	1.25	after Transfer Out-1
	Transfer In-1	-	0.167	1.25	after Leach-1
	Store-1	-	0.167	1.25	starts with Transfer In-1 in P-2
P-2 in LD-101	Cool-1	-	0.167	1.25	starts with Store-1
	Transfer Out-1	-	0.167	1.17	after Cool-1
	Evacuate-1	-	0.083	1.25	after Transfer Out-1
P-3 in PM-103	Pump-1	0.083	0.167	1.25	starts with Transfer Out-1in P-2
P-4 in RVF-101	Filter-1	0.25	0.833	2.08	starts with Transfer Out-1 in P-2
P-5 in MX-101	Mix-1	-	0.167	2.25	after Filter-1
	Transfer In-1	-	0.167	2.25	starts with Mix-1in P-5
	Store-1	-	0.167	2.25	starts with Transfer In-1 in P-6
	Cool-1	-	0.167	2.5	starts with Store-1
	Transfer-Out-1	-	0.167	2.67	after Cool-1
P-6 in LD-102	Evacuate-1	-	0.083	2.75	after Transfer Out-1
P-7 in FSP-101	Split-1	-	90	92.67	starts with Transfer In-1 in P-6
	Dry-1	0.25	90	92.92	after Split-1 in P-7
P-8 in SDR-101	CIP-1	-	0.083	93	after Dry-1
	Dry-1	0.25	90	92.92	after Split-1 in P-7
P-9 in SDR-102	CIP-1	-	0.083	93	after Dry-1
P-10 in MX-102	Mix-1	1	90	92.67	after Dry-1

3.1.1 Throughput analysis for the base case process model

Based on the annual operating time of 7920 hrs and the specification of scheduling details of each processing step in the unit procedures, the minimum cycle time and number of batches of the annual production for the base case process model were found to be 90.08 hrs and 85 batches respectively as shown in Table 1. This corresponds to 382.50 kg of Herb 25 powdered extract produced per annum. However, in the long run, this production rate will not be sufficient to fulfill the market needs as Herb 25 powder extract demand is predicted to exceed more than 700% of the current production rate. On the other hand, preliminary economic analysis conducted on the base case process model revealed that the current `production scheme has relatively high capital (assuming that all process equipment were newly purchased based on the equipment price reported by SuperPro Designer® [11], and operating cost as compared to its total annual revenue. Reasonable values could not be obtained in gross margin, return on investment (ROI), payback time and net present value (NPV) of the model. Therefore, there is need to improve the economic performance of the production scheme for a more feasible profitable production.

3.1.2 *Identification of process bottleneck from the base case process model*

Figure 6 depicts the throughput analysis based on size, time and combined utilization for process bottleneck identification of the base case process model. The process bottleneck that limits the present production must be identified so as to improve the process throughput. The processing step with the highest combined utilization was recognized as the process bottleneck. The spray drying identical twin procedures (P-8/SDR-101) and (P-9/SDR-102) were found to be the process bottlenecks due to their highest combined utilization. The capacity utilization of these procedures have reached up to 97.05% (due to the limitation of their feed flow rate of 0.01923 L/min); while their equipment uptime are relatively high (drying operation duration of 90.08 hours) as shown in Figure 6. Thus, P-8 and P-9 were considered to be the process scheduling bottlenecks which limit the annual production to only 85 batches. Therefore, debottlenecking strategies were focused on the minimization of the spray drying operation time in order to increase the number of batches and in turn improve the annual production.

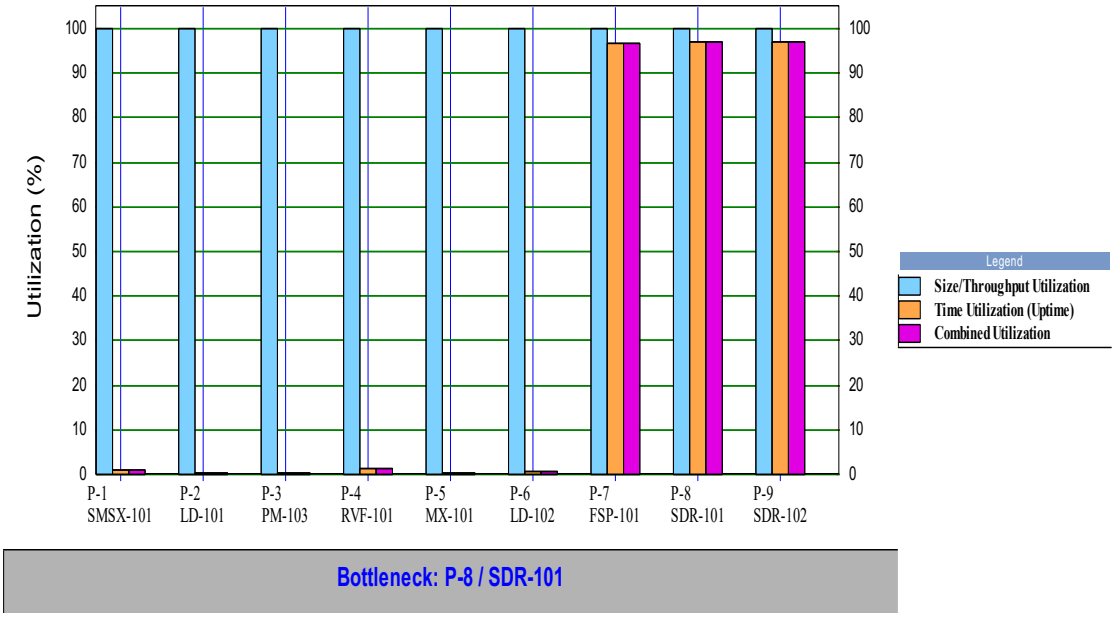

Figure 6. Throughput analysis for bottleneck identification.

3.1.3 *Process improvement through debottlenecking strategies*

The outcome of base case process simulation indicated that the current production plan of Herb 25 powdered extracts is economically not profitable due to the low revenue generated by the low annual production. However, attempts to improve the production rate were constrained by the process scheduling bottleneck, the spray drying operation. In an effort to get rid of the process bottleneck, two alternative debottlenecking process schemes were synthesized, designed, analyzed, and optimized based on the simulation results of the base case process model. These options were considered in order to examine their possibility for improving the annual plant throughput. Likewise, the economic

evaluation was carried out based on the same economic factors for evaluating all process design schemes so as to identify the more feasible and economically manufacturing option.

3.1.4 Process options based on debottlenecking suggested schemes

It can be seen as shown in Figure 7 that Scheme I process model adds a new unit procedure, single effect (P-7/EV-101) to concentrate the water extract prior to the spray drying operation. That led to the reduction of high volume of water associated with Herb 25 extract, and consequently significant reduction in the minimum cycle time from 90.08 hours to 12.33 hours due to addition and subtraction of some unit procedures. Whereas Scheme II process model as shown in Figure 8 replaces rotary vacuum filtration procedure RVF-101 in P-4 with plate and frame filtration procedure PFF-101 and combines the strategies in the previous scheme in further concentrating the water extracts by evaporation prior to spray drying. However, single effect procedure EV-101 in P-7 was replaced with thin film evaporator TFE-101. That led to further reduction in the minimum cycle time from 12.33 hours to 8.00 hours due to substitution of some unit procedures. It can also be observed from Table 2 that all of the proposed debottlenecking schemes demonstrate significant improvement on the annual throughput. This is mainly due to the reduction of minimum cycle time as a result of decrease in the process time of the spray drying procedure due to addition, subtraction and substitution of some unit procedures. Finally, Scheme II debottlenecking process model appears to have the highest annual process throughput with highest economic viability prospects, hence it was found to be the debottlenecking strategy and was chosen as the most promising processing route and its detailed process equipment designs were carried out with their working drawings with AutoCAD. These results are not presented here because of the limited space but can be found in Isah [5].

3.2 Design test-running for some of the process variables and parameters

Three batches namely: Batch A, Batch B and Batch C were test run throughout this stage except in the case of spray drying procedure where it involved several batches. Existing equipment were used but operated under equivalent design conditions for the validation exercise. The results are presented in Table 3. In the leaching procedure, it was observed that there is a clear linear relationship between the degree of agitation and extract yield when other design variables were kept constant. The filtration operation was done manually due to the absence of plate and frame filter press. In the evaporation operation, a climbing film tubular evaporator was used for concentrating Herb 25 water extracts. It was observed that the operation under vacuum was only possible between 0.25 – 0.3 bar and was very slow.

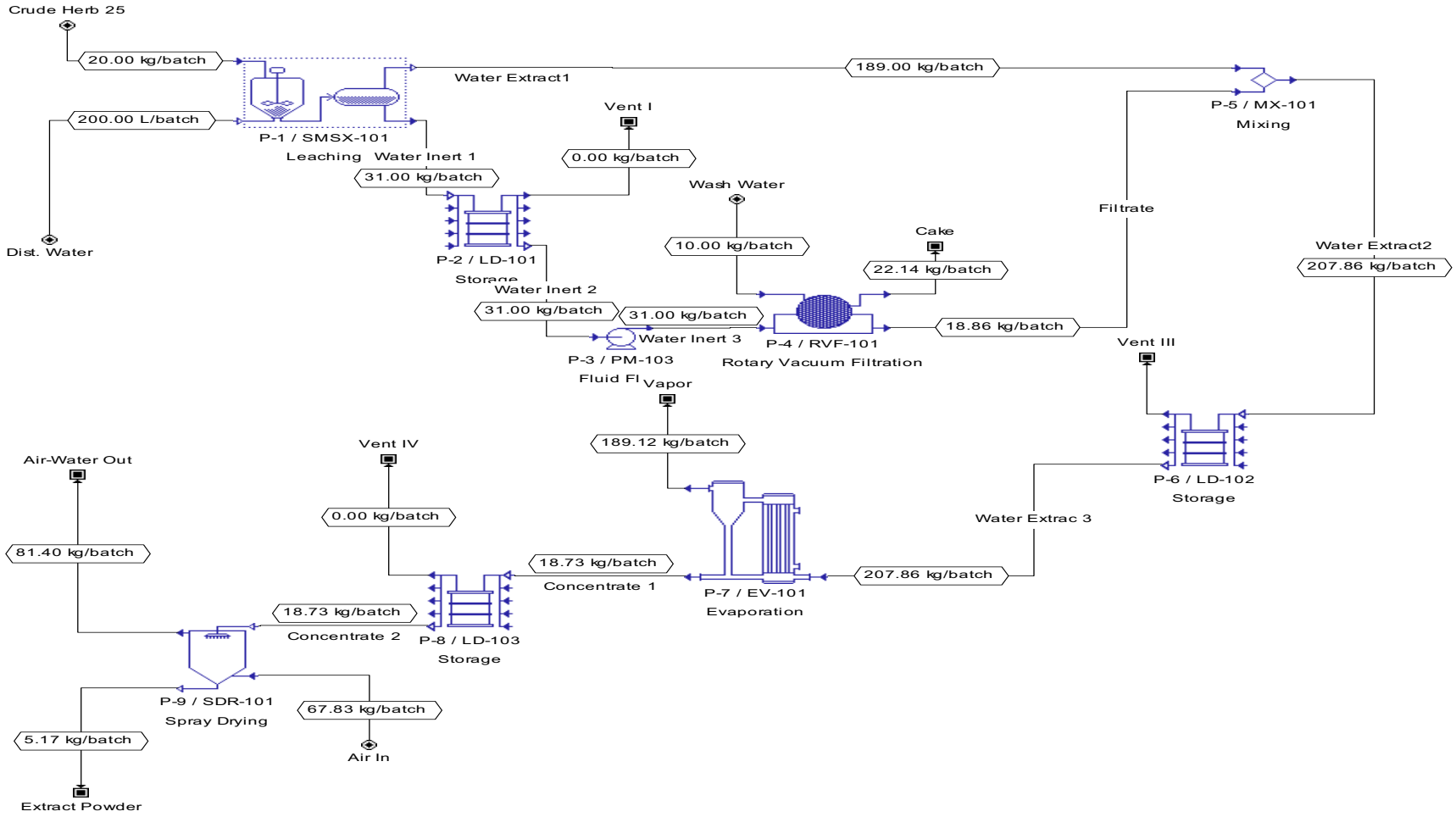

Figure 7. Process flow diagram (PFD) for scheme I process model.

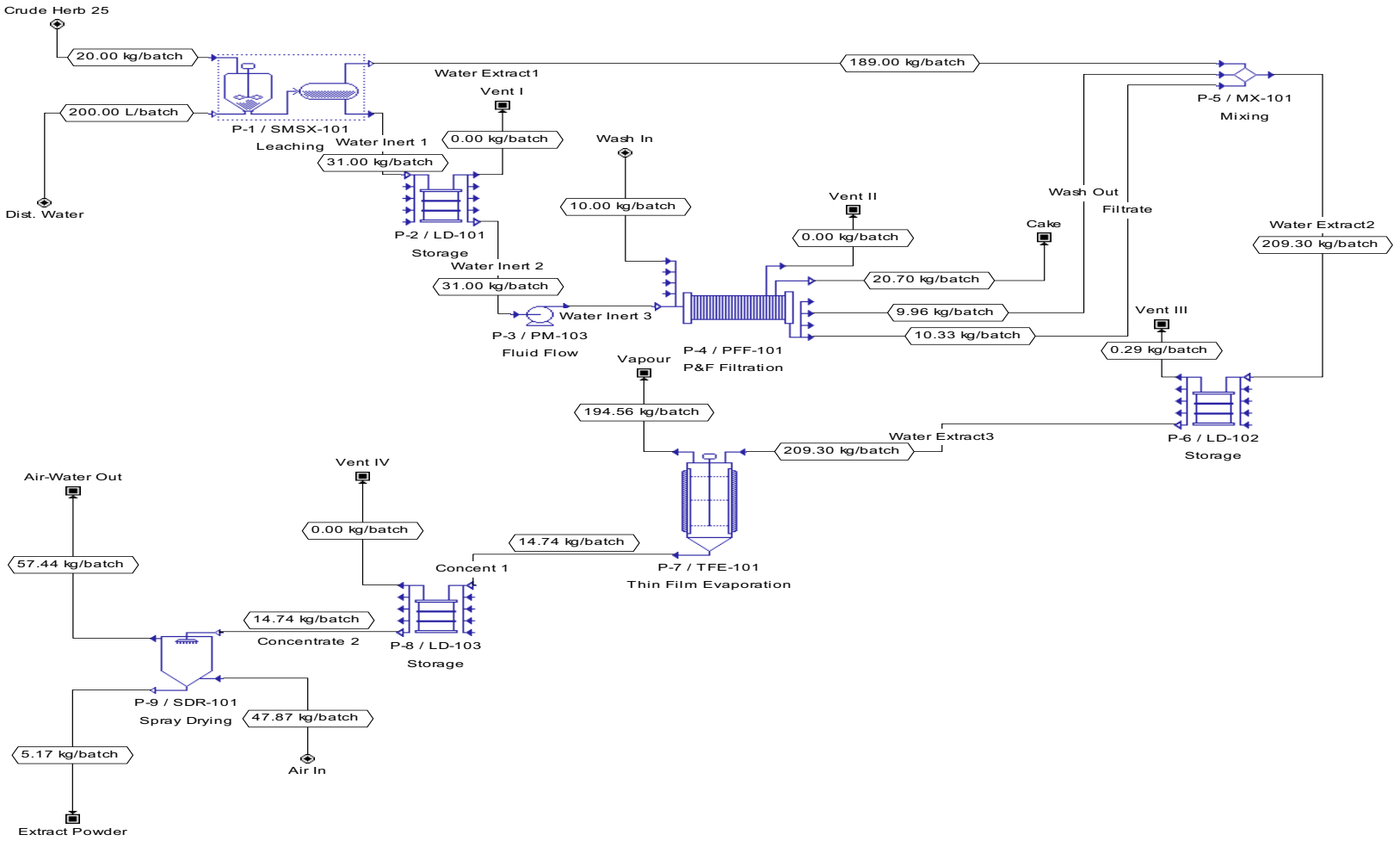

Figure 8. Process flow diagram (PFD) for scheme II process model.

Table 2. Comparative analysis of the base case, schemes I and II process models.

Process Parameters	Base Case	Scheme 1	Scheme II
Throughput			
Product Yield (%)	22.5	22.5	22.5
Recipe Batch Time (hr)	93.00	16.00	12.78
Min. Recipe Cycle Time (hr)	93.08	12.33	8.79
Number of Batches per Year	85	495	619
Batch Throughput (kgMP)	4.50	4.50	4.50
Annual Throughput (kgMP)	382.50	2, 227.50	2, 785.50
Economics			
Total Capital Investment ($)	110, 000.00	116, 000.00	121, 000.00
Operating Costs ($)	839, 000.00	1,013, 000.00	1,218, 000.00
Unit Production Cost($)/kgMP	2, 193.03	454.91	437.09
Total Revenues ($/yr)	185, 000.00	1,073, 000.00	1, 342, 000.00
Gross Margin (%)	-353.99	5.60	9.29
ROI (%)	-590.87	35.63	65.68
Payback Time (yrs)	-1.00	2.81	1.52
NPV (at 7.0% Interest)	-5, 082,000.00	140, 000.00	374, 000.00

Table 3. Test-run of some of the design process variables and parameters.

Equipment	Operating Conditions	Green Product Yield
S-L Extractor (Leaching Tank)	Temperature: 65 °C Solid-liquid ratio: 1:10 Degree of agitation: (450-600) rpm Time for leaching: 15 min	Extract yield: (22.5-23.0)%
Evaporator (Climbing Film)	Column temperature: (65-69.10) °C Column pressure: (0.25-0.3) bar Feed temperature (28-30) °C Steam pressure: (5.5-8) bar Feed concentration: (0.022-0.0225) g/cm^3	Concentrate: (0.030-0.035) g/cm^3
Dryer (Spray Dryer)	Inlet air temperature: (27-30) °C Heated air temperature: (140-200) °C Compressed air pressure: (0.5-0.6) bar Feed temperature (28-30) °C Feed pump pressure: (0.18-0.20) bar Inlet fan speed : (38.60-51.99) km/hr Exhaust temperature: (69.0-98.5) °C Chamber pressure: -(0.14- 0.71) mbar Cyclone pressure: (5.1-6.3) mbar Percentage relative humidity: (2.4-15.0)	Powdered extract moisture content: (15.95-17.52) % dry basis

However, if thin film plate evaporator is used as specified in the design, the evaporation rate can be improved. In drying operation, a tall form spray dryer was used to get the powdered extracts. The most critical parameter of all parameters in spray drying operation is the final percentage relative humidity of the products. It is a function of several variables that can give valuable information about the behaviour of the dryer. These variables include hot air temperature, both inlet and exhaust fan controllers, feed flow rate, feed pump pressure, compressed air pressure, nozzle position, etc. During operation, it was observed that the condition where drying was taking place was when the percentage relative humidity was between 2% and 13%. It was also found that drying was very slowly between 2% and 5%; drying was requiring sufficient air flow between 5% and 10% to ensure that the powdered extract was not fully dried but relatively faster and can handle higher throughput than the region between 2% and 5%; and most efficient region of full drying was between 10% and 13% that can handle the highest throughput.

3.3 Product analysis and evaluation

Figures 9 and 10 display the final green products obtained during the validation exercise of the process variables, and design parameters using existing equipment. The powdered extracts obtained were analyzed to ascertain the product quality. These analyses included the moisture content and melting point determinations, preliminary phytochemical analysis, and Fourier Transforms Infrared (FT-IR) spectroscopy.

Figure 9. Green products of Herb 25 powdered extracts obtained at different operating conditions.

Besides, the thin layer chromatography (TLC), column (CC) chromatography and scanning electron microscopy (SEM) were performed. Some of the results are presented in Figure 11 and Tables 4 to 6. Figure 11 (a) and (b) exhibit the detailed microstructure of the Herb 25 anti-malarial powdered extracts obtained at different air-drying temperatures using JOEL JSM-5900LV SEM. The

effect of air-drying temperature on the resulting structure of the powdered extract can be observed from the Figure 11 (a) and (b).

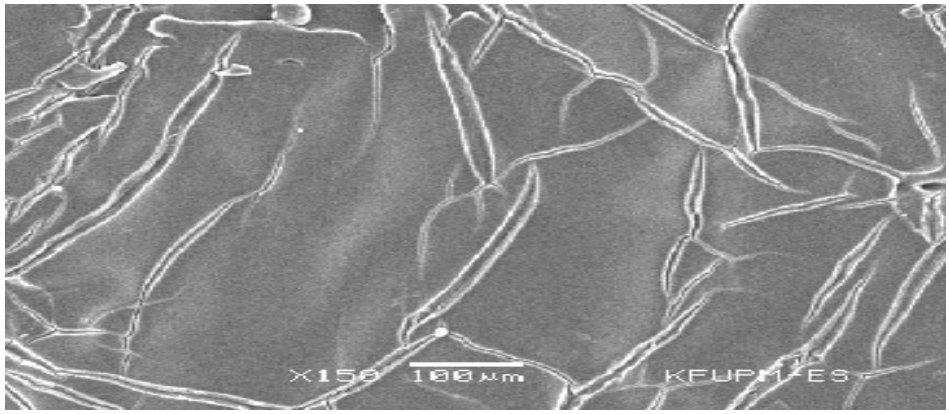

Figure 10 (a). Scanning electron microscopy (SEM) for green product A1 of Herb 25 powdered extracts obtained at air drying temperature T_g=190°C.

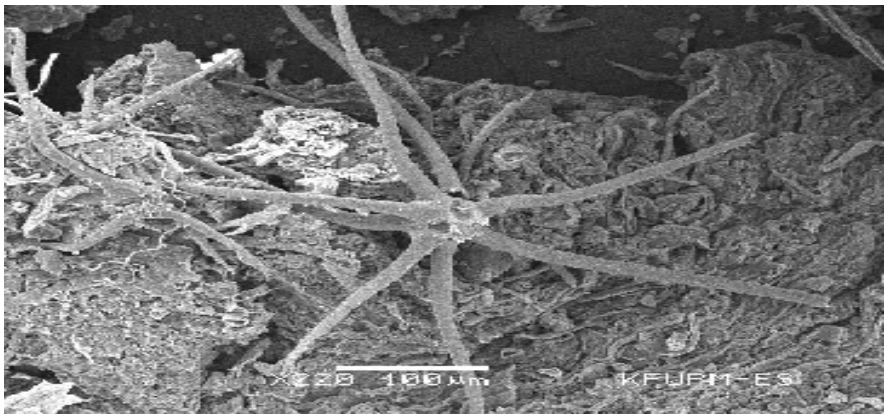

Figure 10 (b). Scanning electron microscopy (SEM) for green product B2 of Herb 25 powdered extracts obtained at air drying temperature T_g=150°C.

Table 4. Melting point and moisture content determinations for green product of Herb 25 powdered extracts, by-product and crude Herb 25 raw material.

Green Product	Moisture (% Dry Basis)	Melting Point (°C)
Product A_1 @ RH: 10.6 %	15.96	243.8
Product B_1@ RH: 5.2 %	17.01	221.3
Product C_3 @ RH: 3.6 %	17.52	216.8
Byproduct inert solids	-	271.3
Crude Herb 25 raw material	-	263.8

Rh-*Relative humidity*

From the moisture content analysis and melting point determination as shown in Tables 3, it can be observed that the moisture content of the green product of Herb 25 powdered extracts lie between 15.96% and 17.52% which does not exceed the design specification of 20% dry basis moisture content. Moreover, it can be seen that melting point temperature increases with decrease in moisture content of powdered extracts. The byproduct inert solids was found to have the highest melting point of 271.63°C, more than the products of powdered extracts ranging from 216°C to 243°C and initial raw material, crude Herb 25 of 263°C. It can be seen from the results of preliminary phytochemical analysis for the green product of Herb 25 powdered extracts as shown in Tables 5 contained a lot of phytochemical active components. These include both primary and secondary metabolites such carbohydrates, free reducing sugars, ketoses, pentoses, deoxy-sugars, steroidal rings, saponins, flavonoids, tannins and alkaloids contents.

Table 4. Preliminary phytochemical analysis for green product of Herb 25 powdered extracts.

Green Products of Herb 25 Powdered Extract Constituents	**Test**	**Inference**
Carbohydrates	Molisch's test	+ ve
Free reducing sugars	Fehling's test	+ ve
Ketoses	Selivanoff's test	+ ve
Pentoses	HCl + Phloroglucinol test	+ ve
Glycosides	General test	- ve
	Fehling's test	- ve
	$FeCl_3$ test	- ve
Anthraquinones	Borntrager's test	- ve
	Modified test	- ve
Cardiac glycosides	Kella-Killiani's test	+ ve
	Salkowsk's test	+ve
Saponins	Honey comb test	+ ve
Flavonoids	NaOH tests	+ve
Tannins	Lead sub-acetate	+ ve
	$FeCl_3$ test	+ ve
Alkaloids	Meyer's test	- ve
	Dragendoff's test	+ ve
	Wagner's test	+ ve

Thus, these might be responsible for anti-malarial activity of Herb 25. It can be observed from Table 6 that the spectral data for three different batches of products of powdered extracts look very much alike even though there are some slight discrepancies in their peak positions. That might be due to some variations in their operating parameters.

Table 4. FTIR spectral data interpretation for the green product of Herb 25 powdered extracts.

Peaks	Product Position Range (wave number cm^{-1})	Reported Peak Position (wave number cm^{-1})	Assignment
1	3366.34-3375.25	3200-3400 3300-3500	-OH stretching, high concentrations alcohols, phenols C-H bending stretching
2	2930.84-2931.51	2967-2877 2960-2870	Aliphatic C-H stretching Methyl specific type of medium to strong bond
3	2364.89-2371.94	2360.24	C-C or C-N triple bond butyramide
4	1604.90-1605.41	1600-1625 1550-1610 1560-1640 1600-1700	Dienes specific type of strong bond of aromatic ring or conjugated C-C N-H or C-N bending primary amines COO stretching of carboxylate amino acids zwitterions C=O stretching peptide bond
5	1408.96-1411.00	1395-1430	C-H bending of methyl and tert-butyl
6	1063.55-1068.23	1020-1250 1000-1250 1050	Primary aliphatic amines CO stretching indicated by alcohol OH group
7	615.12-616.28	540-760	Chloroalkanes

3.4 Impact of green product and process development

The main drivers for the green product and process development are the socio-economic and environmental responsibilities to avoid the use and generation of toxic and hazardous substances on the ecosystems. The replacement of volatile organic and other carcinogenic solvents with green solvents such as water for the extraction of active ingredients can solve the problems of human toxicity or carcinogenicity, lower aquatic and terrestrial pollutions. This can also result in the improvements of environment, air, and water qualities. Moreover, the dangers of global warming, ozone depletion, photochemical smog formation, increased carbon footprint, and habitat destruction can be reduced. On the other hand, this kind of business venture can create more employments; economically reduce the capital expenditure and variable costs of the process. It can also meet up with customers' need for qualitative and safe phytochemical products over synthetic counterparts at lower prices.

Conclusions

A green process of a pilot scale production with a capacity to produce 4.50 kg per batch of anti-malarial powdered extracts from 20 kg per batch of raw Herb 25 (NAFDAC Reg. No: NRN-A7-0155L) was successfully developed through a blend of hand computation, design heuristics, laboratory experimentation, modelling, simulation, and validation. It was found that the use of PS and production scheduling tools can facilitate and hasten the green process development for herbal and/or upstream phytochemical products. From the simulation results, the profitability analysis has shown the debottlenecking scheme II process model to have a better return on investment (ROI) of 65.68% and payback time of 1.52 years. Thus, this would be a lucrative business.

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Conflict of interest

The authors declare that there is no known conflict of interest in this research paper.

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