Letter of Transmittal

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Dear Dr. Alex Marchut, Professor Bruce Vrana, and Dr. Miriam Wattenbarger,

The design report consists of both the batch and hybrid processes to manufacture a small molecule drug product formulation called Albatol at low and high demands ranging from 160 million to 1.6 billion tablets per year. Each unit operation including the blending, granulating, drying, milling, press, and coating process were evaluated in regards to its material balances, energy balances, utility requirements, and purchase costs. The estimated cost of the manufacturing facility with the net present value (NPV), the return of investment (ROI), the internal rate of return (IRR) of the plant based on the free raw materials with the selling price of $0.03 per tablet were calculated at low and high demand for both processes.

For a cost of conversion of three cents per tablet with the low demand of 160 million tablets per year, the hybrid process had an IRR of 8.3% and an ROI of 3.11%, while the batch process had an IRR of 3.93% and an ROI of 0.83%. At a high demand of 1.6 billion tablets per year, the hybrid process had an IRR of 108% and an ROI of 146%, while the batch process had an IRR of 97.0% and an ROI of 127%. The economic analysis showcases that the hybrid process is not only more efficient but also more profitable in comparison to the batch process. A sensitivity analysis was performed with the selling price ranging from $0.01 to $0.05 per tablet for the low demand, high demand, and at 500 million tablets per year. Decreasing and increasing the selling price only emphasizes that the hybrid process is always more profitable than the batch process. Thus, it is recommended to use a hybrid process when producing Albatol tablets.

Best regards,

Yanapong Chaisithikarnkha	Simon Oros	Ethan Spellmeyer	Sophia Tran

Drug Product Production for a Highly Variable Supply Chain

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April 18, 2023

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Section 1: Abstract

Efficient mass production of drug products is crucial for providing innovative treatments for reducing blood pressure. Batch production has traditionally been the preferred method in the pharmaceutical industry, but hybrid manufacturing offers economic advantages. This project presents a comprehensive economic evaluation of batch and hybrid manufacturing of a high-volume small molecule drug product called Albatol. The production facility was designed from the ground up, considering both low and high demands ranging from 160 million to 1.6 billion tablets per year. The production process was evaluated at the unit-operation level, including granulation, drying, milling, blending, compression, and coating. The estimated cost of the manufacturing facility, including the net present value (NPV), the return of investment (ROI), and the internal rate of return (IRR) of the plant, was calculated based on free raw materials with a selling price of $0.03 per tablet. The analysis revealed that hybrid manufacturing is more profitable than batch production. For a cost of conversion of three cents per tablet with the low demand of 160 million tablets per year, the hybrid process had an IRR of 8.3% and an ROI of 3.11%, while the batch process had an IRR of 3.93% and an ROI of 0.83%. At a high demand of 1.6 billion tablets per year, the hybrid process had an IRR of 108% and an ROI of 146%, while the batch process had an IRR of 97.0% and an ROI of 127%. The results suggest that hybrid manufacturing is a more profitable and viable option for producing Albatol at a large scale.

Disciplines
Biochemical and Biomolecular Engineering | Chemical Engineering | Engineering

Section 2: Introduction and Objective–Time Chart

Section 2.1 Project Background

Albatol is an oral solid drug product approved by the The United States Food and Drug Administration used to treat high blood pressure with minimal side effects. Given that there are other pharmaceutical companies already in the market manufacturing similar drug treatments, it is difficult to predict the forecasted demand for Albatol. The general estimated demand ranges from the low end of 160 million to a high end of 1.6 billion tablets per year. These tablets are 100 mg each, meaning that the company must build a tableting plant capable of producing anywhere between 16,000 to 160,000 kg of Albatol per year. The current economic environment allows the plant to earn $0.03/tablet produced.

The final composition of the drug product consists of 10% active pharmaceutical ingredient (API), 61% lactose, 20% Avicel, 3% coating solution, 3% PVP-K90 binder, 2% water, and 1% magnesium stearate. The active pharmaceutical ingredient (API) is the component within the tablet that is responsible for the desired therapeutic effect from the product. The API is combined with other supported excipients that aids the drug production process. Lactose is a common diluent and serves as a filler with excellent compressibility. Avicel-101 is a brand of microcrystalline cellulose that promotes efficient dry blending of ingredients. It has great compressibility properties that lead to tablets with high hardness and low friability [7]. However, Avicel loses some of its compressibility upon prolonged exposure to water during wet granulation, while lactose does not. Additionally, pure lactose is more brittle while Avicel exhibits plastic deformation [18]. As these examples show, both of these excipients have “weaknesses” that are covered by the other’s “strengths”. Using a combination of the two fillers

creates a more ideal filler material that exhibits the best properties, and this practice is fairly standard across the pharmaceutical industry. PVP-K90 is a water-soluble polymer with strong stabilizing properties that aid the wet granulation process. Magnesium stearate is a powder lubricant that greatly enhances flow properties, preventing granules from adhering to industry equipment [27]. Applying a film coating to the tablet provides an aesthetic enhancement, increases the shelf-life, helps to mask any disagreeable taste, and helps control drug release and dissolution. A small amount of water is left in the tablets to provide better adhesion.

For each step of the drug tableting process, the company wants to evaluate both batch and continuous equipment options. Certain processes, such as tablet compression, are always continuous at production scale. But most unit operations have both batch and continuous designs, depending on the type of equipment. If an overall process uses both batch and continuous unit operations, it is said to be “a hybrid process”. The company would like to determine the optimal combination of equipment for the process.

Section 2.2 Project Goals

The primary goal of the project is to create a design for a drug tableting plant that can produce anywhere from 160 million to 1.6 billion 100 mg tablets per year, or 16,000 to 160,000 kg/year. Another goal is to compare the viability of batch process units, continuous process units, and a hybrid mix. Ideally, the plant will be profitable for a variety of economic scenarios and demand-driven production rates. The optimal hours of operation will be determined along with an hour-by-hour schedule. The plant should be structured in accordance with Good Manufacturing Practices, with proper cleaning protocols and implemented safety measures.

Section 2.3 Project Scope

The project scope includes the design of a drug tableting facility capable of high shear granulation, blending with excipients, compression, and coating. Estimating the cost of manufacture and profitability at different production rates under different economic circumstances is also in scope. The chemical reactions used to create the API and other excipients are not relevant to the project. Transportation of these raw materials to the facility is not considered; however, the form in which they arrive and their containment vessels are considerations. Similarly, the transportation of completed tablets to a downstream packaging line is not within scope, but the storage of finished tablets transportation to the packaging site is relevant. It is assumed that the plant is part of a larger facility owned by our parent company, and thus the construction and utility installation are out of scope. Although testing and quality control may be considered scheduling, actual testing methods and process control details are not within scope.

Section 2.4 Project Deliverables

In order to provide a facility design, the project must present specific appropriate equipment with regards to the goals of accommodating variable demand, producing consistent pharmaceutical-grade product, and maximizing profitability. Process flow diagrams, material balances, and energy balances must be presented for ease of understanding and logical consistency. The proposed design must justify the batch, continuous, or hybrid nature of the overall design by comparing it to less viable alternatives. Economic analysis must be conducted to show that the project is financially feasible, and adaptive to the scenarios that the facility is

likely to face. It should be demonstrated that miscellaneous factors such as plant layout, location, scheduling, safety regulations, and others have been considered.

Section 2.5 Design Process

The project was first approached by dividing it into two types of processes: a primarily batch process and an almost entirely continuous process. It was not possible to design a process of all one type, since essentially all tablet presses are continuous and most coaters are batch. The efficiency and logistical simplification of the continuous operation units is preferred to a batch process. However, certain aspects of the continuous design process, mostly preparation steps involving mixing and blending, lacked a level of material consistency that was available via batch units. Thus, some modifications were made to create a more optimal hybrid process. The overall process was still largely continuous, so 24/7 operating hours were chosen to minimize the need for startups and shutdowns. During this time, the almost entirely batch process continued to be developed, both to serve as a comparison and to obtain useful information about scheduling. The sizing of equipment pieces were closely evaluated in order to be capable of accommodating the high end of yearly demand. Based on the assumption that the plant would be part of a larger facility owned by the parent company in the pharmaceutical/biotechnology hub of Boston, lower demand would be run at the same high throughput but for a shorter time. For the rest of the year, the process equipment would either be repurposed by the company or contracted to another for tableting business.

Section 2.6 Project Time Chart

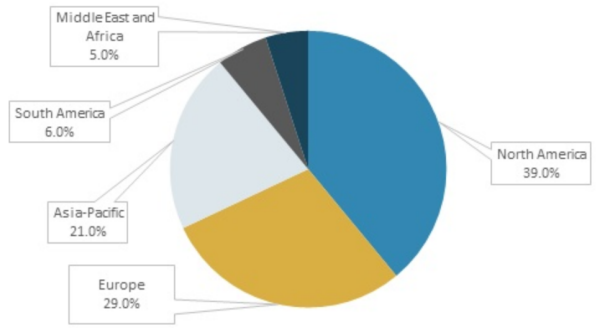
Months	**Project Tasks**
January	Preliminary research on the drug tableting process and specific unit operations
February	Further research on specific unit operations Material balances on all unit operations
	Batch process finalized
March	Hybrid process finalized
	Specific equipments selected for each unit operation
	Reach out to manufacturers for further information on equipments and costs
	Energy balances on all unit operations
April	Economic analysis on batch and hybrid process
	First and final draft of written report
	Final presentation presenting the proposed final design

Section 3: Innovation Map (N/A)

Section 4: Market and Competitive Assessment

The global market for antihypertensives, or drugs that treat high blood pressure, is anticipated to reach $27.8 billion this year in 2023. The compound annual growth rate (CAGR) is the rate of return that would be required for an investment to grow from its beginning balance to its ending balance, assuming the profits were reinvested at the end of each period of the investment's life span. The CAGR of this market is around 1.1%, driven by the increased prevalence of hypertension in an aging population, a strong pipeline for combination drug products, and strong R&D investment by large pharmaceutical companies. Additionally, in 2017, the American College of Cardiology and the American Heart Association redefined their guidelines on hypertension to be a blood pressure ≥130/80 mm Hg. The new guidelines encapsulate 105.3 million US adults, whereas the prior 2014 guidelines of blood pressure ≥140/90 mm Hg only included 74.1 million individuals (NIH). Technicality results in more people being recommended for hypertension treatment within the US. As of February 2019, key players in the market include Daiichi Sankyo Co. Ltd. with a market share of 7.6%, Novartis AG with a share of 7.3%, and United Therapeutics with a share of 5.8%. It is worth mentioning that less prominent companies and generics account for 49.1% of the market share. Branded antihypertensives are increasingly impacted by the penetration of generic competitors, which typically cost 20% to 50% less than their branded alternatives. North America is the main market for antihypertensives, but the Asia-Pacific market is growing at a faster rate due to increasing awareness and healthcare efforts in developing countries. For example, in May 2022, Namya Smile Foundation (NSF) organized an awareness campaign in India related to hypertension (Mordor). The organization held a community event where they checked people's blood pressure and made them aware of various aspects of hypertension.

Global Market Share for Antihypertensive Drugs, by Region, 2017 (%)



Global Market for Antihypertensive Drugs, by Region, Through 2023 ($ Millions)

Region	2017	2018	2023	CAGR% 2018–2023
North America	10,140.0	10,237.0	10,787.8	1.1
Europe	7,540.0	7,605.2	7,978.2	1.0
Asia-Pacific	5,460.0	5,536.2	5,961.4	1.5
South America	1,560.0	1,578.6	1,683.0	1.3
Middle East and Africa	1,300.0	1,316.3	1,407.6	1.4
Total	26,000.0	26,273.3	27,818.0	1.1

Figure 4.1. Schematic shows global market share for antihypertensive drugs by region in 2017 through 2023 [4].

The drug tableting facility outlined in this report produces a novel antihypertensive referred to as Albatol. It has already gained FDA approval, and is currently in the process of being approved by other governmental regulatory agencies worldwide. By the time the product launches, it will be available in the US, UK, EU, Switzerland, Japan, South Korea, Taiwan, Australia, and New Zealand. Within the next few years, Brazil, Russia, India, and China will be approved markets, and other countries will follow suit. Albatol has been clinically shown to have a significantly reduced side effect profile compared to existing products. However, competitor antihypertensive drugs have already gained large chunks of market share and established their brand. As a result, it is difficult to predict the yearly demand for Albatol. Current estimates for the global production rate are between 160 million and 1.6 billion tablets per year.

Section 5: Customer Requirements and CTQ Variables

Table 5.1. Summary of the Customer Requirements and CTQ Variables		
Customer Requirement	Critical-to-Quality Variable	Goal Value
Effectively lowers high blood pressure	API composition	10%
	Uniform distribution	AV ≤ 15.0 (USP <905>)
	Dissolution	Compliant with Acceptance Table 1 (USP <711>)
Easy to handle and swallow	Weight	100 mg per tablet
	Size dimensions	Cylinder shape; 8 mm diameter; 3 mm thickness
	Friability	0.5 - 1% friability after test
	Dryness	2% water
Safe to consume	No contamination	≤ 0.2% impurities

Other design constraints are as follows:

1. The tableting plant must abide by all Current Good Manufacturing Practices (cGMP) set in place by the Food and Drug Administration. Of key importance is containment: the process must be enclosed and thus isolated from cross-contamination or safety concerns.
2. The API must not exceed 80 °C at any point during the process, so as not to affect the integrity and effectiveness of the active ingredient.

Section 6: Product Concepts (N/A)

Section 7: Superior Product Concepts (N/A)

Section 8: Competitive (Patent) Analysis

Assume that the company that will produce Albatol has a patent registered for the API used within Albatol and its use to treat indications of hypertension. The company will likely apply for a formulation patent based on the product composition of the final tablet. The overall manufacturing process should also be patented in order to dissuade competitors, especially generic producers, from copying the exact design after this report is published. Each patent should cost around $15,000 - $20,000 to fully process. If not already done, “Albatol” should be registered as a trademark for commercial use. The profitability of this plant is largely dependent on the remaining lifespan of Albatol’s API patent. Once this patent expires, generic competitors will be able to enter the market by tweaking the formulation and designing slightly different manufacturing procedures. Then, since anyone will be allowed to commercialize the API, Albatol will no longer be the only product with the advantage of a significantly low side effect profile. However, the antihypertensives market is already a fairly crowded and non-exclusive space. Thus, it is likely that Albatol will take a hit to its demand once the patent expires. But this hit will not be as severe as that experienced by other branded drugs when they lose exclusive markets.

Section 9: Preliminary Process Synthesis

Section 9.1 Blending

The content uniformity of the API as well as other excipients is critical to the drug product dosage form as the failure to meet uniform criteria may lead to consequences such as health risks or lack of efficiency. Moreover, it is possible for one batch to have more API than one with less and thus, would not meet FDA quality standards. The inhomogeneity of the mixture may be caused by particle segregation during the manufacturing process of the product. There are three primary mechanisms for blending: convection, diffusion, and shear [31]. Convection blending consists of the mixing of the particle through a force movement by an agitator. Diffusion blending is known for its slow movement of the blender allowing for the random motion in between particles. Shear facilitates in delumping the particles through a velocity gradient created by the relative motion between the rotating and stationary components of the blender. There are many different types of blenders such as the ribbon blender, V cone blender, and double cone blender. Despite the varied kinds of blenders that exist within the pharmaceutical industry, the bin blender was chosen as a batch mixer due to its efficiency, homogeneous blend consistency, and removed risk of cross contamination or environmental exposure. The L.B.Bohle PM 400 blender was selected as the model equipment for the initial blending in both the batch and hybrid process. The bin blender was chosen for the initial blending in the hybrid process to ensure the precision of the inlet feed. The model equipment was selected because the company is known for their leading technology in all aspects of the pharmaceutical solid productions. It was also chosen as it satisfied the input capacity of what was initially calculated.

Furthermore, a continuous mixer was selected in the hybrid process to avoid the risk of contamination from the operators as further mixing is necessary in between the milling and the tablet pressing process. Additionally, a mixer has a greater tablet output in comparison to a batch mixer within a given time frame [31]. The continuous mixer is positioned horizontally at which the shaft blade is attached to the center for the blender allowing for radial and axial mixing. The Gericke GCM 250 continuous mixer was chosen as the model equipment for the hybrid process as it was able to satisfy the capacity criteria.

Section 9.2 Granulation

Granulation is the process in which fine particles are formed into a grain and/or granule. Granules are produced to allow for greater flowability, ensure the uniformity of the API in the final product, and to avoid the risk of dust exposures that may lead to consequences such as a dust explosion [43]. There are two varied mechanisms to granulation: dry and wet granulation. The principle behind dry granulation is to have the dry powder compacted together using a mechanical compression whereas a wet granulation utilizes liquids such as binders and solvents in order to facilitate the agglomeration of the fine powders [43]. A high shear granulation and fluidized bed granulation are both wet granulations processes. Fluidized bed granulation involves suspending the fine powders through a nozzle and utilizing a top-down spray to apply the binder solution onto the particles. In a high shear granulation, the power particles are sprayed by a binder solution while it is mixing. A high shear wet granulation was utilized for the batch process as it was used in previous development batches to make this product. The Glatt TDG high shear wet granulation was the chosen model equipment as it was able to satisfy the capacity criteria of 25 kg/hr.

A continuous granulation was chosen for the hybrid process to avoid the risk of contamination. Although continuous granulation has not been fully explored within the pharmaceutical industry, there are literatures that have proven to show its efficiency, as mentioned by our project author. Thus, a twin-screw extruder was recommended by our project author. The Leistritz ZSE-27 HP twin-screw granulator was the chosen model equipment for the granulation process. It was selected based on the company recommended by one of our industrial consultants and for its representable reputation on extruders.

Section 9.3 Drying

Drying is a necessary process in the drug production process as it allows for the drug product to reach its moisture composition and evaporates any unnecessary water from the tablet. There are three different types of dryers: direct drying, indirect drying, and radiant drying [46]. Direct drying is a process that requires heat transfer to occur by convection. Hence, the material must have direct contact with another material for heat transfer to occur. Indirect drying transfers heat through the means of conduction, which allows for the solid materials to be heated inside of a closed chamber. This particular process is utilized by many pharmaceutical industries as it reduces the risk of contamination given that it avoids being in contact with other materials. Radiant drying transfers its own thermal energy into the material via direct electromagnetic waves. There are many batch dryers such as tray drying, vacuum drying, pan drying, freeze drying. A batch vacuum tray dryer was utilized to take advantage of the drying efficiency and fast drying time. The Industrial Fabricators IFVTD72 was chosen for the batch process as it was able to meet the capacity criteria. A continuous dryer was chosen for the hybrid process in order to avoid the risk of contamination. A conveyor belt dryer was considered given that it was

suggested by our project author to not use a continuous fluidized bed dryer. The HuaMao DW Series Conveyor Dryer was chosen for the model equipment.

Section 9.4 Milling

The milling process is a continuous process that involves breaking down coarse granules into uniform particles through the shear tension between the screen and impeller. Quadro SLS Comil PsD d90 was the chosen equipment for the milling process. It is used for both the batch and hybrid process. It was selected as the company has a renowned reputation on milling and the equipment was able to meet the specific capacity of 25 kg/hr with a 1.5 mm round hole screen.

Section 9.5 Compression

The tablet press is a continuous mechanical system that involves the application of force in order to compress a varied blend of powders into tablets with uniform composition, size, and weight. The top and the bottom of the tablet press punch comes together by pressure to form the tablet. The distance between the top and bottom determines the thickness of the tablet. There are two different types of tablet compressions: single-sided rotary tablet press and double punch rotary press [47]. The double punch rotary press was considered for both the batch and hybrid process. The Fette P1010 was the chosen equipment for the tablet press as the Fette systems are widely used by pharmaceutical companies and suggested by one of our industrial consultants, Sabrina Green. The system consists of an enclosed compression area to avoid the risk of cross-contamination and advanced technology to automatically set the RPM based on what the inlet feed is, ensuring greater accuracy and reliability. The Fette P1010 has a total of 32 punch

stations with the punch shaft diameter being 22.22 mm. The equipment was also selected as it was able to meet the required capacity ranging up to 230,400 tablets per hour.

Section 9.6 Coating

Coating the tablets are often used for marketing purposes as well as to mask the taste and the color of the drug product. There are three different types of tablet coaters, which consist of the standard coating pan, the perforated pan, and the fluidized bed/air suspension system [42]. The standard coating pan consists of a rotated circular metal pan that is tilted at an angle; the rotation of the pan allows for the tablets to tumble in slow motion while coating solution is sprayed through varied nozzles for even distribution. The perforated rate consists of an enclosed perforated drum that rotates on its horizontal axis. The coating solution in the system is also applied through a spraying nozzle which is placed within the drums themselves. The fluidized bed coater consists of a cylindrical vertical chamber in which the tablets are fluidized through the exhaustion of air from the bottom of the cylinder. The tablets move upwards and then downwards, following the direction of the air flow. As the tablets' motion fluctuates, the coating solution is applied through a spraying nozzle positioned on the top and bottom of the chamber. The air capacity, coating composition, tablet surface area, and efficiency of the equipment were parameters that were considered when selecting the specific equipment. Hence, the perforated drum coating machine was considered for both the batch and hybrid process. The Thomas Engineering Flex 500 60B Tablet Coating System was selected to model the tablet coating process as it is a fully integrated system with exchangeable drums. It consists of features such as the three-axis external gun positioning which allows for an even distribution of the coating solution and a patented Thomas Spray Bar that provides turbulence-free air flow.

Section 10: Assembly of Database

The composition of the drug product consists of 10% active pharmaceutical ingredient (API), 61% lactose, 20% Avicel, 3% coating solution, 3% PVP-K90 binder, 2% water, and 1% magnesium stearate.

Section 10.1 Reactant/Product Properties

To perform calculations and to understand the behavior of the materials modeled, fundamental properties of all the reactants and products are provided. The relevant materials are ibuprofen, acetaminophen, lactose, water, and magnesium stearate. Given that the properties of the API were proprietary and confidential, ibuprofen and acetaminophen were utilized as modeled APIs for the purpose of the project. The relevant properties are molecular weight, density, heat capacity, and heat of formation. The processes studied in this report involve solids handling, and do not involve any chemical reactions. The prices of each component are assumed to be zero for simplicity. Different amounts of excipients enter the process at different times through various unit operations are calculated as a percent by weight.

Table 10.1: Fundamental Molecular Properties				
Chemical	Molecular Weight (g/mol)	Density (kg/m^3)	Heat Capacity (J/mol.K)	Heat of Formation (kJ/mol)
Ibuprofen	206	1030	172	-431.4
Acetaminophen	151	1260	190	-297.3
Water	18.0	1000	75.9	-286.3
Lactose	342	1520	418	-1959.7
Avicel	370	1460	590	Information not found
PVP-K90	111.14	1690	$1.39 * 10^4$	Information not found
Magnesium Stearate	591	1092	298	-3712.3

Section 10.2 Excipient Addition Schedule

Table 10.2: Excipient Addition Schedule		
	Percent API Added	Percent Excipient Added
Initial Blending	100	92.1
Granulation	0	3.4
Drying	0	0
Milling	0	0
Second Blending	0	1.1
Compression	0	0
Tablet Press	0	0
Coating	0	3.4

Section 11: Process Flow Diagrams and Material Balances

Section 11.1 Batch Material Balance

11.1.1 Batch Size Selection

The determination of batch size is an optimization problem governed by multiple parameters. The primary objective is to minimize the batch size, as it directly correlates with the reduction in equipment costs. However, smaller batch sizes can lead to operational and scheduling inefficiencies due to the increased frequency of material transfers between unit operations.

As the batch unit operation size decreases, the cycle time per kilogram of tablet produced increases. To meet the high tablet production demand of 160,000 kg/year, the cycle time per kilogram of tablet produced must be optimized. The optimization process evaluates batch sizes of 480, 240, 160, and 120 kg per batch, with the corresponding cycle times for each size presented in Table 11.1.1.

Table 11.1.1. Batch Process Production Rates for Various Batch Sizes		
Batch Size (kg)	Cycle Time for 10 Batches (hours)	Tablets Produced in 351 Days (kg)
480	201	201,253
240	117	172,554
160	81	166,571
120	67	150,970

One cycle constitutes 10 sequential batch productions followed by two 8-hour shifts reserved for major cleaning. Batch processing systems introduce unique scheduling challenges, as minor cleaning tasks (such as vacuuming residual dust and wiping down dirty surfaces) must be carried out between each batch. This ensures the prevention of unintended build-up within the machinery and avoids cross-contamination between batches. Additionally, time must be allocated to properly sanitize and disinfect machinery to ensure the final tablet maintains the quality and guidelines of Good Manufacturing Practice (GMP).

From Table 11.1.1, a batch size of 120kg is not permissible because the tablets produced in one operating year is less than the high demand requirements. The 160 kg is the smallest batch size that still meets the high demand requirement of 160,000 kg/year. Thus, a 160 kg batch size is optimal.

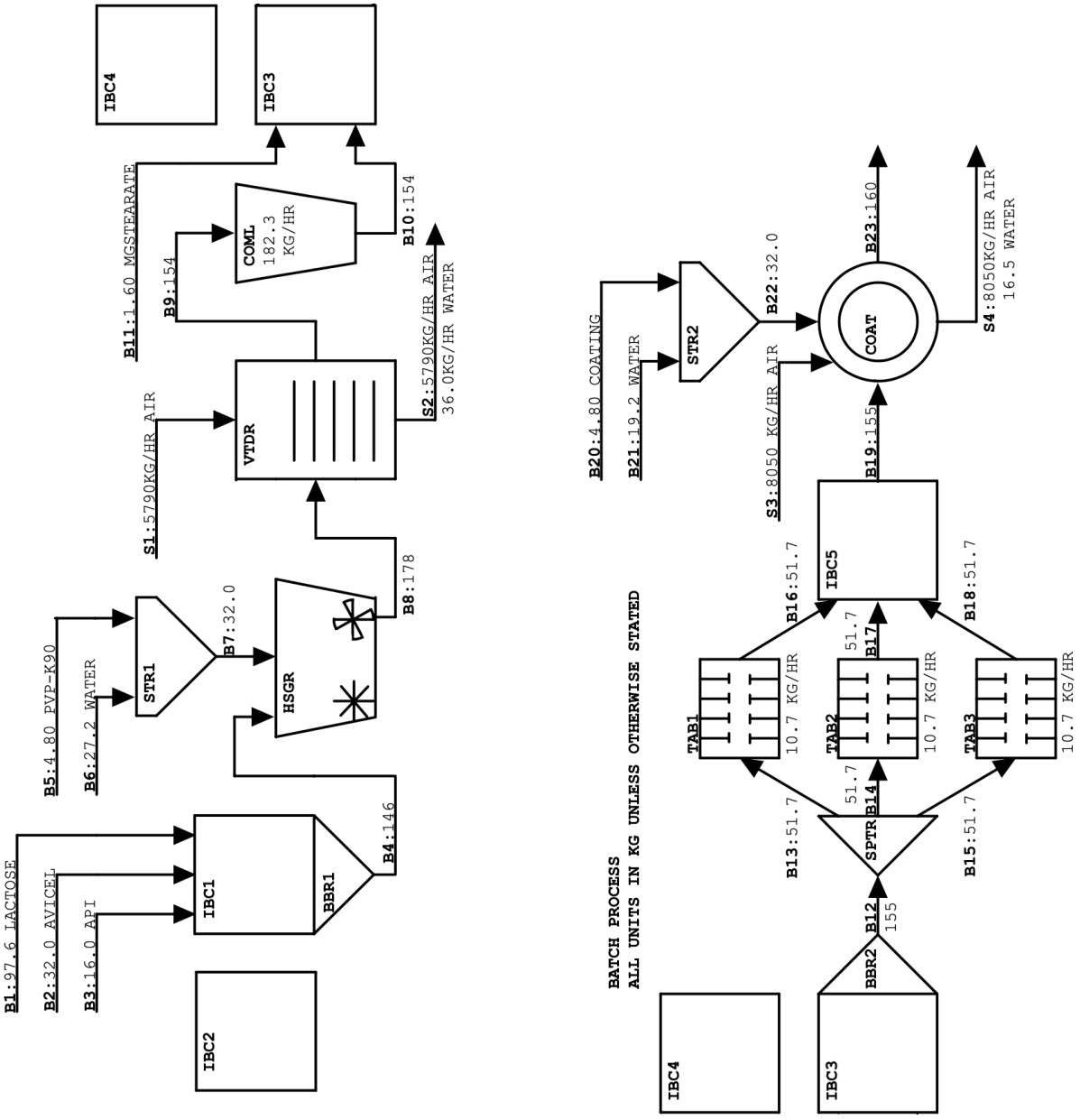
11.1.2 Batch Match Balance

To begin the discussion regarding the mass balance for the batch process, the abbreviations for all all unit operations and large storage vessels used in the batch process are abbreviated in Table 11.1.2.

Table 11.1.2. Abbreviation Dictionary for Batch Process Unit Operations	
IBC1, IBC2, IBC3, IBC4, IBC5	Intermediate bulk container
BBR1, BBR2	Bin blender
STR1, STR2	Continuous stirred tank
HSGR	High shear granulator
VTDR	Vacuum tray dryer
COML	Conical comil
SPTR	Funnel with three spouts
TAB1, TAB2, TAB3	Tablet press
COAT	Tablet coater

Based on a final batch size of 160 kg of tablets as well as final tablet component weight fractions, a batch block flow diagram is presented in Figure 11.1.2. The block flow diagram only shows the use of bins IBC1 and IBC3; in practice, the process will utilize bins IBC2 and IBC4 every other batch. While almost every piece of equipment is operated in batch, the cone mill (COML) and the tablet presses (TAB1,TAB2,TAB3) are continuous processes which are described by mass flow rates instead of batch sizes. Additionally, SPTR symbolizes the funnel with three spouts that will roughly evenly separate lubricated granules to the three tablet presses (TAB1, TAB2, and TAB3). Both the vacuum tray dryer (VTDR) and the coater (COAT) have convective drying components that require substantial air flow, with input and exhaust rates documented in the diagram.

Figure 11.1.2. Batch Process Design Mass Flow and Transfer Diagram



Due to the nature of combining batch and continuous processes in one overall process, the material flow diagram considers material transfer amounts (kg) when batch operations take place and material flow rates (kg/hr) to describe continuous operations. Specifically, the cone mill (COML) and tablet presses (TAB1, TAB2, and TAB3) have material processing rates depicted within the material flow diagram.

Referencing streams defined in Figure 11.1.2.1, a complete material balance for the batch process is summarized in Table 11.1.2.1.B. Generally, streams representing continuous material flow are labeled “S” and streams representing batch material transfer are labeled “B.” Streams labeled “S” describe intake and exhaust gas flow rates for the drying operations of the dryer (VTDR) and coater (COAT). While streams B9, B10, and B12-18 represent streams either leaving or entering continuous processes, mass balances for these streams are still given in units of mass (as opposed to mass flow rates) to denote the amount of material that must flow to complete one batch.

Table 11.1.2.B. Stream and Transfer Mass Balances for Batch Process

	B1	B2	B3	B4	B5	B6	B7	B8	S1	S2	B9	B10	B11	B12
Lactose	97.6			97.6				97.6			97.6	97.6		97.6
Avicel		32.0		32.0				32.0			32.0	32.0		32.0
API			16.0	16.0				16.0			16.0	16.0		16.0
PVP-K90					4.80		4.80	4.80			4.80	4.80		4.80
Water						27.2	27.2	27.2		36.0	3.20	3.20		3.20
Magnesium Stearate													1.60	1.60
Opadry® II White														
Air									5790	5790				
Total	97.6	32.0	16.0	146	4.80	27.2	32.0	178	5790	5826	154	154	1.60	155

	B13	B14	B15	B16	B17	B18	B19	B20	B21	B22	S3	S4	B10
Lactose	32.5	32.5	32.5	32.5	32.5	32.5	97.6						97.6
Avicel	10.7	10.7	10.7	10.7	10.7	10.7	32.0						32.0
API	5.33	5.33	5.33	5.33	5.33	5.33	16.0						16.0
PVP-K90	1.60	1.60	1.60	1.60	1.60	1.60	4.80						4.80
Water	1.07	1.07	1.07	1.07	1.07	1.07	3.20		19.2	19.2		16.5	3.20
Magnesium Stearate	0.533	0.533	0.533	0.533	0.533	0.533	1.60						1.60
Opadry® II White								4.80		4.80			4.80
Air											8051	8051	
Total	51.7	51.7	51.7	51.7	51.7	51.7	155	4.80	19.2	24.0	8051	8068	160

Key		
Units	kg	kg/hr

11.1.3 Sizing Batch Unit Operations

Now that the optimal batch size has been determined, bulk densities of the material as it passes through the batch process determines the size of unit operations necessary. The bulk density of the material deposited in the initial bin blender is well approximated by calculating the weighted average of initial raw material bulk densities. Bin blenders produce optimal mixtures when IBC's are filled to 50-60% capacity [38]. Thus, IBC1 and IBC2 should be the smallest standard IBC that accommodates 1.67-2.00 the volume of one batch's worth of API, lactose, and Avicel-101.

For STR1 and STR2, the density of the solution is closely approximated as the density of water. However, the bulk density of the material changes as it goes through HSGR. Wet granulation not only increases the density of the mixture through wetting, but the impellers and paddles create dense granules that increase the overall bulk density. First, the bulk density of dry granules can be approximated from external bulk density data [23]. As the majority of the granule is composed of lactose, the bulk densities of α-Lactose monohydrate passed through a high shear mixer and 450 μm sieve (0.51 kg/L) serves as a feasible estimate. Next, the additional increase in density due to wetting can be approximated by taking a weighted average of water's density and the density of the dry granule estimation, resulting in a final value of 0.606 kg/L. After passing through VTDR, the bulk density can be estimated to go back down to 0.52 kg/L despite the presence of a small amount of unevaporated water, which has no significant effect on the overall bulk density of the dried granule. This bulk density carries over to IBC3/IBC4.

To size IBC5 and COAT, a bulk density of tablets was calculated by multiplying the density of each pressed tablet by an estimated random packing density. As the tablets are unorderly dispensed in IBC5 and tumbled around in the drum of COAT, the random packing

density accounts for the void in between tablets and ensures the IBC5 and COAT is sized properly. First, given the assumption that each 100 mg tablet is a cylinder with a height of 3mm and a width of 8mm, the density of the tablet is 0.663 kg/L. Next, the random packing density can be correlated with the aspect ratio of the cylinder, which is ⅜. The packing density of cylinders at an aspect ratio of ⅜ can be estimated at 0.68 which means the bulk density of the tablets is 0.45 [25]. Assuming the batch of tablets after the coating has been applied is 160 kg, this would mean the tablets take up 355 L of space in the coating drum.

Estimated bulk density values for materials entering and exiting batch unit operations are summarized in Table 11.1.3. Additionally, the maximum material volume within each batch unit operation is determined as the larger of either the volume of material pre-unit operation or post-unit operation. Finally, standard unit sizes that accommodate the capacity of the maximum material volume are presented.

Table 11.1.3. Bulk Density Estimates and Equipment Sizes for the Batch Process				
Units	Estimated Material Bulk Density Inlet (kg/L)	Estimated Material Bulk Density Outlet (kg/L)	Max Material Volume (L)	Standard Unit Size
IBC1/IBC2	0.412	0.412	354	600L
STR1	0.997	0.997	32.1	40L
HSGR	0.412	0.606	431	600L
VTDR	0.606	0.52	342	72 No. Trays
IBC3/IBC4	0.52	0.52	295	600L
IBC5	0.45	0.45	345	400L
STR2	0.997	0.997	32.1	40L
COAT	0.45	0.45	355	48 in.

11.1.4 Scheduling the Batch Process

Batch scheduling begins by first estimating each batch unit processing time. Generally, processing one batch involves allocating time for an operator to transfer material to the unit, for the material to process, and for the operator to subsequently transfer material out of the unit. Additionally, operators need to do minor cleaning between each batch; to facilitate effortless removal of leftover residue from prior batches, operators should promptly perform minor cleanings following each processing cycle. Additional considerations for estimating batch unit processing times include allocating labor time for operators to test material dried granules coming out of the vacuum tray dryer for dryness to ensure the final tablet has the correct water weight of 2%. Additional points where the design would benefit from sample testing is right after the coater. The coated tablet is this design's final product, thus laboratory testing methods (likely

spectroscopy) will be used to ensure correct tablet properties like size and composition are achieved.

For the batch equipment in the batch process, generally all process batch sizes range from 146-187 kg. The amount of time it takes for a batch mass in that range to be received or dispensed from a typical batch operation is estimated to be 10 minutes, meaning that material needs to be transferred at a rate of 0.243-0.312 kg/hr. The rate is easily achievable if gravity is used or the material has great flowability which is the case with IBC1/IBC2/BBR1, HSGR, IBC3/IBC4/BBR1, IBC5, and COAT. On the other hand, the VTDR has 72 trays that need to be manually filled with material and scraped off. 40 minutes is assumed for VTDR material loading and 30 minutes is assumed for unloading. This means that 1.80 trays need to be loaded, and 2.40 trays need to be unloaded every minute. For the cleaning, equipment with many moving parts such as VTDR take longer to clean (40 minutes) than simpler and smaller units like STR1 (5 minutes). A summary of processing time estimates for all batch design unit operations are presented in Table 11.1.4.

Unit	IBC1/IBC2		BBR1		STR1		HSGR		VTDR		COML	
Type	Batch		Batch		Batch		Batch		Batch		Continous	
Schedule (min)	Hoisting	10	Attatching	5	Charging	5	Charging	10	Charging	40	Cleaning	20
	Charging	10	Blending	20	Dissolving	10	Granulating	15	Drying	40	Startup	5
	Blending	30	Detatching	5	Discharging	5	Discharging	10	Testing	20	Milling	50
	Discharging	10			Cleaning	10	Cleaning	20	Discharging	30	Shutdown	5
	Cleaning	20							Cleaning	40		
Total (hrs)	1.33		0.500		0.500		0.917		2.83		1.33	
Total In (kg)	146		146		32		178		178		154	
Total Out (kg)	146		146		32		178		154		154	
Required Capacity	146	kg	145.6	kg	32	kg	178	kg	178	kg	184	kg/hr
Unit	IBC3/IBC4		BBR2		TAB1/TAB2/TAB3		IBC5		STR2		COAT	
Type	Batch		Batch		Continous		Batch		Batch		Batch	
Schedule (min)	Charging	10	Attatching	5	Cleaning	20	Accumulation	310	Charging	5	Charging	10
	Blending	30	Blending	20	Startup	10			Dissolving	10	Coating	70
	Discharging	10	Detatching	5	Pressing	290			Discharging	5	Testing	20
	Cleaning	20			Shutdown	10			Cleaning	10	Discharging	10
											Cleaning	20
Total (hrs)	1.17		0.500		5.50		5.17		0.500		2.17	
Total In (kg)	155		154		155		155		32.0		155	
Total Out (kg)	155		155		155		155		32.0		160	
Required Capacity	155	kg	154	kg	10.7	kg/hr	155	kg	32.0	kg	160	kg

Key
Minor Cleaning, Operator Required
Non-Cleaning Labor, Operator Required
Sampling and Testing, Operator Required
Equiptment in Use, Operator Not Required

Table 11.1.4. Batch Design Processing Times

The Gantt chart in figure 11.1.4.A depicts that the batch process design can be operated by having two operators on site at all times. While two operators are required for efficient operation, both operators are simultaneously directly laboring only 28.8% of the production time (not counting major cleaning shifts). Thus, there is ample opportunity for operators to either combine forces to complete one-man tasks or to take required breaks. Additionally, there are periodic instances where no direct operator intervention is required; these periods of time can be used for shift changes.

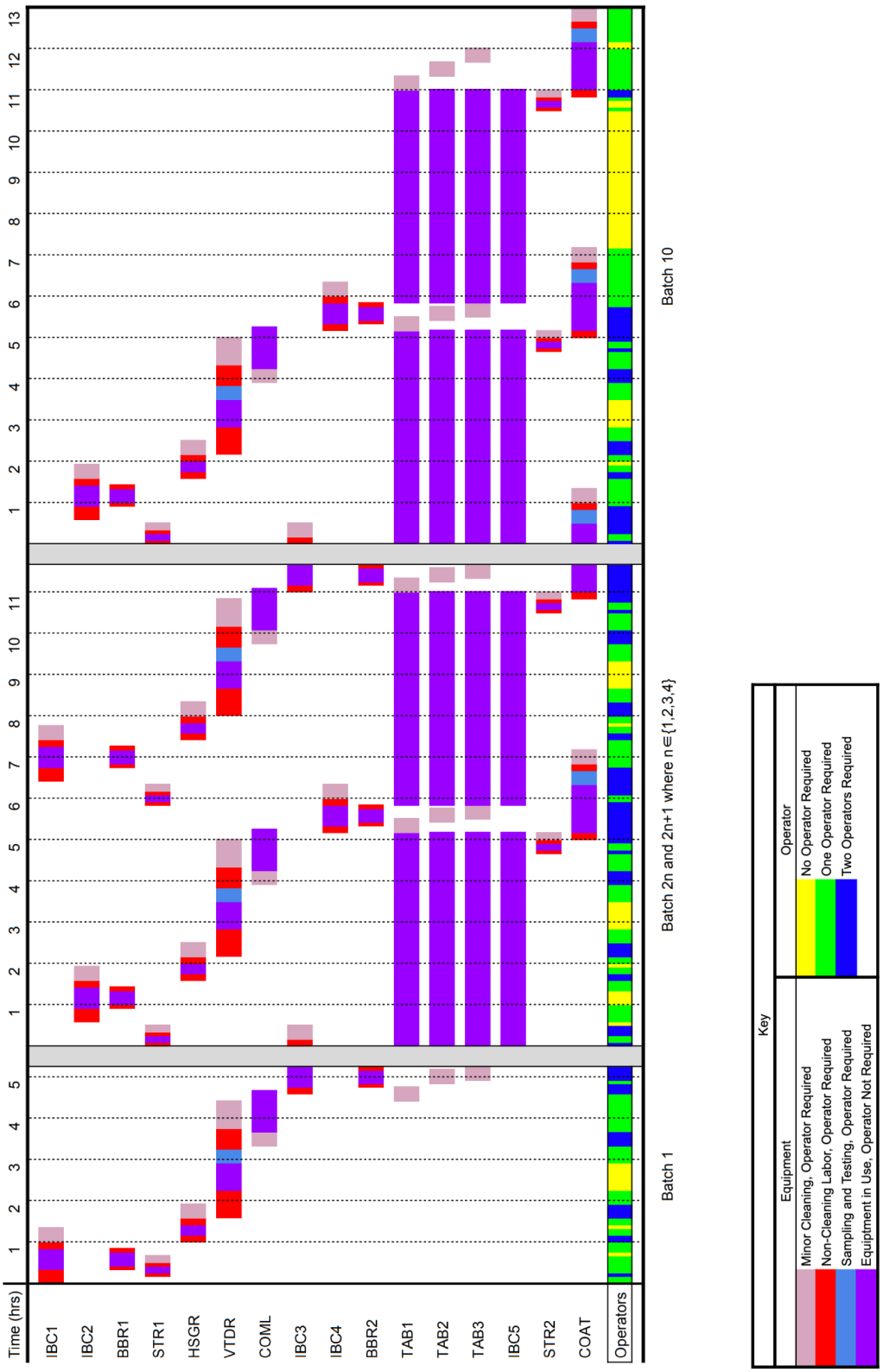


Figure 11.1.4.A. Batch Process Design Operation Gantt Chart

The time of continuous operation that it takes to complete 10 batches is 64.9 hours. Accounting for major cleaning (two 8 hour shifts) in between each set of 10 batches yields a total cycle time of 80.9 hours. If 160 kg of tablets are produced in each batch, and there are 10 batches within a cycle, then each cycle produces 1,600 kg of tablets. Assuming two weeks are reserved for scheduled and emergency maintenance in a year, 104 cycles are completed in 351 operational days per year. Thus, in one operational year, 167,000 kg of tablets are produced under this schedule. This production rate exceeds the 160,000 kg/yr high-demand production rate. Assuming a 4.13% yield loss which can be caused by operator error and cleaning losses, the high-demand production rate is met exactly.

The scheduling in situations of low-demand for the batch design process does not change; a lower demand instead will affect the number of operating days in a year, not including days reserved for maintenance. Figure 11.1.4.B presents the operating days per year required to meet variable demands. For example, it takes 36 operating days to produce a year's worth of tablets during the lowest possible demand (16,000 kg/yr).

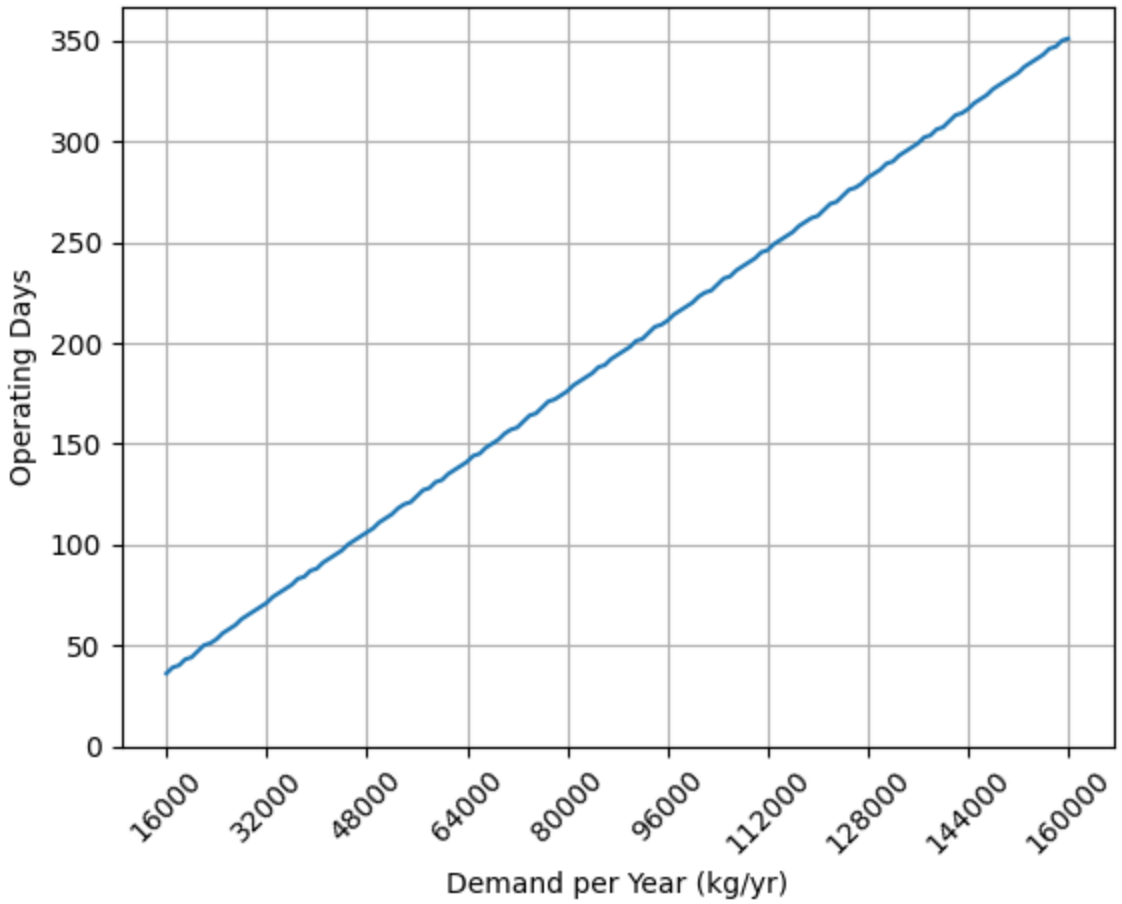


Figure 11.1.4.B. Operating Days vs. Demand per Year not Including Maintenance with an Assumed 4% Yield Loss for the Batch Design

Section 11.2 Hybrid Material Balance

11.2.1 Hybrid Process Mass Balance

To begin the discussion regarding the mass balance for the hybrid process, the abbreviations for all all unit operations and large storage vessels used in the hybrid process are abbreviated in Table 11.2.1.

Table 11.2.1. Abbreviation Dictionary for Hybrid Process Unit Operations	
IBC1, IBC2, IBC3, IBC4	Intermediate bulk container
BBR1	Bin blender
STR1, STR2	Continuous stirred tank
TSER	Twin screw extruder
CBDR	Conveyor belt dryer
COML	Cone mill
CTMR	Continuous mixer
SPLT	Funnel with two spouts
TAB1, TAB2	Tablet press
COAT	Tablet coater

Based on a final batch size of 160 kg of tablets and a tablet production rate of 21.0 kg/hr, a block flow diagram is presented in Figure 11.2.1. The block flow diagram only shows the use of bins IBC1 and IBC3; in practice, the process will utilize bins IBC2 and IBC4 every other batch. While many pieces of equipment are operated in batch, the twin screw extruder (TSER), the conveyor belt dryer (CBDR), the cone mill (COML), the continuous mixer (CTMR), and the tablet presses (TAB1,TAB2,TAB3) are continuous processes which are described by mass flow rates instead of batch sizes. Additionally, SPLT symbolizes the funnel with two spouts that will

roughly evenly separate lubricated granules to the two tablet presses (TAB1, and TAB2). Both the conveyor belt dryer (CBDR) and the coater (COAT) have convective drying components that require substantial air flow, with input and exhaust rates documented in the diagram.

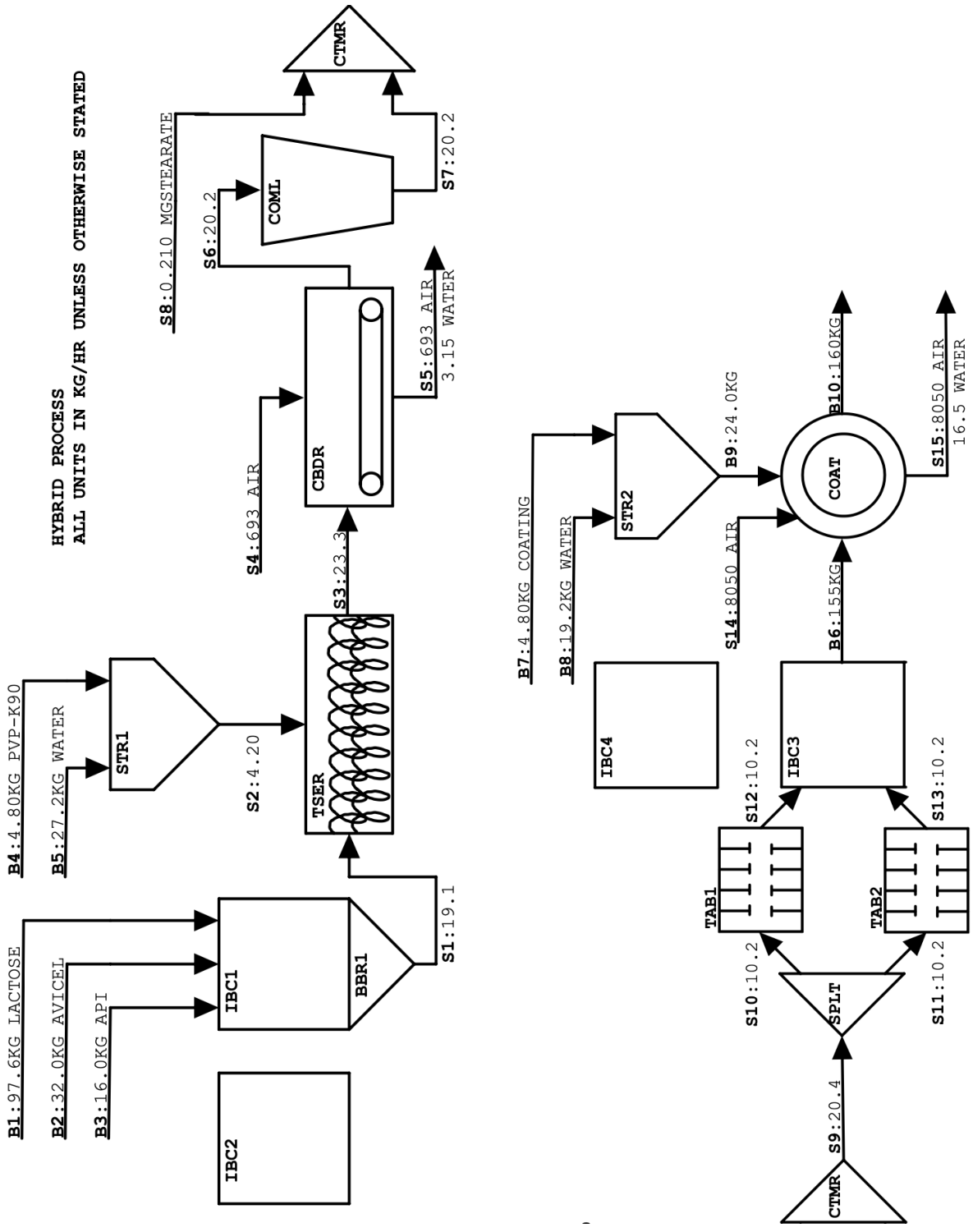


Figure 11.2.1. Hybrid Process Design Mass Flow and Transfer Diagram

Due to the nature of combining batch and continuous processes in one overall process, the material flow diagram considers material transfer amounts (kg) when batch operations take place and material flow rates (kg/hr) to describe continuous operations. Specifically, the cone mill (COML) and tablet presses (TAB1,TAB2,TAB3) have material processing rates depicted within the material flow diagram.

Referencing streams defined in Figure 11.2.1, a complete material balance for the hybrid process is summarized in Table 11.2.1.B. Generally, streams representing continuous material flow are labeled “S” and streams representing batch material transfer are labeled “B.” Streams labeled “S” describe intake and exhaust gas flow rates for the drying operations of the dryer (CBDR) and coater (COAT).

Table 11.2.1.B. Stream and Transfer Mass Balances for Hybrid Process

	B1	B2	B3	S1	B4	B5	S2	S3	S4	S5	S6	S7	S8
Lactose	97.6			12.8				12.8			12.8	12.8	
Avicel		32.0		4.20				4.20			4.20	4.20	
API			16.0	2.10				2.10			2.10	2.10	
PVP-K90					4.80		0.631	0.631			0.631	0.631	
Water						27.2	3.57	3.57		3.15	0.420	0.420	
Magnesium Stearate													0.210
Opadry® II White													
Air									693	693			
Total	97.6	32.0	16.0	19.1	4.80	27.2	4.20	23.3	693	696	20.2	20.2	0.210

	S9	S10	S11	S12	S13	B6	S14	B7	B8	B9	S15	B10
Lactose	12.8	6.41	6.41	6.41	6.41	97.6						97.6
Avicel	4.20	2.10	2.10	2.10	2.10	32.0						32.0
API	2.10	1.051	1.051	1.051	1.051	16.0						16.0
PVP-K90	0.631	0.315	0.315	0.315	0.315	4.80						4.80
Water	0.420	0.210	0.210	0.210	0.210	3.20			19.2	19.2	16.5	3.20
Magnesium Stearate	0.210	0.105	0.105	0.105	0.105	1.60						1.60
Opadry® II White								4.80		4.80		4.80
Air							8051				8051	
Total	20.4	10.2	10.2	10.2	10.2	155	8051	4.8	19.2	24.0	8068	160

Key		
Units	kg	kg/hr

11.2.2 Residence time for continuous operations

Continuous equipment scheduling is defined not only by material flow rates, but also by residence times which describe the amount of time that material spends processing within continuous equipment. The residence time dictates the amount of time that occurs before any processed material leaves the outlet of a continuous unit operation at start-up. It also describes the amount of time it takes a continuous unit operation to fully dispense all of its contents once material inflow is stopped at shut-down. When scheduling a process with continuous equipment, high residence times lower production rates because subsequent equipment sit idle until earlier equipment begins material outflow.

The residence times of continuous equipment implemented in the hybrid process are summarized in Table 11.2.1. Calculations and methods used to predict mean residence time are provided in the appendix, section 24.2.

Table 11.2.1. Residence Time Estimation Summary

Continuous Unit	Approximate Mean Residence Time
TSER	15.8 min
CBDR	6.24 hr
COML	0
CTMR	~1 min
TAB1/TAB2/TAB3	5-10 min

In addition to approximating residence times, the distribution of residence times for each continuous operation is a critical process parameter that needs to be considered. Decreasing the rotation speed of continuous equipment tends to increase the width of the distribution of residence times. In other words, residence times become more variable. While the mean

residence time plays the biggest role in predicting the time lost at start-up and shut-down, an increase in the variability of residence times creates unpredictability when it comes to control, leading to potential accumulation between continuous process equipment. Additionally, for unit operations such as CTMR a predictable residence time of dried granules is necessary in order to ensure magnesium stearate is being mixed in the correct proportion. Thus, variable residence times can lead to departures from critical quality attributes of the final product such as incorrect final tablet compositions. During the initial stages of production, process parameters of continuous unit operations such as impeller speeds should be adjusted and tested with the goal of limiting residence time distribution.

11.2.3 Hybrid Process Schedule

The advantages of hybrid scheduling includes extended periods of time where continuous unit operations are processing materials without the need for direct operator intervention. Thus, there is no need for complex scheduling to work around the limited number of operators, even in regards to the batch processes throughout the hybrid process (IBC1/IBC2/BBR1, STR1, STR2, COAT).

The hybrid process scheduling involves estimating the loss in production time caused due to start-up and shut-down which is the cumulative sum of residence times, 6.69 hr. Additionally, shut-down also includes time reserved for the batch operation of the coater at the end of the process which takes 2.00 hours. Thus, the start-up time loss is 6.69 hr and the shut-down time loss is 8.69 hr.

While the overall process produces tablets at 21.0 kg/hr, considering start-up and shut-down times is essential for ensuring that the hybrid design is able to meet yearly high demand. The operation shuts down every month for two days of major equipment cleaning.

Thus, this reduces operational days by 12 and reduces operational time by 12 start-up and shut-down sequences. Additionally, 2 weeks of scheduled maintenance are reserved for the end of the year and 6 yearly unexpected shutdowns due to maintenance are estimated which reduces operational time by 6 start-up and shut-down sequences. Overall, this means that the hybrid design is operational for 339 days. Additionally, 11.5 days are lost due to start-up and shut-down. With 24 hour per day operation, the hybrid facility produces 165,000 kg of tablets annually. This exceeds the high demand. Additionally, assuming a 3.00% yield loss, the factory will meet the 160,000 kg/yr high demand exactly, indicating that the hybrid process design has room for yield loss due to operator error, cleaning, or rejected batches.

If low demand is expected and continuous machinery is to be operated at the same capacity, it would take 37.4 continuous days of production to meet the demand with 3.00% yield loss, not accounting for start-up, shut-down, nor major cleaning. Accounting for initial start-up and shut-down as well as one start-up and shut-down either for maintenance or major cleaning, the plant should operate for 40.4 days. A good approximation for intermediate demands' affects on the number of operating days (not including 2 week maintenance period) is a linear relationship between the number of operating days and the yearly demand. Using the high demand and low demand operating days, the relationship is plotted in Figure 11.2.3.

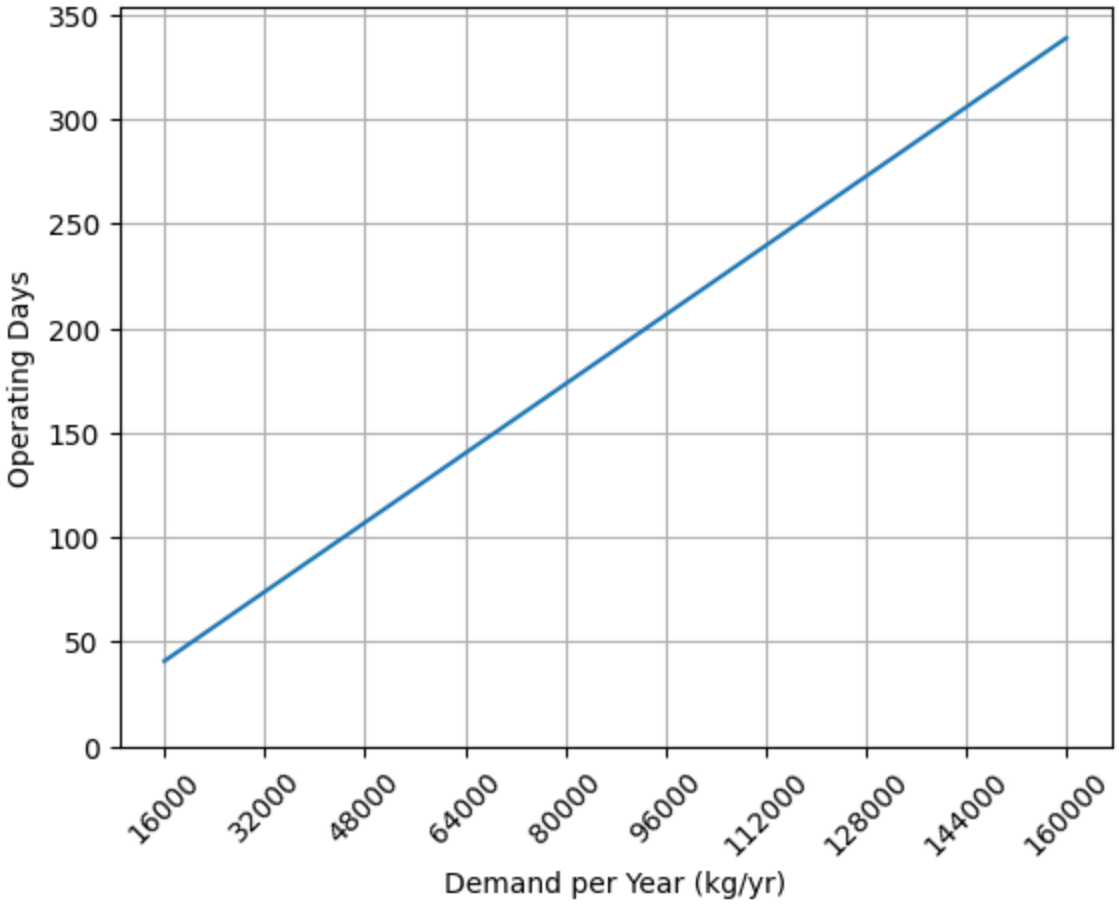


Figure 11.2.3. Operating Days vs. Demand per Year not Including Maintenance with an Assumed 3.00% Yield Loss for the Hybrid Design

Section 12: Process Descriptions

This section describes narrative descriptions of the equipment chosen and function of each major piece of equipment for both batch and hybrid processes.

Section 12.1 Batch Process

In this section, all unit operations are batch machinery, except for the Comil (COML) and the three tablet presses (TAB1, TAB2, and TAB3).

12.1.1 Bin Blender

The bin blender is a piece of equipment used for blending dry powder materials including lactose, Avicel, and API. The blending operation is a fully closed process and is used to ensure that the inputs are thoroughly mixed together before being sent to the granulator. An even distribution of all components in the mixture is the goal of this process because if the ingredients are not well mixed, the tablets may not have the correct dose or may have inconsistent physical properties such as hardness or dissolution rate. The process begins by hoisting up powdered lactose, Avicel PH-101, and API to the second floor using a series of forklifts. Here, a simple valve system allows gravity to dispense the raw excipients and API onto a weighting receptacle that further dispenses directly into an intermediate bulk container (IBC1) bin. The bin of raw materials around 160 kg is moved over horizontally to a bin blender (BBR1) that attaches to and rotates the bin at 5 RPM. After 100 revolutions, the material is well mixed. A second IBC (IBC2) is available at this stage that can be utilized in alternating batches. The process benefits from having two bins because one bin can be prepared to receive the next batch of raw materials while the other bin is in use.

Blending involves several process parameters, such as the loading order of materials into the blender, the blender's rotation speed, and the fill level in comparison to other inputs [15]. If all excipients are added first, they may not spread evenly throughout the mixture and could remain in one part of the blender, resulting in improper homogenization. Therefore, two approaches can be taken to add the inputs to the blender from the mill and the excipients. The excipients can either be entirely from the mill already in the blender, or both inputs can be added in alternating layers – a layer of mill output, followed by a layer of excipients, and so on. Employing either of these methods to load the blender guarantees uniform mixing of API and excipients [30].

A blender's total volume (or capacity) is the total amount of material the vessel can hold; the LB Bohle container blender (PM-400) has a load capacity of 400kg. Among different commonly used mixing mechanisms in the pharmaceutical industry, diffusion and axial blending is chosen since the inputs are not significantly cohesive or lumpy and that have enough cohesion to prevent sifting. All tumble blenders (also called gravity blenders) operate primarily on the principles of diffusion blending (up and down, around and around) and axial blending (side to side) [40]. In a tumbling bin blender, the material is loaded into a rotating bin or drum, and the rotation of the bin causes the material to tumble and mix. The rotation distributes materials along an ever changing angle of the repose surface. This motion promotes the mixing of the lactose and API by continuously exposing different parts of the mixture to each other, ensuring that all particles come into contact with each other. The speed and duration of the tumbling motion can be adjusted based on the specific requirements of the mixture, in this case, from 2-6 rpm. By adjusting these parameters, the mixing can be optimized to achieve the desired level of homogeneity. In addition to mixing a large quantity of materials, the bin blender chosen has an

advantage over other traditional bin blenders that have the drive mechanism and blending bin integrated, which can make it difficult to charge, discharge, and clean the equipment. IBC 1 and 2 can be easily removed from the drive mechanism, and this separation allows for more efficient use of the equipment because the bin can be charged, discharged, and cleaned separately. For example, one bin can be charged with materials while another bin is being blended, increasing the overall production efficiency. The separate blending bin also allows for easier cleaning of the equipment. Since the bin can be removed, it can be thoroughly cleaned and sanitized, reducing the risk of contamination and improving product quality. This feature is particularly important in the pharmaceutical and food industries, where cleanliness and product purity are critical.

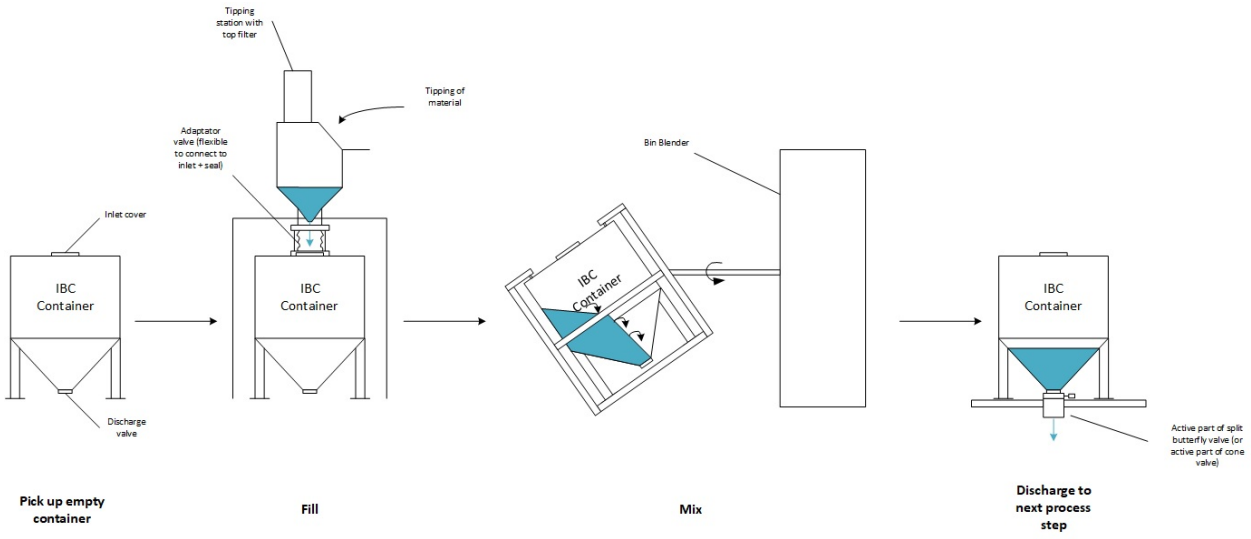


Figure 12.1.1. Schematic showing how a bin blender works [38].

12.1.2 High-shear mixer Granulator

Granulation is a fundamental unit operation employed in the production of pharmaceutical dosage forms, such as tablets and capsules, involving the technique of particle enlargement through agglomeration [2]. During this process, small particles, whether fine or

coarse, are transformed into larger agglomerates, referred to as granules. In general, granulation follows the initial dry mixing of the required powder ingredients, including the active pharmaceutical ingredient (API), to achieve a uniform distribution of each ingredient throughout the powder mixture. The particle size of granules utilized in the pharmaceutical industry ranges from 200 to 400 μm, with a size range of 200 to 500 μm being predominantly produced as an intermediary. These granules are either packed as a dosage form or mixed with other excipients before tablet compaction or capsule filling [3].

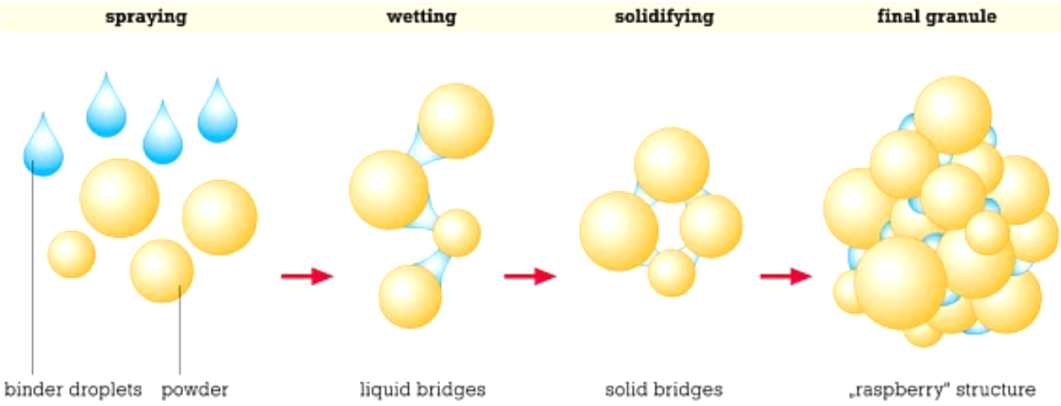


Figure 12.1.2. Schematic representation of particle-bonding granulation from powders undergo wetting and solidifying processes to uniform granules with good flowability and more easily compressed [8].

Granules are produced to enhance the uniformity of the API in the final product, to increase the density of the blend so that it occupies less volume per unit weight for better storage and shipment, to facilitate metering or volumetric dispensing, to reduce dust during granulation process to reduce toxic exposure and process-related hazards, and to improve the appearance of the product [3]. The granulation technique may be widely categorized into two types, dry granulation and wet granulation, based on the type of method used to facilitate the agglomeration of powder particles. Dry granulation uses mechanical compression (slugs) or compaction (roller compaction) to facilitate the agglomeration of dry powder particles, while the wet granulation

uses granulation liquid (binder/solvent) to facilitate the agglomeration by formation of wet mass by adhesion [43]. The ideal characteristics of granules in pharmaceutical production include spherical shape, narrow particle size distribution, sufficient fines, and appropriate moisture and hardness. These properties improve flow, content uniformity, compaction and compression characteristics, and prevent breaking and dust formation during the manufacturing process. The characteristics of particles obtained through granulation are determined by various factors such as the size of the drug and excipients, the concentration and volume of binders and solvents used, granulation time, type of granulator employed, and drying rate.

For the batch process, two unit operations are required for granulation. First, powdered binder (PVP-K90) and water is weighed out on a bench scale and added to a continuously stirred-tank (STR1) to dissolve. The binder solution is dispensed manually into the high-shear granulator (HSGR). Additionally, the contents of the bin (IBC1/IBC2) are dispensed into the high-shear granulator, and granulation can proceed. Once granulation is complete, operators conduct a minor cleaning of the batch granulator. After granulation, the mixture is dispensed by operators onto trays and taken to a vacuum tray dryer (VTDR). Extra time needs to be accounted for the loading, unloading, and cleaning of individual trays. Additionally, granules are sampled and tested for 2.0% water composition at this stage to ensure a final tablet water composition of 2.0%. Granulation will be performed under saturated conditions, and exhaust air will leave the vessel at a temperature of 25ºC and a saturated absolute humidity of 19.4 g water/kg air.

12.1.3 Batch Tray Dryer

After the granulation process, the wet granules need to undergo thorough drying. This can be achieved using a batch tray dryer, which has been widely adopted in the food production and pharmaceutical field. Dryers are typically categorized as direct dryers, where hot air at or close

to atmospheric pressure is used to supply heat for evaporating water or solvents from the product. Another significant type of dryer is the vacuum dryer, which utilizes a low-pressure environment surrounding the product. The vacuum technology utilized in the process involves the passage of a heated fluid through direct heating shelves, which results in the conduction of heat to the feedstock. This method operates at low pressure, causing a reduction in the boiling point of the solvent. Consequently, the drying process occurs at lower temperatures and faster rates, resulting in highly efficient drying. A major advantage to vacuum drying is its energy conservation – less energy is needed for drying, cutting down on the economic and environmental costs. Vacuum drying offers a less damaging drying process, which tends to retain the integrity of the original item without degrading the heat-sensitive drug product. Using vacuum-drying equipment also reduces risks to workers. With a vacuum dryer, ventilation does not occur, and personnel working near the dryer are safer [34].

The majority of dryers are of the direct (or convective) type, where hot air is used both to supply the heat for evaporation and to carry away the evaporated moisture from the product. Vacuum drying is a process in which materials are dried in a reduced pressure environment, which lowers the heat needed for rapid drying. Vacuum dryers offer low temperature drying of thermolabile materials and are suitable for solvent recovery from solid products containing solvents. Heat is usually supplied by passing steam or hot water through hollow shelves. Unlike a direct-heat dryer — in which the material is immersed directly into the heating media (usually a hot gas stream) and is dried by convection — a vacuum dryer is an indirect-heat dryer. That is, the heat is transferred to the material as it contacts the dryer's heated surface, drying the material by conduction. In vacuum dryers, heat transfer occurs mainly through conduction or radiation, and the drying trays are placed in a large evacuated cabinet. Condensation of water vapor is often

utilized to enable vacuum pumps to handle non-condensable gasses. Vacuum tray dryers consist of a heated main body to prevent condensation, and shelves that are uniformly heated through a fluid distribution collector for optimal heat distribution. The inner walls and the shelves are perfectly polished. The shelves are heated inside the vacuum chamber. This technique can apply heat indirectly to the product by forcing physical contact with the shelf. A hot medium flows through the shelves, thus enabling it to conduct heat to the tray, which is positioned on the shelves [34].

12.1.4 Milling

Cone milling is a widely used unit operation in the pharmaceutical, food, chemical, and related industries for various purposes such as size reduction, deagglomeration, and delumping of powders and granules. In the direct compaction route, mills serve as material delumping process units, while in granulation routes, they are used for particle size reduction. In the wet granulation route, mills are utilized to reduce the size of oversize granules from the granulation and drying unit, and in the dry granulation route, mills break compacted ribbons from a roller compaction process into granulated products [5].

Trays of dried granulations are scraped off into a funnel-like receptacle feeding into a Comil (COML), at a conical vessel equipped with perforations, known as a screen. The screen is a part of a Comil machine that features a vertically mounted impeller which rotates and pushes the granules across the screen, causing a cutting action that operates at low velocity. Granules that are of the right size pass through the screen, while those that are too large remain in the cutting chamber until they are reduced to the desired size. The mill head is where the material is introduced by gravity, and it contains a high-speed rotating impeller along its central axis. As the impeller collides with the granules, they are imbued with kinetic energy, resulting in a reduction

in size, at which the material gets continuously milled through a 150 mesh sieve [22]. The Comil's exit stream enters an angled spout that feeds directly into an IBC (IBC3). While milled granules accumulate, operators weigh out magnesium stearate and add the powdered lubricant to the IBC as well. A second IBC (IBC4) is available at this stage which allows operators to prepare one bin for the next batch while the former batch's bin is still in use dispensing material into the tablet presses. Once the entire batch has processed through the Comil into the IBC, operators conduct minor cleanings on the Comil and the bin is horizontally transported to a bin blender (BBR2) where the granules and powdered lubricant are mixed for 100 revolutions at 5RPM resulting in granules with better flowability.

12.1.5 Rotary Tablet Press

After the IBC is disconnected from the bin blender and lifted with a forklift above a receptacle for the tablet presses (TAB1, TAB2, and TAB3), contents of the bin are dispensed into a funnel-like receptacle which has three spouts, with each spout leading to a different tablet press. The upgraded flowability of the granules due to the magnesium stearate coating at this stage should ensure nearly even flow of granules into each tablet press. In pharmaceutical tablet production, the rotary tablet press is a key machine used to compress granules or powders into tablet form. The pre compression roller gives the granules the initial compression force and gets rid of excess air that is trapped in the die. The process starts with filling the feed hopper with the materials that are to be compressed, which helps reduce the bulk volume of a material. The main compression roller applies the final compression force that formulates the tablets. These materials are then fed into the die cavity through the feeding system. The upper and lower punches come together to compress the material into the die cavity, forming the tablet, as illustrated in Figure 12.1.3. The elastic recovery or relaxation of the tablet starts when one punch

leaves the tablet and continues after ejection [37]. After that the lower punch moves upward to eject the tablet from the die, and the upper punch has already left the die when the process of ejection starts. Next, the tablet is ejected out of the die cavity and onto a chute or conveyor belt. The press must be cleaned between batches to prevent cross-contamination, lubricated to prevent sticking, and regularly maintained to ensure consistent operation. The quality of the resulting tablets depends on various factors such as formulation, compression force, speed of the press, and maintenance of the machine and tooling.

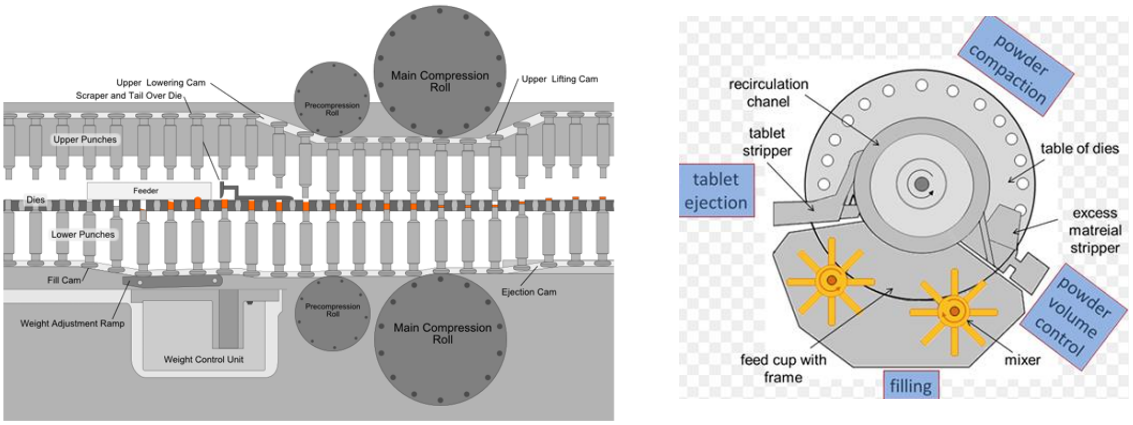


Figure 12.1.3. Schematic of how a rotary tablet press works. In this process, the powder blend will be placed in the dies and compressed using the precompression roll and main compression roll before being ejected [9].

12.1.6 Batch Fully Perforated Coating Pan

After tablets are pressed, they are dispensed into spouts leading to an IBC (IBC5). While tablets accumulate in the bin, an operator prepares a coating solution by dissolving Opadry® II. The coating machine consists of a rotating pan with perforations on the surface. Tablets are loaded into the pan, and a coating material is added. As the pan rotates, the tablets are tumbled

and the coating material is sprayed onto them through the spray guns with the hot air flowing through the perforations. In general, the coating material may be a solution or suspension of a polymer or other material. The process continues until the tablets are coated to the desired thickness. The batch perforated coating pan mechanism ensures uniform coating and facilitates drying of the tablets.

White coating powder in water in a stir tank (STR2). Once the entire batch has been pressed into tablets and has accumulated in the IBC, the bin is completely dispensed into a fully perforated side vented coating pan (COAT) equipped with four Schlick 931/7-1 S35 (ABC) spray guns charged with the previously prepared coating solution. The drying air flows from the perforations and leaves through the exhaust. The fully perforated pan shows increasingly versatile coating capability and is more efficient than other methods of drying as shown in Figure 12.1.4 [24]. The operators clean the tablet presses, the IBC, and the coating solution preparation stir tank while the coater runs. After coater dispenses and dries an even film coating on the tablets, the batch of final tablets is packaged into two 55-gallon pharmaceutical-grade drums. Finally, operators conduct minor cleanings of the tablet coater and final tablet quality testing, finalizing the production of one batch.

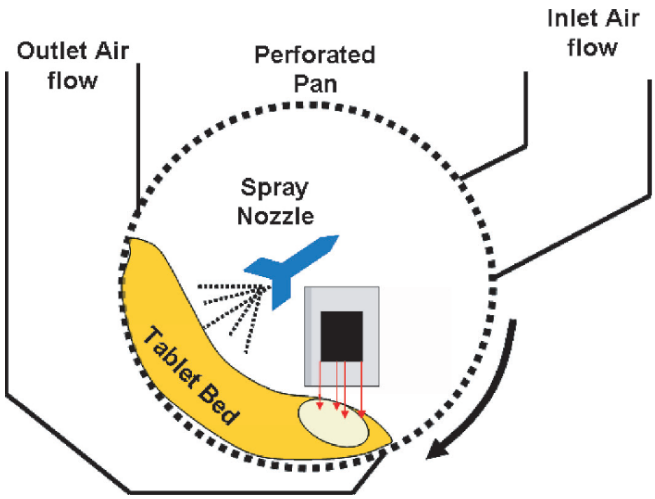


Figure 12.1.4. Schematic of Fully Perforated drum for a batch process. In this process, the tablets are coated in the tablet with a coating solution using a spraying arm and dried with air as the perforated pan is rotated [48].

Section 12.2 Hybrid Process

12.2.1 Bin Blender

The same bin blenders are used for the hybrid process. Please see Section 12.1.1.

12.2.2 Continuous Twin-Screw Granulation

While the equipment selected is different from the one in the batch process, the main principles described in Section apply for continuous granulation. For this process, a continuous twin-screw wet granulator (TSG) will be used. In the past decade, there has been a significant increase in the adoption of continuous manufacturing techniques by the pharmaceutical industry, largely due to their well-established benefits (as shown in Figure 12.2.1). This is a departure from conventional batch manufacturing, where the size of the batch is limited solely by the dimensions of the equipment used [49]. Several studies have been reported relating to TSG optimization by investigating the effect of the formulation composition and operational variables such as screw configuration, pitch and length of conveying element, thickness and angle of kneading element, or influence of kneading blocks [14]. A schematic diagram of a TSG line is illustrated in Figure 12.2.2.

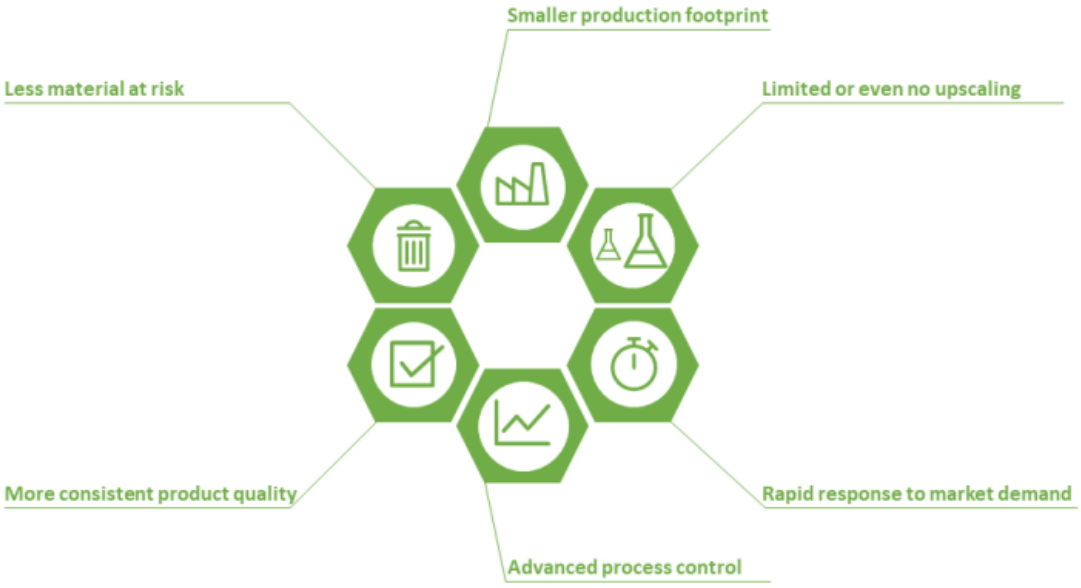


Figure 12.2.1. Advantages of continuous manufacturing [49].

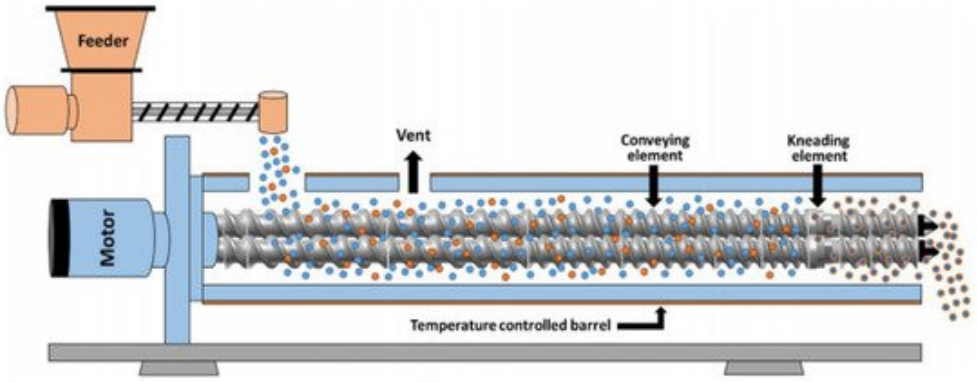


Figure 12.2.2. Schematic representation of a twin screw granulator [20].

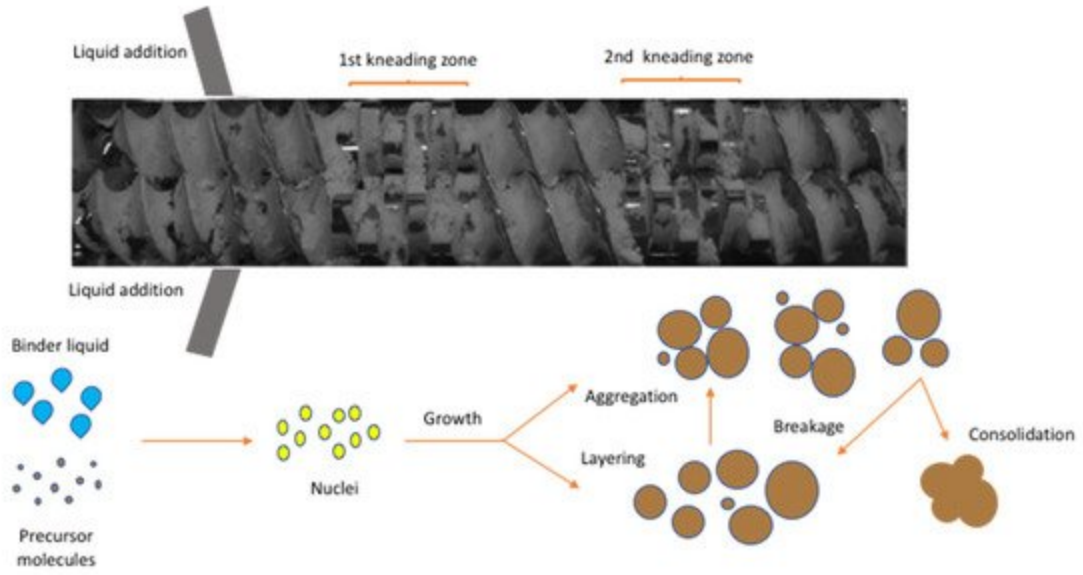


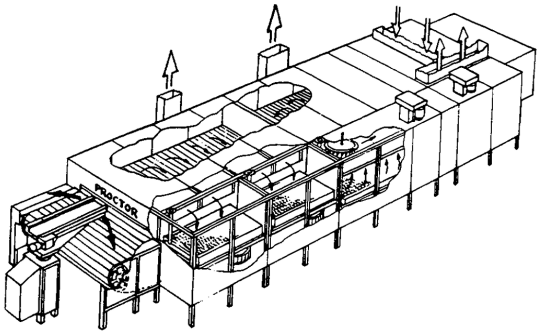
Figure 12.2.3. Screw configuration with 12 kneading disks illustrating the formation of granules in TSG [21].

As shown in Figure 12.2.3, the dry powder is fed in the barrel through the feeding zone while the granulating liquid is added using two nozzles (for each screw). The granule formation takes place through a combination of capillary and viscous forces facilitating particle binding in the wet stage. Subsequently, the wet material is distributed, compacted and elongated in the kneading elements (mixing zone) transforming the particle morphology from small (microstructure) to large (macro structure) irregular and porous granules. Other sub-processes such as aggregation and breakage can also take place during granulation. Eventually, the formed granules leave the discharge zone and are pneumatically fed in the conveyor belt dryer [14].

12.2.3 Continuous Conveyor Belt Drying

A conveyor belt dryer usually has several stages, per Figure 12.2.4. The wet product from the twin-screw wet granulator is fed on the left end of the dryer. The materials are then conveyed through the various stages until the dry product is discharged on the right end of the dryer, as

shown in Figure 12.2.5. As the materials are being conveyed along the dryer, ambient air is fed into the drying chamber which is equipped with an individual heating utility and fans for air circulation through the product. Heat exchange units operating with steam are used to heat the air. Fresh air is mixed with recirculated air below the heat exchangers upon entering the chamber. Typically, the temperature and humidity of the drying air stream that enters the product within each drying chamber are controlled, along with the temperature difference upon leaving [19]. The drying air flows in opposite directions in successive stages, for example, the air is blown downwards in stage 1; while the air is blown upwards in stage 2. At the product particle level, the moisture migrates from the center to the surface where it is evaporated by convection. Evaporative cooling reduces the surface temperature, and at the same time, drying air heats up the tablet particle by convective heating [1].



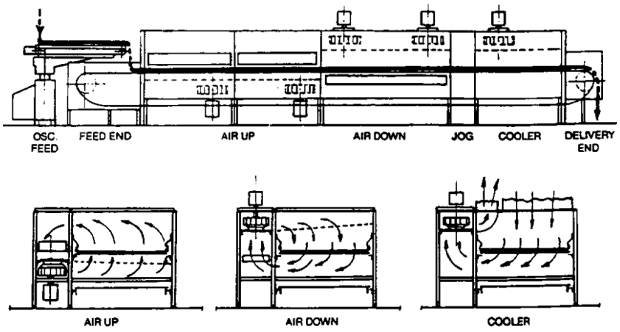


Figure 12.2.4. (Left) Cutaway view of single-convoyeur belt dryer. **Figure 12.2.5.** (Right) Side elevation of single-conveyor dryer [1].

12.2.4 Comil

The same comil is used for the hybrid process. Please see Section 12.1.4.

12.2.5 Continuous Mixer

The output from the mill is pneumatically conveyed and fed to the continuous mixer, that is the product is moved through a pipeline or a duct using air or another gas as the conveying medium. In this process, the product is introduced into the pipeline or duct, and air is forced or pulled through it, creating a flow of the product-air mixture. The flow of air carries the product through the pipeline or duct and delivers it to the continuous mixer. Once the product-air mixture reaches the continuous mixer, it is fed into the mixer, where it is combined with magnesium stearate. The continuous mixer is suitable for mixing a wide range of powders, flakes and granulates and viscous products, also in combination with spraying of liquids [10]. The mixers are equipped with a motorized shaft that is positioned axially in the center of the blender and has multiple blades along its length [32]. An advantage of using a continuous mixer is it lowers the risk of segregation after blending because the particles are blended continuously, and the blend is transported to the tablet press using a flexible screw conveyor. Continuous mixers also have the advantage of being more compact, occupying less space, and being easily scalable to obtain higher throughputs. Lastly, continuous mixing is fully automated and requires fewer operators.

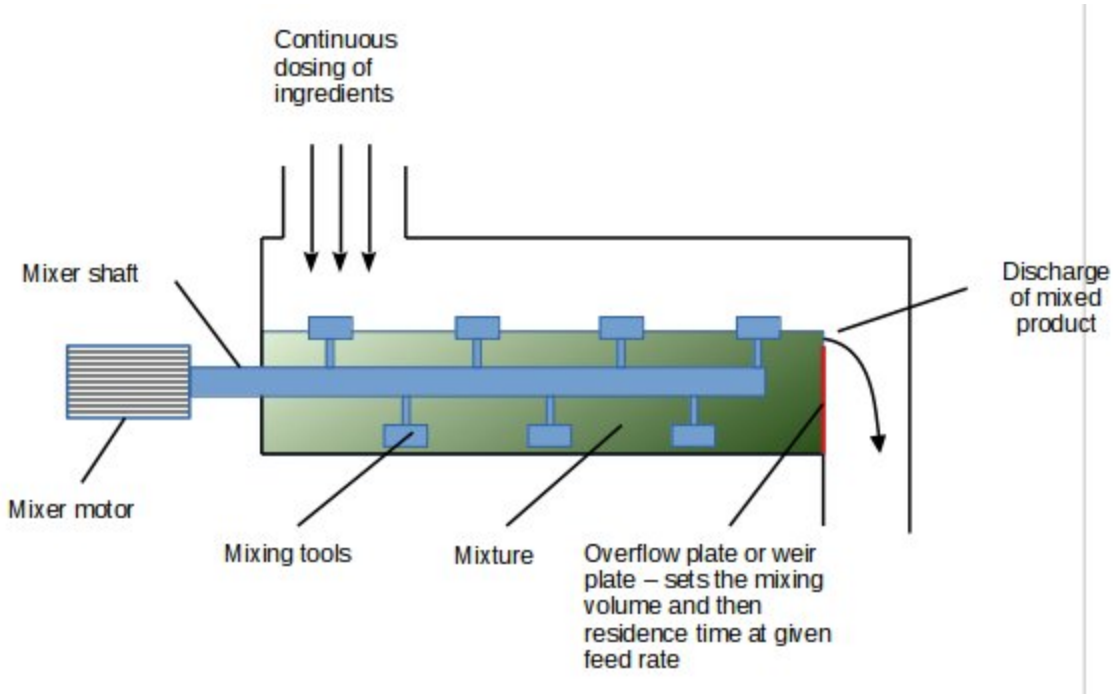


Figure 12.2.6. Schematic of a continuous mixer [38].

12.2.6 Rotary Tablet Press

The same rotary tablet presses are used for the hybrid process. Please see Section 12.1.5.

12.2.7 Batch Fully Perforated Coating Pan

The same coating pan is used for the hybrid process. Please see Section 12.1.6.

Section 13: Energy Balance and Utility Requirements

Section 13.1 Energy Balance and Utility Requirements for the Batch Process

13.1.1 Bin Blender

When considering combining API and excipients together, heat is created due to the collisions between particles. Energy calculations were made in order to estimate the amount of heat being absorbed by the material and lost to the surroundings. The heat absorbed by the ingredients can be calculated based on the difference between the inlet and outlet temperatures of the solids as well as the heat capacity which is based on the weighted average of the composition. The blender rotational speed was concluded to be 5 RPM, which was provided by one of the industrial consultants. The temperature difference was 3℃ as the inlet temperature was 22℃ and the outlet temperature was 25℃, respectively. The motor power requirements were 5.5 kW for each bin blender utilized. Energy calculations can be found in Section 24.1.1.

Table 13.1.1. Utility Requirements for the Bin Blender

Unit	Motor Power (kWh/day)	Steam (kg/batch)	Water (kg/batch)
BBR1 (B)	4.13	-	-
BBR2 (B)	4.13	-	-

13.1.2 Granulator

The energy balance of the high shear granulator is based on the heat provided by the air, the sensible heat of the solids, the enthalpy provided by the water, and the motor power requirement. The heat provided by the hot air can be calculated based on the temperature difference and the heat capacity of the hot air. The mass flow rate of the hot air was 535 kg/hr with the inlet and outlet temperatures being 60℃ and 45℃. The sensible heat of the solids and the enthalpy provided by the water was calculated in the same manner. The heat capacity of the solid was calculated based on the weighted average of the composition. The mass flow rate of the solids was 145.6 kg/hr with the inlet and outlet temperatures being 25℃ and 28℃, respectively. The mass flow rate of the water was 27.2 kg/hr with the same temperature parameters. The heat of the evaporation of the water was calculated based on the mass flow rate and the latent heat of evaporation of water. The motor requirement was 37 kW according to the Glatt TDG specification sheet.

Table 13.1.2. Utility Requirements for the High Shear Granulator

Motor Power (kWh/day)	Steam (kg/batch)	Water (kg/batch)
12.4	0.839	27.2

13.1.3 Tray Dryer

For convective drying, the hot air dissipated in the chamber is utilized to evaporate the water. The inlet mass flow rate of the hot air was calculated to be 5790 kg/hr with the inlet and outlet temperatures of 60℃ and 55℃ respectively. The heat provided by the hot air can be calculated based on the temperature difference and the heat capacity of the hot air. The evaporation load was evaluated with the change in moisture composition as 0.144 kg/kg. The heat absorbed by the ingredients can be calculated based on the difference between the inlet and outlet temperatures of the solids as well as the heat capacity which is based on the weighted average of the composition. The inlet and outlet temperatures of solids were 25℃ and 55℃, respectively. Even though the heat provided by the hot air is expected to be dissipated into the material and the evaporation load, heat was still released to the surroundings. Energy calculations can be found in Section 24.1.3.

Table 13.1.3. Utility Requirements for the Tray Dryer

Motor Power (kWh/day)	Steam (kg/batch)	Water (kg/batch)
124	45.1	-

13.1.4 Comil

The energy balances can be calculated similarly to the bin blenders due to the rotation of the impellers. It was calculated to evaluate the amount of energy absorbed by the solid material. The heat absorbed by the ingredients can be calculated based on the difference between the inlet and outlet temperatures of the solids as well as the heat capacity which is based on the weighted average of the composition. The comil rotational speed was concluded to be 600 RPM due to the small size in diameter. The temperature difference was 3℃ as the inlet temperature was 25℃ and the outlet temperature was 28℃, respectively. The motor power requirements were 0.55 kW. Energy calculations can be found in Section 24.1.4.

Table 13.1.4. Utility Requirements for the Comil

Motor Power (kWh/day)	Steam (kg/day)	Water (kg/day)
13.2	-	-

13.1.5 Rotary Tablet Press

The energy balances were calculated to estimate the amount of energy required by the tablet press by evaluating the heat absorbed by the material and the work of compression. The heat absorbed by the material is estimated The energy balances were calculated to estimate the amount of energy required by the tablet press by evaluating the heat absorbed by the material and the work of compression. The heat absorbed by the material is estimated based on the difference between the inlet and outlet temperatures of the solids as well as the heat capacity. The inlet and outlet temperatures of the solids were 23℃ and 25℃, yielding to a 3℃ difference. The heat capacity was based on the weighted average of the composition within the unit operation. The work of compression was considered as the compression force is one of most important parameters that can be adjusted for a tablet press, based on the product requirement. The work of compression was provided by the Fette P1010 technical brochure. The energy balances were applied to all three equipment. Energy calculations can be found in Section 20.1.5.

Table 13.1.5. Utility Requirements for Rotary Tablet Press

Unit	Motor Power (kWh/day)	Steam (kg/day)	Water (kg/day)
TAB1 (B)	240	-	-
TAB2 (B)	240	-	-
TAB3 (B)	240	-	-

13.1.6 Tablet Coater

Energy balances were evaluated to estimate the amount of heat dissipated in the solid materials. When estimating the amount of heat being absorbed by the ingredients, the heat provided by the hot air, the evaporation load, the coating solution must be considered. The heat provided by the hot air is based on the difference between the inlet and outlet temperatures as well as the heat capacity of hot air at 25℃. The inlet and outlet temperatures of the air were 45℃ and 30℃, respectively. The evaporation load was calculated based on the change in moisture composition and the latent heat of evaporation of water. Given that the moisture composition did not change, the evaporation load can be neglected. The heat sensitivity of the solids was estimated based on the difference between the inlet and outlet temperatures of the solids as well as the heat capacity. The inlet and outlet temperatures of the solids were 25℃ and 30℃. The heat capacity was based on the weighted average of the composition within the unit operation. The heat sensitivity of the coating solution can be calculated in the same manner with similar parameters. The total motor power requirements were 39.0 kW. Energy calculations can be found in Section 20.1.6.

Table 13.1.6. Utility Requirements for Batch Perforated Pan Tablet Coater

Motor Power (kWh/day)	Steam (kg/batch)	Water (kg/batch)
270	42.7	19.2

Section 13.2 Energy Balance and Utility Requirements for the Hybrid Process

13.2.1 Bin Blender

When considering combining API and excipients together, heat is created due to the rotation of the mixer. Energy calculations were made in order to estimate the amount of heat being absorbed by the material and lost to the surroundings. The heat absorbed by the ingredients can be calculated based on the difference between the inlet and outlet temperatures of the solids as well as the heat capacity which is based on the weighted average of the composition. The blender rotational speed was concluded to be 5 RPM. The temperature difference was 3℃ as the inlet temperature was 22℃ and the outlet temperature was 25℃, respectively. The motor power requirements were 1.32 kW for the initial blender. Energy calculations can be found in Section 24.1.1.

Table 13.2.1. Utility Requirements for Bin Blender

Motor Power (kWh/day)	Steam (kg/batch)	Water (kg/batch)
4.13	-	-

13.2.2 Twin-Screw Granulator

The energy balance for twin-screw granulator is based on the energy dissipated in the solid material, the heat transfer from the granulator jacket into the particles, and the motor power (Jiang 2008). The mass flow rate of the solids was 17.43 kg/hr with the inlet and outlet temperatures being 25℃ and 28℃. The heat capacity of the solids was based on the weighted average of the composition at the specific unit operation. The conductivity and the inner surface area of the granulator jacket was considered in order to determine the heat transfer. The motor requirement was 18.6 kW, which was provided through a quote by a Leistritz representative.

Table 13.2.2. Utility Requirements for the Twin-Screw Granulator

Motor Power (kWh/day)	Steam (kg/day)	Water (kg/day)
224	-	81.6

13.2.3 Conveyor Belt Dryer

The energy balances for the conveyor belt dryer can be calculated in the same manner as the batch vacuum tray dryer as both utilize convective drying. The inlet mass flow rate of the hot air was calculated to be 693 kg/hr with the inlet and outlet temperatures of 60℃ and 55℃. The heat provided by the hot air can be calculated based on the temperature difference and the heat capacity of the hot air. The evaporation load was evaluated with the change in moisture composition as 0.144 kg/kg. The heat absorbed by the ingredients can be calculated based on the difference between the inlet and outlet temperatures of the solids as well as the heat capacity which is based on the weighted average of the composition. The inlet and outlet temperatures of solids were 25℃ and 55℃, respectively. Even though the heat provided by the hot air is expected to be dissipated into the material and the evaporation load, heat was still released to the surroundings. Energy calculations can be found in Section 24.1.3.

Table 13.2.3. Utility Requirements for the Conveyor Belt Dryer

Motor Power (kWh/day)	Steam (kg/day)	Water (kg/day)
274	195	-

13.2.4 Comil

The comil in the batch process was also utilized in the hybrid process with the same parameters. The energy balance details can be found in Section 13.1.4 and the energy calculations can be found in Section 24.1.4.

Table 13.2.4. Utility Requirements for the Comil		
Motor Power (kWh/day)	Steam (kg/day)	Water (kg/day)
13.2	-	-

13.2.5 Continuous Mixer

The energy balances for the continuous mixer can be calculated in the same methodology as the bin blender. The energy balance description can be found in Section 13.1.1. The mass flow rate of the solids was 17.4 kg/hr with the inlet and outlet temperatures being 22℃ and 25℃. The mixer rotational speed was 10 RPM. The motor requirements were 1.32 kW. The energy energy calculations can be found in Section Section 24.1.1.

Table 13.2.5. Utility Requirements for the Continuous Mixer		
Motor Power (kWh/day)	Steam (kg/day)	Water (kg/day)
15.8	-	-

13.2.6 Rotary Tablet Press

The energy balance description can be found Section 13.1.5. The inlet and outlet temperatures of the solids were 23℃ and 25℃, respectively. The energy balances were applied to both tablet presses for the process. Energy calculations can be found in Section 24.1.5.

Table 13.2.6. Utility Requirements for Rotary Tablet Press

Unit	Motor Power (kWh/day)	Steam (kg/batch)	Water (kg/batch)
TAB1 (H)	240	-	-
TAB2 (H)	240	-	-

13.2.7 Tablet Coater

The tablet coater in the batch process was also utilized in the hybrid process with the same parameters. The energy balance details can be found in Section 13.1.6 and the energy calculations can be found in Section 24.1.6.

Table 13.2.7. Utility Requirements for Tablet Coater

Motor Power (kWh/day)	Steam (kg/batch)	Water (kg/batch)
270	31.4	19.2

Section 14: Equipment List and Unit Descriptions

Section 14.1 Equipment List and Unit Descriptions for the Batch Process

14.1.1 Bin Blender

The bin blender is a closed container that homogeneously mixes dry powders together in addition to lubricating the API to prevent the granules from sticking from one another and/or the equipment. The L.B.Bohle 400 Bin Blender was selected due to its components which consists of the standard arm connection and round forks on the lift arm with clamps. The bin blender contains two main aspects: the IBC container and the blender itself. The IBC container is loaded into the blender for the blending process to occur. Once all the drying products are transported, the IBC container is then locked, lifted at an angle, and rotated in 360 degrees up to 6 rpm. The mixing efficiency is maximized as varied aspects of the product mixture can come in contact due to the changes in velocities.

BBR1 (B) / BBR2 (B)	
Batch/Continuous	Batch
Pressure (atm)	1
Temperature (C)	25
Power (kW)	5.50

14.1.2 High Shear Granulator

The Glatt TDG 600 was selected as a model equipment for the batch granulation process. During high shear wet granulation, the dry powder is pushed and mixed in a vessel using an agitator and a chopper. The fine powders are sprayed with binding solution through varied nozzles while they are being mixed. The agitator rotates in the horizontal plane to ensure a uniform mixture. The chopper lays vertically to reduce the particle sizes and deagglomerates any masses that may occur.

HSGR (B)	
Batch/Continuous	Batch
Pressure (atm)	1
Temperature (C)	25
Power (kW)	37.0

14.1.3 Batch Tray Dryer

The Industrial Fabricator IFVTD72 was the chosen model equipment for the batch drying process. The stainless steel vacuum tray dryer consists of 72 solid trays which are held in a small chamber for the purpose of drying the granulated material at its expected moisture composition. For every batch, the tablets are loaded by the operator onto the trays into the cabinet until the drying time is completed. The trays are stacked vertically with sufficient space in between in order to enable for the air to travel parallelly to them. The drying of the tablets occurs by conduction at which the the pressure of the air is reduced through a vacuum pump, allowing for steam to pass through the free spaces in between trays.

VTDR (B)	
Batch/Continuous	Batch
Pressure (atm)	1
Temperature (C)	60
Power (kW)	18.3

14.1.4 Comil

The purpose of milling is to reduce the particle size through the use of intense shear on the particles. The Quadro SLS Comil PsD d90 conical mill screen was the chosen equipment for the milling process due to its SMARTdetect functionality that allows for the equipment to set its own RPM and has the ability to change the heads if necessary. The stainless steel screen consists of 1.5 mm round holes.

COML (B)	
Batch/Continuous	Continuous
Pressure (atm)	1
Temperature (C)	25
Power (kW)	0.550

14.1.5 Rotary Tablet Press

The Fette P1010 was selected as the model equipment for the continuous rotary tablet press due to its minimal space requirements. It is designed with an enclosed compression to avoid the possibility of contamination. The rotary press consists of a total maximum of 32 stations with a tablet output of 230,400 tablets per hour.

TAB1 (B) / TAB2 (B) / TAB3 (B)	
Batch/Continuous	Continuous
Pressure (atm)	1
Temperature (C)	25
Power (kW)	10.0

14.1.6 Batch Perforated Pan Tablet Coater

The Thomas Engineering Flex 500 60B Biconical Drum was the chosen equipment for the batch tablet coating process. The coater consists of unique features such as auto unload, patented Thomas Spray Bar (TSB), and exchangeable drums. The TSB is a modular spray manifold that creates a smooth velocity profile for the airflow to reduce the air turbulence, increasing the efficiency of the spraying performance.

COAT (B)	
Batch/Continuous	Batch
Pressure (atm)	25
Temperature (C)	1
Power (kW)	39.0

Section 14.2. Equipment List and Unit Descriptions for the Hybrid Process

14.2.1 Bin Blender

Please see Section 14.1.1 for the description.

BBR1 (H)	
Batch/Continuous	Batch
Pressure (atm)	1
Temperature (C)	25
Power (kW)	5.50

14.2.2 Twin-Screw Granulator

The Leistritz ZSE-27 HP was the chosen equipment for the continuous granulation process. The equipment is provided through a base 304 stainless steel cabinet that holds the extruder and the electrical system and controls. The extruders are modular barrels heated by electric heaters at a capacity of 25 C. The equipment also consists of a barrel heat exchanger, stainless steel vacuum, a digital loss-in-weight feeder fabricated of 316L stainless steel, and a liquid diaphragm pump.

TSER (H)	
Batch/Continuous	Continuous
Pressure (atm)	1
Temperature (C)	25
Power (kW)	18.6

14.2.3 Continuous Dryer

The HuaMao DW Series Conveyor Belt dryer was the chosen equipment for the continuous drying process. The conveyor dryer is 8 meters long in length with the ability to recycle the air.

CBDR (H)	
Batch/Continuous	Continuous
Pressure (atm)	1
Temperature (C)	60
Power (kW)	11.4

14.2.4 Comil

Please see Section 14.1.4 for the description.

COML (H)	
Batch/Continuous	Continuous
Pressure (atm)	1
Temperature (C)	25
Power (kW)	0.550

14.2.5 Continuous Mixer

The Gericke GCM 250 was the chosen equipment for the continuous mixing process due to its high mixing efficiency and tablet output with minimal space requirements. The mixer consists of a gravimetric feeder that weighs out the ingredients which allows for the tablets to precisely be placed into the mixer. Thus, the feeder rate is controlled. Due to the structure of the system, it provides the optimal mixing through a single shaft radially and axially.

CTMR (H)	
Batch/Continuous	Continuous
Pressure (atm)	1
Temperature (C)	25
Power (kW)	1.32

14.2.6 Rotary Tablet Press

Please see Section 14.1.5 for the description.

TAB1 (H) / TAB2 (H)	
Batch/Continuous	Continuous
Pressure (atm)	1
Temperature (C)	25
Power (kW)	10.0

14.2.7 Batch Tablet Coater

Please see Section 14.1.6 for the description.

COAT (H)	
Batch/Continuous	Batch
Pressure (atm)	25
Temperature (C)	1
Power (kW)	39.0

Section 15: Specification Sheets

Section 15.1 Batch Process Specification Sheets

15.1.1 Bin Blender

Item No.		BBR1 (B) / BBR2 (B)	
Model		PM 400 Bin Blender	
Vendor		L.B.Bohle	
No. Required		2	
Function		Combines the API, lactose, and Avicel together	
Operation (Batch/Continuous, Time)		Batch, 15 minutes for BBR1 (B), 10 minutes for BBR2 (B)	
		BBR1 (B)	BBR2 (B)
Material Input	API (kg/batch)	16.0	16.0
	Lactose (kg/batch)	97.6	97.6
	Avicel (kg/batch)	16.0	16.0
	PVP-K90 (kg/batch)	0	4.80
	Water (kg/batch)	0	3.20
	Magnesium Stearate (kg/batch)	0	1.60
Properties	Material	Stainless Steel	
	Size (L)	400	
	Capacity (kg)	400	
	RPM	5	
	Motor Power	5.50	

	BBR1 (B)	BBR2 (B)
Temperature (C)	25	25
Pressure (atm)	1	1

15.1.2 High Shear Granulator

Item No.		HSGR (B)
Model		TDG 600
Vendor		Glatt
No. Required		1
Function		Converts the fine powder into granules
Operation (Batch/Continuous, Time)		Batch, 15 min.
Material Input	API (kg/batch)	15
	Lactose (kg/batch)	97.6
	Avicel (kg/batch)	32.0
	PVP-K90 (kg/batch)	4.80
	Water (kg/batch)	27.2
Properties	Material	Stainless Steel
	Size (mm)	2250 x 3700 x 3700 (W x H x T)
	Capacity (L)	150 - 480
	Motor Power (kW)	37
Temperature (C)		25
Pressure (atm)		1

15.1.3 Batch Tray Dryer

Item No.		VTDR (B)
Model		IFVTD72
Vendor		Industrial Factor
No. Required		1
Function		Dries the tablet to the expected moisture level
Operation (Batch/Continuous, Time)		Batch, 135 mins
Material Input	API (kg/batch)	15
	Lactose (kg/batch)	97.6
	Avicel (kg/batch)	32.0
	PVP-K90 (kg/batch)	4.80
	Water (kg/batch)	27.2
	Magnesium Stearate (kg/batch)	15
Properties	Size (in)	60 x 72 x 72 (L x W x H)
	No. of Trays	72
	Motor Power (kW)	18.3
Temperature (C)		60
Pressure (atm)		1

15.1.4 Comil

Item No.		COML (B)
Model		SLS Comil PSD d90
Vendor		Quadro
No. Required		1
Function		Reduces the sizes of the wet granulations and delumps powder granules
Operation (Batch/Continuous, Time)		Continuous
Material Input	API (kg/hr)	15.9
	Lactose (kg/hr)	97.6
	Avicel (kg/hr)	32.0
	PVP-K90 (kg/hr)	4.80
	Water (kg/hr)	3.21
Properties	Material	Stainless Steel
	Screen Size	1.5 mm
	Capacity	50 g to 150 kg/hr
	Motor Power (kW)	0.550
Temperature (C)		25
Pressure (atm)		1

15.1.5 Rotary Tablet Press

Item No.		TAB1 (B) / TAB2 (B) / TAB3 (B)		
Model		P1010		
Vendor		Fette		
No. Required		3		
Function		Compresses granule powders into uniform tablet form and size		
Operation (Batch/Continuous, Time)		Continuous, 285 minutes		
		TAB1 (B)	TAB2 (B)	TAB3 (B)
Material Input	API (kg/hr)	5.33	5.33	5.33
	Lactose (kg/hr)	32.5	32.5	32.5
	Avicel (kg/hr)	10.7	10.7	10.7
	PVP-K90 (kg/hr)	1.60	1.60	1.60
	Water (kg/hr)	1.07	1.07	1.07
	Magnesium Stearate (kg/hr)	0.533	0.533	0.533
Properties	Material	Stainless Steel		
	Size (mm)	900 × 1,163 × 1,888		
	Capacity (tablets/hr)	27,000 to 216,000		
	Motor Power (kW)	10		
		TAB1 (B)	TAB2 (B)	TAB3 (B)
Temperature (C) [50]		25	25	25
Pressure (atm)		1	1	1

15.1.6 Batch Perforated Pan Tablet Coater

Item No.		COAT (B)
Model		Flex 500 60B
Vendor		Thomas Engineering
No. Required		1
Function		Coats the tablet with coating solution for mainly marketing purposes
Operation (Batch/Continuous, Time)		Batch, 135 min
Material Input	API (kg/batch)	15.9
	Lactose (kg/batch)	97.6
	Avicel (kg/batch)	32.0
	PVP-K90 (kg/batch)	4.80
	Water (kg/batch)	30.4
	Magnesium Stearate (kg/batch)	1.59
	Opadry® II White (kg/batch)	4.80
Properties	Material	Stainless Steel
	Drum Diameter Size (in.)	60
	Capacity (L)	460
	Motor Power (kW)	2.20
Temperature (C)		25
Pressure (atm)		1

Section 15.2 Hybrid Process Specification Sheets

15.2.1 Bin Blender

Item No.		BBR1 (H)
Model		PM 400
Vendor		L.B.Bohle
No. Required		1
Function		Combines the API, lactose, and Avicel together
Operation (Batch/Continuous, Time)		Batch, 15 minutes
Material Input	API (kg/batch)	16.0
	Lactose (kg/batch)	97.6
	Avicel (kg/batch)	32.0
Properties	Material	Stainless Steel
	Size (L)	400
	Capacity (kg)	400
	Motor Power (kW)	5
Temperature		25 C
Pressure		1 atm

15.2.2 Twin-Screw Granulator

Item No.		TSER (H)
Model		ZSE-27HP GMP-Format
Vendor		Leistritz Extrusion Technology
No. Required		1
Function		Mixes the API, excipients, and polymers together to enhance greater flowability
Operation (Batch/Continuous, Time)		Continuous, 415 minutes
Material Input	API (kg/hr)	2.10
	Lactose (kg/hr)	12.8
	Avicel (kg/hr)	4.20
	PVP-K90 (kg/hr)	0.631
	Water (kg/hr)	3.57
Properties	Material	Stainless Steel
	Diameter (mm)	27
	Capacity (kg/hr)	15 - 20
	RPM	600
	Motor Power (kW)	18.6
Temperature (C)		25
Pressure (atm)		1

15.2.3 Continuous Dryer

Item No.		CBDR (H)
Model		DW-1.2 -8A
Vendor		HuaMao
No. Required		1
Function		Dries granules to the expected moisture level
Operation (Batch/Continuous, Time)		Continuous, 415 minutes
Material Input	API (kg/hr)	2.10
	Lactose (kg/hr)	12.8
	Avicel (kg/hr)	4.20
	PVP-K90 (kg/hr)	0.631
	Water (kg/hr)	3.57
Properties	Length (m)	8
	Motor Power (kW)	11.4
Temperature (C)		60
Pressure (atm)		1

15.2.4 Comil

Item No.		COML (H)
Model		SLS Comil PSD d90
Vendor		Quadro
No. Required		1
Function		Reduces the sizes of the wet granulations and delumps powder granules
Operation (Batch/Continuous, Time)		Continuous
Material Input	API (kg/hr)	2.10
	Lactose (kg/hr)	12.8
	Avicel (kg/hr)	4.20
	PVP-K90 (kg/hr)	0.631
	Water (kg/hr)	0.420
Properties	Material	Stainless Steel
	Screen Size (mm)	1.50
	Capacity	50 g to 150 kg+/hr
	Motor Power (kW)	0.550
Temperature (C)		25
Pressure (atm)		1

15.2.5 Continuous Mixer

Item No.		CTMR (H)
Model		GCM 250
Vendor		Gericke Group
No. Required		1
Function		Combines the API, excipients, and magnesium stearate together
Operation (Batch/Continuous, Time)		Continuous, 415 min
Material Input	API (kg/hr)	2.10
	Lactose (kg/hr)	12.8
	Avicel (kg/hr)	4.20
	PVP-K90 (kg/hr)	0.631
	Water (kg/hr)	0.420
	Magnesium Stearate (kg/hr)	0.210
Properties	Material	Stainless Steel
	Capacity (kg/hr)	1-25
	Motor Power (kW)	1.32
Temperature		25 C
Pressure		1 atm

15.2.6 Rotary Tablet Press

Item No.		TAB1 (H) / TAB1 (H)	
Model		P1010	
Vendor		Fette	
No. Required		2	
Function		Compresses granule powders into uniform tablet form and size	
Operation (Batch/Continuous, Time)		Continuous, 415 minutes	
		TAB1 (H)	TAB2 (H)
Material Input	API (kg/hr)	1.05	1.05
	Lactose (kg/hr)	6.41	6.41
	Avicel (kg/hr)	2.10	2.10
	PVP-K90 (kg/hr)	0.315	0.315
	Water (kg/hr)	0.210	0.210
	Magnesium Stearate (kg/hr)	0.105	0.105
Properties	Material	Stainless Steel	
	Size (mm)	900 × 1,163 × 1,888	
	Capacity (output/hr)	27,000 to 216,000	
	Motor Power (kW)	10	
		TAB1 (H)	TAB2 (H)
Temperature (C)		25	25
Pressure (atm)		1	1

15.2.7 Batch Tablet Coater

Item No.		COAT (H)
Model		Flex 500 60B
Vendor		Thomas Engineering
No. Required		1
Function		Coats the tablet with coating solution for mainly marketing purposes
Operation (Batch/Continuous, Time)		Batch, 70 min
Material Input	API (kg/batch)	16.0
	Lactose (kg/batch)	32.0
	Avicel (kg/batch)	97.6
	PVP-K90 (kg/batch)	4.80
	Water (kg/batch)	3.20
	Magnesium Stearate (kg/batch)	1.60
	Opadry® II White (kg/batch)	4.80
Properties	Material	Stainless Steel
	Drum Diameter Size (in)	60.0
	Capacity (L)	115 - 460
	Motor Power (kW)	2.20
Temperature (C)		25
Pressure (atm)		1

Section 16: Equipment Cost Summary

Despite efforts to contact manufacturers directly for pricing information, few quotes were obtained overall. A few points of contact were made, but only Leistritz Extrusion Technology and Quadro Engineering followed through by providing full documentation including descriptions, specifications, and a quote. The majority of purchase costs were estimated using the six tenths rule, drawing from reference sizes and prices found in academic reports or mentioned by consultants. The following price estimates were presented to multiple pharmaceutically experienced consultants and were agreed to be reasonably accurate.

Section 16.1 Equipment Cost Summary for Hybrid Process

Equipment Description	Quantity	Purchase Cost	Data Source	Bare Module Factor	Bare Module Cost
LB Bohle PM Blender 400	1	$176,000	*Formulation of a High-Volume Small Molecule Drug Product*	3.21	$565,000
ZSE 27 HP-PH Twin Screw Extruder	1	$751,000	Quote from Steve Post, Leistritz Extrusion	3.05	$2,290,000
HuaMao DW Series Conveyor Dryer	1	$21,000	KODI Industrial Conveyor on Alibaba	2.06	$43,000
Quadro PsD d90 Conical Mill	1	$34,000	Quote from Lee Tassoni, Quadro Engineering	2.3	$78,000
Gericke Group GCM 250	1	$166,000	*Formulation of a High-Volume Small Molecule Drug Product*	3.21	$532,000
Fette P1010 Tablet Press	2	$1,427,000	Sabrina Green, Merck	3.21	$4,580,000
Thomas Engineering Flex 500 60B Coater	1	$850,000	*Formulation of a High-Volume Small Molecule Drug Product*	3.21	$2,730,000
NCD 50 M Mixing Vessel	2	$14,400	Anco Equipment	3.21	$46,000
100 Gallon Open Head Drum	21	$22,500	Bubba’s Barrels	1	$22,500
Total Bare Module Cost					**$10.89 M**

Section 16.2 Equipment Cost Summary for Batch Process

Equipment Description	Quantity	Purchase Cost	Data Source	Bare Module Factor	Bare Module Cost
LB Bohle PM Blender 400	2	$352,000	*Formulation of a High-Volume Small Molecule Drug Product*	3.21	$1,230,000
Glatt TDG 600 Granulator	1	$420,000	Wonsen on Alibaba	3.05	$1,280,000
Industrial Factor Vacuum Tray Dryer 72	1	$22,000	Shiv Shakti Process Equipment on Alibaba	2.06	$45,300
Quadro PsD d90 Conical Mill	1	$34,000	Quote from Lee Tassoni, Quadro Engineering	2.3	$78,000
Fette P1010 Tablet Press	3	$2,140,000	Sabrina Green, Merck	3.21	$6,870,000
Thomas Engineering Flex 500 60B Coater	1	$850,000	*Formulation of a High-Volume Small Molecule Drug Product*	3.21	$2,730,000
NCD 50 M Mixing Vessel	2	$14,400	Anco Equipment	3.21	$46,000
IBC	2	$7,000	Alibaba	1	$7,000
Total Bare Module Cost					**$12.29 M**

Section 17: Fixed Capital Investment Summary

The Profitability Analysis spreadsheet was used to calculate the economic costs for the manufacturing facility. The equipment purchase costs mentioned in Section 16 were inputted into the “Equipment Cost” tab, classified as “Process Machinery”. Storage drums and intermediate bin containers were defined as “Storage”. The default bare module factor for all the equipment was 3.21 if it was unknown. The known bare module factors were calculated based on the definitions of the equipment from Seider et al.

The total fixed capital investment was calculated based on the total bare module costs, the direct permanent investment, total depreciable capital, total permanent investment, and working capital. The default calculations and total bare module costs were used to calculate the total permanent investment by evaluating the costs of the site preparation, service facilities, allocated for utility plants and related facilities, contingencies and contractor fees, land, and plant start-up. There is no considered royalty cost.

Table 17. 1. Contributing factors to Total Permanent Investment

Cost of Site Preparation	5.00% of Total Bare Module Costs
Cost of Service Facilities	5.00% of Total Bare Module Costs
Allocated Costs for Utility Plants and Related Facilities	$0
Costs of Contingencies and Contractor Fees	18.00% Direct Permanent Investment
Cost of Land	0.00% of Total Depreciable Capital
Cost of Royalties	$0
Cost of Plant Start-Up	10.00% of Total Depreciable Capital

The working capital was calculated based on the number of days regarding the accounts receivable, cash reserves (excluding raw materials), accounts payable, product inventory, and raw materials. The accounts receivable, cash reserves, and accounts payable were set to 30 days. The product inventory was set to 4 days and raw materials was set to 2 days as default.

The maximal demand for tablets per year is one order of magnitude larger than the minimal demand. 500,000 tablets per year is half an order of magnitude larger than the lower demand. This value was selected as a reasonable approximation for the average tablet demand per year and provided an appropriate intermediate demand for sensitivity analysis.

Section 17.1 Hybrid Process for Base Case Scenario of 500 Million Tablets per Year at $0.03 per Tablet

The total capital investment of the hybrid process is $18.6 million. Specific costs are shown in Figure. 17.1.1.

Figure 17.1.1. Total Capital Investment for the Hybrid Process of 500 Million Tablets per Year at $0.03 per Tablet

Investment Summary

Total Bare Module Costs:			
Fabricated Equipment	$	-	
Process Machinery	$	10,865,224	
Spares	$	-	
Storage	$	22,500	
Other Equipment	$	-	
Catalysts	$	-	
Computers, Software, Etc.	$	-	
Total Bare Module Costs:			**$ 10,887,724**
Direct Permanent Investment			
Cost of Site Preparations:	$	544,386	
Cost of Service Facilities:	$	544,386	
Allocated Costs for utility plants and related facilities:	$	-	
Direct Permanent Investment			**$ 11,976,496**
Total Depreciable Capital			
Cost of Contingencies & Contractor Fees	$	2,155,769	
Total Depreciable Capital - Unadjusted			**$ 14,132,266**
Site Factor			1.10
Total Depreciable Capital			**$ 15,545,492**
Total Permanent Investment			
Cost of Land:	$	-	
Cost of Royalties:	$	-	
Cost of Plant Start-Up:	$	1,554,549	
Total Permanent Investment - Unadjusted			$ 15,686,815
Site Factor			1.10
Total Permanent Investment			**$ 17,255,496**

Working Capital

	2024	2025	2026
Accounts Receivable	$ 604,110	$ 302,055	$ 302,055
Cash Reserves	$ 148,434	$ 74,217	$ 74,217
Accounts Payable	$ (3,685)	$ (1,842)	$ (1,842)
Insert Product Here Inventory	$ 80,548	$ 40,274	$ 40,274
Raw Materials	$ -	$ -	$ -
Total	**$ 829,407**	**$ 414,703**	**$ 414,703**
Present Value at 15%	*$ 721,223*	*$ 313,575*	*$ 272,674*

Total Capital Investment	**$ 18,562,969**

Section 17.2 Batch Process for Base Case Scenario of 500 Million Tablets per Year at $0.03 per Tablet

The total capital investment of the batch process is $20.6 million. Specific costs are shown in Figure. 17.2.1.

Figure 17.2.1. Total Capital Investment for the Hybrid Process of 500 Million Tablets per Year at $0.03 per Tablet

Investment Summary

Total Bare Module Costs:			
Fabricated Equipment	$	-	
Process Machinery	$	12,178,564	
Spares	$	-	
Storage	$	7,000	
Other Equipment	$	-	
Catalysts	$	-	
Computers, Software, Etc.	$	-	
Total Bare Module Costs:			$ 12,185,564
Direct Permanent Investment			
Cost of Site Preparations:	$	609,278	
Cost of Service Facilities:	$	609,278	
Allocated Costs for utility plants and related facilities:	$	-	
Direct Permanent Investment			$ 13,404,120
Total Depreciable Capital			
Cost of Contingencies & Contractor Fees	$	2,412,742	
Total Depreciable Capital - Unadjusted			$ 15,816,862
Site Factor			1.10
Total Depreciable Capital			$ 17,398,548
Total Permanent Investment			
Cost of Land:	$	-	
Cost of Royalties:	$	-	
Cost of Plant Start-Up:	$	1,739,855	
Total Permanent Investment - Unadjusted			$ 17,556,717
Site Factor			1.10
Total Permanent Investment			$ 19,312,389

Working Capital

	2024	2025	2026
Accounts Receivable	$ 616,438	$ 308,219	$ 308,219
Cash Reserves	$ 125,394	$ 62,697	$ 62,697
Accounts Payable	$ (1,186)	$ (593)	$ (593)
Insert Product Here Inventory	$ 82,192	$ 41,096	$ 41,096
Raw Materials	$ -	$ -	$ -
Total	**$ 822,838**	**$ 411,419**	**$ 411,419**
Present Value at 15%	*$ 715,511*	*$ 311,092*	*$ 270,515*

Total Capital Investment	**$ 20,609,506**

Section 18: Operating Cost - Cost of Manufacture

Section 18.1 Operator Costs

For both the hybrid and batch processes, the tableting plant will run 24 hours and 7 days a week in Massachusetts in order to maximize efficiency by minimizing startup and shutdown costs and time consumption. Both processes will require 2 weeks of equipment maintenance out of the year. The hybrid plant will undergo deep cleaning for 2 days at the start of each month, and run for a total of 327 days out of the year at highest demand. The batch plant will undergo a 16 hour deep cleaning after every 10 batches, and will run for 351 days per year at highest demand. Deep cleaning will be conducted with industrial steam cleaning equipment [12]. For both the hybrid and batch processes, 8 operators will be hired with two people doing 8 hours of overtime in a given week. This way, 2 people can be on site at the plant at all times. Operators will be paid holiday wages when appropriate. The API and excipient raw materials are considered free and provided by the parent company.

Section 18.2 API and Ingredients

It is assumed that the API, excipients, and other raw materials are provided at no cost given that it is manufactured in the same facility.

Section 18.3 Utility Costs

Electricity, water, and steam were required to calculate the total utility costs. The cost for each utility is shown in Table 18.2.1. The total utility requirements for both the batch and hybrid processes were evaluated and presented in Table 18.2.2 and Table 18.2.3.

Table 18.2.1. Utility Costs (Based in Massachusetts)			
Utility	Electric Rates	Water	Steam
Cost	0.21 cent / kWh	$2.96 / 1000 kg	$35.94 / 1000 kg

18.2.1. Utility Costs for the Batch Process

Table 18.2.2. Total Utility Requirements for the Batch Process			
Unit	Motor Power (kWh/day)	Steam (kg/batch)	Water (kg/batch)
Bin Blender	4.13	-	-
Bin Blender	4.13	-	-
Granulator	12.4	0.839	27.2
Tray Dryer	124	45.1	-
Comil	13.2	-	-
Rotary Tablet Press	240	-	-
Rotary Tablet Press	240	-	-
Rotary Tablet Press	240	-	-
Tablet Coater	270	42.7	19.2
Total (**per day**)	**1148**	**266**	**139**

18.2.2. Utility Costs for the Hybrid Process

Table 18.2.3. Total Utility Requirements for the Hybrid Process			
Unit	Motor Power (kWh/day)	Steam (kg/day)	Water (kg/day)
Bin Blender	4.13	-	-
Granulator	224	-	81.6
Conveyor Belt Dryer	274	195	-
Comil	13.2	-	-
Continuous Mixer	15.8	-	-
Rotary Tablet Press	240	-	-
Rotary Tablet Press	240	-	-
Tablet Coater	270	94.2	57.6
Total (**per day**)	**1281**	**289**	**139**

Section 18.4 Fixed Cost Summary

The fixed cost is based on the default operations, maintenance, operating overhead, property taxes and insurance, and other annual expenses from Seider et al. For both the batch and hybrid process, it is assumed that there are 2 operators for every shift (5 shifts). The direct wages and benefits are set to $40 per hour. See Section 18.1 to see specific details about the operations for both processes. See Figure 18.4.1 for the fixed costs breakdown calculations.

Figure 18.4.1. Fixed Costs Breakdown

Operations						
	Operators per Shift:	2	(assuming	5	shifts)	
	Direct Wages and Benefits:	$40	/operator hour			
	Direct Salaries and Benefits:	15%	of Direct Wages and Benefits			
	Operating Supplies and Services:	6%	of Direct Wages and Benefits			
	Technical Assistance to Manufacturing:	$60,000.00	per year, for each Operator per Shift			
	Control Laboratory:	$65,000.00	per year, for each Operator per Shift			
Maintenance						
	Wages and Benefits:	4.50%	of Total Depreciable Capital			
	Salaries and Benefits:	25.00%	of Maintenance Wages and Benefits			
	Materials and Services:	100.00%	of Maintenance Wages and Benefits			
	Maintenance Overhead:	5.00%	of Maintenance Wages and Benefits			
Operating Overhead						
	General Plant Overhead:	7.10%	of Maintenance and Operations Wages and Benefits			
	Mechanical Department Services:	2.40%	of Maintenance and Operations Wages and Benefits			
	Employee Relations Department	5.90%	of Maintenance and Operations Wages and Benefits			
	Business Services	7.40%	of Maintenance and Operations Wages and Benefits			
Property Taxes and Insurance						
	Property Taxes and Insurance:	2.00%	of Total Depreciable Capital			
Straight Line Depreciation						
Direct Plant:	8.00%	of Total Depreciable Capital, less		1.18	times the Allocated Costs	
					for Utility Plants and Related Facilities	
Allocated Plant:	6.00%	of	1.18	times the Allocated Costs for Utility Plants and Related Facilities		
Other Annual Expenses						
Rental Fees (Office and Laboratory Space):		$0				
	Licensing Fees:	$0				
	Miscellaneous:	$0				
Depletion Allowance						
	Annual Depletion Allowance:	$0				

Section 18.4.1 Fixed Costs Summary for the Hybrid Process for Base Case Scenario of 500 Million Tablets per Year at $0.03 per Tablet

The total fixed costs is $2.75 million for the hybrid process.

Figure 18.4.1 Fixed Costs Summary for the Hybrid Process

Fixed Cost Summary

Operations			
	Direct Wages and Benefits	$	260,000
	Direct Salaries and Benefits	$	39,000
	Operating Supplies and Services	$	15,600
	Technical Assistance to Manufacturing	$	120,000
	Control Laboratory	$	130,000
	Total Operations	**$**	**564,600**
Maintenance			
	Wages and Benefits	$	699,547
	Salaries and Benefits	$	174,887
	Materials and Services	$	699,547
	Maintenance Overhead	$	34,977
	Total Maintenance	**$**	**1,608,958**
Operating Overhead			
	General Plant Overhead:	$	83,314
	Mechanical Department Services:	$	28,162
	Employee Relations Department:	$	69,233
	Business Services:	$	86,834
	Total Operating Overhead	**$**	**267,543**
Property Taxes and Insurance			
	Property Taxes and Insurance:	$	310,910
Other Annual Expenses			
	Rental Fees (Office and Laboratory Space):	$	-
	Licensing Fees:	$	-
	Miscellaneous:	$	-
	Total Other Annual Expenses	**$**	**-**
Total Fixed Costs		**$**	**2,752,011**

Section 18.4.2 Fixed Costs Summary for the Batch Process for Base Case Scenario of 500 Million Tablets per Year at $0.03 per Tablet

The total fixed costs is $3.85 million for the batch process.

Figure 18.4.1 Fixed Costs Summary for the Hybrid Process

Fixed Cost Summary

Operations			
	Direct Wages and Benefits	$	832,000
	Direct Salaries and Benefits	$	124,800
	Operating Supplies and Services	$	49,920
	Technical Assistance to Manufacturing	$	120,000
	Control Laboratory	$	130,000
	Total Operations	**$**	**1,256,720**
Maintenance			
	Wages and Benefits	$	782,935
	Salaries and Benefits	$	195,734
	Materials and Services	$	782,935
	Maintenance Overhead	$	39,147
	Total Maintenance	**$**	**1,800,750**
Operating Overhead			
	General Plant Overhead:	$	137,418
	Mechanical Department Services:	$	46,451
	Employee Relations Department:	$	114,193
	Business Services:	$	143,225
	Total Operating Overhead	**$**	**441,287**
Property Taxes and Insurance			
	Property Taxes and Insurance:	$	347,971
Other Annual Expenses			
	Rental Fees (Office and Laboratory Space):	$	-
	Licensing Fees:	$	-
	Miscellaneous:	$	-
	Total Other Annual Expenses	**$**	**-**
Total Fixed Costs		**$**	**3,846,727**

Section 18.5 Variable Costs Summary

The variable cost is based on the raw materials, byproducts, utilities, and general expenses. The general expenses included the selling/transfer expenses, direct research, allocated research, administrative expense, and management incentive compensation. There were no raw materials and byproducts to consider as raw materials were free and there were no byproducts resulting from the process created.

Section 18.5.1 Variable Costs Summary for the Hybrid Process for Base Case Scenario of 500 Million Tablets per Year at $0.03 per Tablet

The variable cost is solely dependent on the utilities which is $0.000183 per tablet of Albatol. See total utility requirements for the hybrid process in Section 18.2.2. The total variable costs of the hybrid process is approximately $954,000.

Figure 18.5.1 Variable Costs Summary for the Hybrid Process

Variable Cost Summary

Variable Costs at 100% Capacity:

General Expenses			
	Selling / Transfer Expenses:	$	-
	Direct Research:	$	300,000
	Allocated Research:	$	75,000
	Administrative Expense:	$	300,000
	Management Incentive Compensation:	$	187,500
Total General Expenses		$	862,500
Raw Materials	$0.000000 per tablet of Albatol		$0
Byproducts	$0.000000 per tablet of Albatol		$0
Utilities	$0.000183 per tablet of Albatol		$91,497
Total Variable Costs		**$**	**953,997**

Section 18.5.2 Variable Costs Summary for the Batch Process for Base Case Scenario of 500 Million Tablets per Year at $0.03 per Tablet

The variable cost is solely dependent on the utilities which is $0.000183 per tablet of Albatol. See total utility requirements for the batch process in Section 18.2.1.

Figure 18.5.1 Variable Costs Summary for the Batch Process

Variable Cost Summary

Variable Costs at 100% Capacity:			
General Expenses			
Selling / Transfer Expenses:		$	-
Direct Research:		$	300,000
Allocated Research:		$	75,000
Administrative Expense:		$	300,000
Management Incentive Compensation:		$	187,500
Total General Expenses		$	862,500
Raw Materials	$0.000000 per tablet of Insert Product He		$0
Byproducts	$0.000000 per tablet of Insert Product He		$0
Utilities	$0.000058 per tablet of Insert Product He		$28,871
Total Variable Costs		**$**	**891,371**

The total variable cost of the batch process is approximately $891,000. The total variable cost of the batch process is greater than the variable cost of the hybrid process due to the greater utility requirements for the continuous process. Despite the differences, the hybrid process is still profitable based on the internal rate of return and net present value. See Section 20.1 and Section 20.2 for details about the profitability analysis for both processes.

Section 19: Other Considerations

Section 19.1 Location Determination

China and India are the most rapidly growing pharmaceutical markets, so selecting them as the production location would have resulted in reduced costs for labor, infrastructure, and equipment. India in particular has strong generic medicine production, while China heavily emphasizes R&D investment. Albatol, however, is a branded drug that is already fully developed and FDA approved, so it does not particularly benefit from these countries' expertise. To streamline economic analysis, sidestep the complexities of international regulations, and keep a closer eye on CGMP compliance, the manufacturing plant will be established in the US. The Boston area is a hub for pharmaceutical and biotechnology activities, and locating our plant there would ensure a ready and nearby supply of innovation, parts manufacturers, and technical expertise. Of particular note is that Kerry, an excipient and coating supplier, has a location in Quincy, MA, which is just 20 minutes drive from Boston. To avoid being directly in the expensive metropolitan area, the plant will likely be placed in a nearby suburb rather than Boston.

Section 19.2 Environmental Factors and Safety Concerns

The granulation and drying stages, as well as the tablet coating phase, of both the batch and continuous manufacturing processes result in the release of exhaust air and evaporated water. These emissions do not pose any environmental hazards. Infact, the significant usage of processing water, steam, and electricity in both processes translates to high demands for energy and water resources. However, in a batch process for drug tablet production, the manufacturing

steps are carried out in discrete batches, and each batch is handled separately. This often involves the manual transfer of materials, which can generate dust during various stages such as dispensing, mixing, granulation, and compression. For instance, the operators would need to manually transfer materials from the vacuum tray dryer to the miller. In contrast, a continuous process involves a continuous flow of materials through the manufacturing line, and there is no need for intermediate handling, which reduces the generation of dust.

In the course of the manufacturing processes, powders are utilized, and various operations within these processes may generate dust. The higher amount of dust generated in a batch process could cause a health hazard for operators as an excess of fine particulate matter in air can lead to respiratory problems, eye irritation, and other health issues. Hence, the use of protective equipment such as respiratory masks, goggles, gloves, and lab coats is essential to safeguard the health and safety of the workers. Given that the excessive presence of fine particulate matter in the air can trigger a dust explosion, it is critical to contain all dust within the manufacturing facilities. To achieve this goal, appropriate equipment has been selected to ensure dust containment. Moreover, operators working in the facilities will be provided with suitable personal protective equipment (PPE) as stated in GMP guideline: "All personnel should wear suitable protective clothing, hair covering and where applicable, beard covering. They should also wear appropriate PPE, including, but not necessarily limited to, gloves, masks, eye protection, and gowns, to protect both product and personnel. PPE should be suitable for the operation to be performed and its cleanliness should be ensured. It should be used and maintained in a manner that prevents microbiological contamination or cross-contamination with other products" [33]. Furthermore, to avoid contaminating medicinal goods, it is crucial that the materials used in production equipment for the pharmaceutical industry be suitable. Due to its

low maintenance requirements, cleanability, and corrosion resistance, stainless steel is usually regarded as the ideal material in accordance with Good Manufacturing Practice (GMP) laws. As a result, all equipment used in the manufacture of pharmaceutical goods must be made of stainless steel or another material that satisfies the standards for use in a pharmaceutical setting, according to GMP rules: "Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements. Materials used in the construction of equipment shall be of appropriate composition so as to facilitate cleaning and maintenance operations, and shall not contribute to the contamination of the drug product" [51].

Section 19.3 Cleaning

Based on a recommendation from our project author, it was assumed that one round of minor cleaning in the batch process would take about 10 minutes in between each batch campaign. Subsequently, after 10 batch campaigns a major cleaning is required and that will take around 4 hours for shutting down the process and disassembling the equipment, 8 hours for cleaning the disassembled equipment, and 4 hours for reassembling the equipment and starting up the process. For the continuous process, it is recommended that major cleaning would take 3 days in each month.

Section 19.4 Production Building Layout

A pharmaceutical tablet plant that utilizes gravity transfer materials would typically have a layout that minimizes the need for mechanical conveyance equipment. This would include building the facility without pumps or conveyors, allowing materials to move naturally through the production process utilizing gravity. In such a facility, raw materials like excipients and active pharmaceutical ingredients (APIs) would be kept in silos or other raised bulk storage containers. They would then be transported to the plant's different processing facilities by a system of gravity chutes and/or pipelines from there. With this reason, we plan to design a two-floor production building with each floor of height around 15 ft or 4.6 m, as shown in the figure below. Raw materials from the top of the second floor are gathered into the IBC container 1 or 2 that is securely clamped onto the drum of the bin blender BBR 1 so that it can rotate in a controlled manner to ensure the materials inside are blended evenly. After that the mixture will be transported by forklifts to the top of the second floor again and later combined with water and PVP-K90 from STR 1, and flow into the high shear granulator HSGR. HSGR is positioned above the tray dryer VTDR and a transfer system is used to direct the granules from the bottom of the granulator into the tray dryer, to the Comil COML and then to the IBC 3 or 4 and BBR 2 respectively. Note that the comil selected here is an 'Underdriven Comil' that is "ideal in situations where mills need to be installed on height-adjustable lifts or columns and so much more compact than its Overdriven counterpart [35]." To elevate materials from the bottom floor to the top floor using a vacuum method, a vacuum conveying system is installed between the two floors. The system consists of a vacuum pump, a conveying pipeline, and a receiving hopper or vessel on the top floor. The materials are loaded into a feeding hopper located on the bottom

floor, which is connected to the vacuum conveying pipeline. The vacuum pump creates a negative pressure inside the pipeline, which causes the materials to be pulled into the pipeline and conveyed upward. The materials move through the pipeline in a controlled manner, as the rate of conveyance can be adjusted based on the pressure and flow rate of the vacuum system. Once the materials reach the top floor, they are deposited into the receiving hopper or vessel, which is designed to collect the materials and prevent them from escaping into the surrounding environment. The receiving hopper or vessel is typically located above the splitter SPTR that will distribute material downwards into the tablet presses (TAB 1, 2 and 3). Finally, tablets are compressed and moved along a transfer conveyor, which moves the tablets from the tablet press to the coater. The conveyor may include features such as vibrating trays, chutes, or other mechanisms to ensure a smooth and even flow of tablets.

Figure 19.4.1. Plant Layout of the Manufacturing Facility for Batch Process

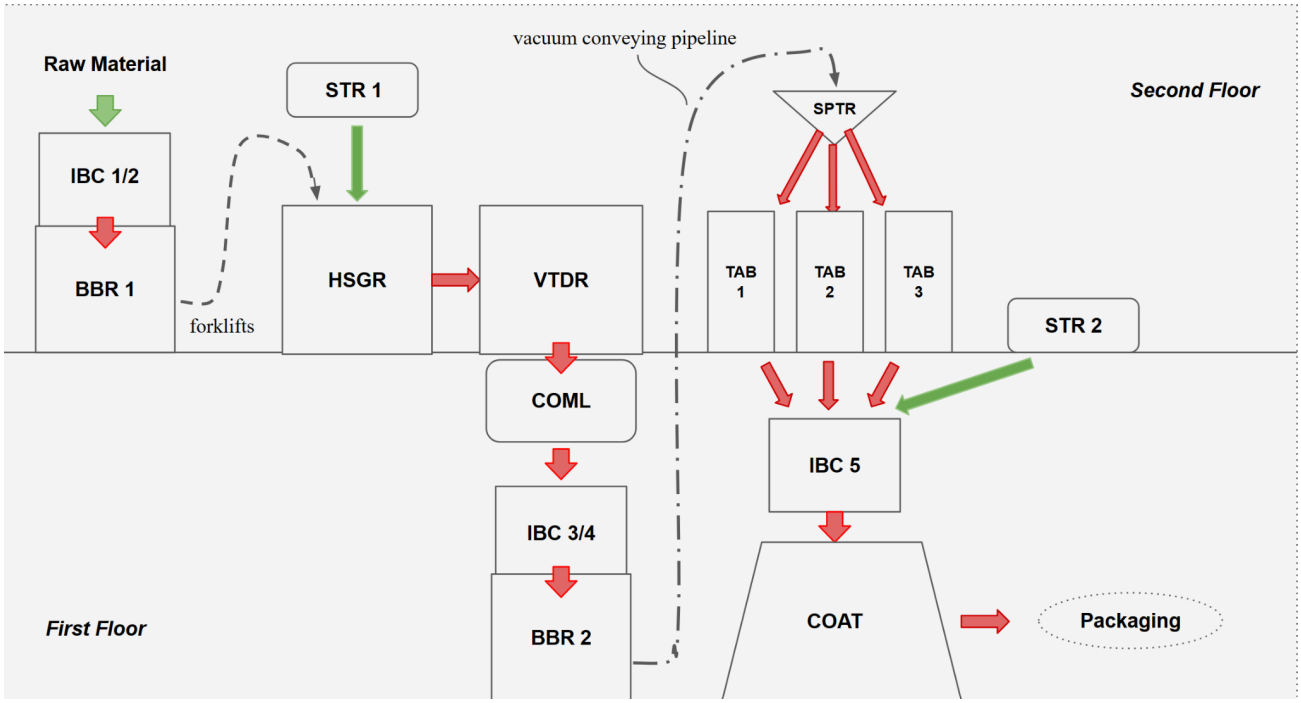
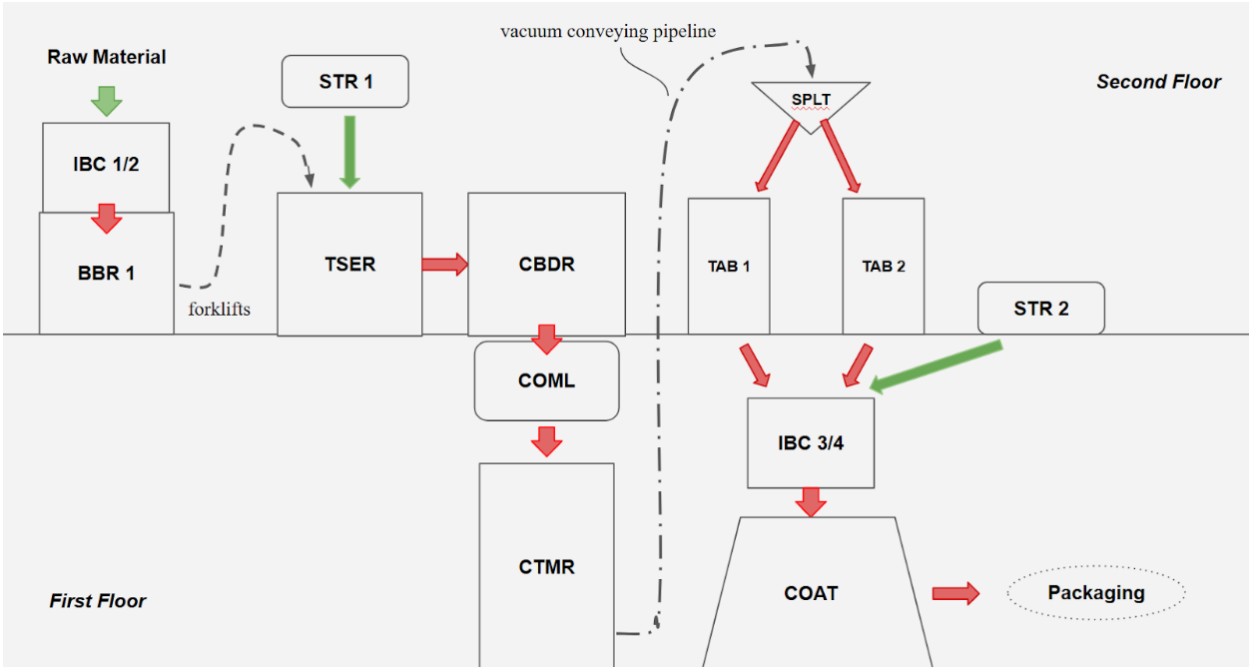


Figure 19.4.2. Plant Layout of the Manufacturing Facility for Hybrid Process



Section 20: Profitability Analysis - Business Case

20.1 Hybrid Process Profitability and Sensitivity Analysis

A profitability analysis was conducted under the assumptions that 1 year of design and 1 year of construction were needed before the plant became operational. The plant would then run at 50% of production capacity for the first year before reaching 75% in the second year of operation, then 100% for all subsequent years. The plant was estimated to run for 20 years of production. The income tax rate was considered 23%, the cost of capital 15%, and the general inflation rate 2%. Selling/transfer expenses were assumed to be zero because the plant is an intermediate step in a larger drug tableting process owned by the same company. Thus, all costs associated with transferring the raw materials in for processing, transferring the tablets out for packaging, and selling the actual packaged tablets can be considered covered by the parent company. The cost of land was also assumed to be zero because the plant is a part of a larger facility already owned by the company. Because of these accommodating factors, the plant is able to run for only part of the year when experiencing lower demand. The equipment pieces can then be repurposed for use by the company for the remainder of the year. Similarly, company operators are only needed for part of the year, and can be transferred to another sector once demand for the year is met. Therefore, the utilities and labor costs of running the plant can be lower depending on the lack of demand. For a standard “base case”, demand is considered to be 500 million tablets per year, which is nearly half a magnitude more than the low demand of 160 million tablets per year. The tableting plant receives $0.03 of revenue per tablet produced. The resulting cash flow is shown below, alongside an ROI analysis of the third production year.

Figure 20.1.1 Cash Flow Model for the Hybrid Process of 500 Million Tablets per Year at $0.03 per Tablet

Cash Flow Summary

Year	Percentage of Design Capacity	Product Unit Price	Sales	Capital Costs	Working Capital	Var Costs	Fixed Costs	Depreciation	Depletion Allowance	Taxible Income	Taxes	Net Earnings	Cash Flow	Cumulative Net Present Value at 15%
2023	0%		-	-	-	-	-	-	-	-	-	-	-	-
2024	0%		-	(17,255,500)	(811,700)	-	-	-	-	-	-	-	(18,067,200)	(15,710,600)
2025	50%	$0.03	7,500,000	-	(405,900)	(445,500)	(2,752,000)	(3,109,100)	-	1,193,300	(274,500)	918,900	3,622,100	(12,971,800)
2026	75%	$0.03	11,475,000	-	(405,900)	(681,700)	(2,807,100)	(4,974,600)	-	3,011,700	(692,700)	2,319,000	6,887,700	(8,443,000)
2027	100%	$0.03	15,606,000	-	-	(927,100)	(2,863,200)	(2,984,700)	-	8,831,000	(2,031,100)	6,799,900	9,784,600	(2,848,600)
2028	100%	$0.03	15,918,100	-	-	(945,600)	(2,920,500)	(1,790,800)	-	10,261,200	(2,360,100)	7,901,100	9,692,000	1,970,000
2029	100%	$0.03	16,236,500	-	-	(964,500)	(2,978,900)	(1,790,800)	-	10,502,200	(2,415,500)	8,086,700	9,877,600	6,240,300
2030	100%	$0.03	16,561,200	-	-	(983,800)	(3,038,400)	(895,400)	-	11,643,500	(2,678,000)	8,965,500	9,860,900	9,947,400
2031	100%	$0.03	16,892,400	-	-	(1,003,500)	(3,099,200)	-	-	12,789,700	(2,941,600)	9,848,100	9,848,100	13,166,800
2032	100%	$0.03	17,230,300	-	-	(1,023,600)	(3,161,200)	-	-	13,045,500	(3,000,500)	10,045,000	10,045,000	16,022,200
2033	100%	$0.04	17,574,900	-	-	(1,044,100)	(3,224,400)	-	-	13,306,400	(3,060,500)	10,245,900	10,245,900	18,554,800
2034	100%	$0.04	17,926,400	-	-	(1,064,900)	(3,288,900)	-	-	13,572,500	(3,121,700)	10,450,900	10,450,900	20,801,200
2035	100%	$0.04	18,284,900	-	-	(1,086,200)	(3,354,700)	-	-	13,844,000	(3,184,100)	10,659,900	10,659,900	22,793,600
2036	100%	$0.04	18,650,600	-	-	(1,108,000)	(3,421,800)	-	-	14,120,900	(3,247,800)	10,873,100	10,873,100	24,560,700
2037	100%	$0.04	19,023,600	-	-	(1,130,100)	(3,490,200)	-	-	14,403,300	(3,312,800)	11,090,500	11,090,500	26,128,200
2038	100%	$0.04	19,404,100	-	-	(1,152,700)	(3,560,000)	-	-	14,691,400	(3,379,000)	11,312,300	11,312,300	27,518,400
2039	100%	$0.04	19,792,200	-	-	(1,175,800)	(3,631,200)	-	-	14,985,200	(3,446,600)	11,538,600	11,538,600	28,751,400
2040	100%	$0.04	20,188,000	-	-	(1,199,300)	(3,703,800)	-	-	15,284,900	(3,515,500)	11,769,400	11,769,400	29,845,100
2041	100%	$0.04	20,591,800	-	-	(1,223,300)	(3,777,900)	-	-	15,590,600	(3,585,800)	12,004,800	12,004,800	30,815,200
2042	100%	$0.04	21,003,600	-	-	(1,247,700)	(3,853,500)	-	-	15,902,400	(3,657,600)	12,244,800	12,244,800	31,675,600
2043	100%	$0.04	21,423,700	-	-	(1,272,700)	(3,930,500)	-	-	16,220,400	(3,730,700)	12,489,700	12,489,700	32,438,700
2044	100%	$0.04	21,852,200	-	1,623,500	(1,298,200)	(4,009,200)	-	-	16,544,900	(3,805,300)	12,739,500	14,363,000	33,201,800

Figure 20.2.2 Return of Investment Analysis for the Hybrid Process of 500 Million Tablets per Year at $0.03 per Tablet

ROI Analysis (Third Production Year)

Annual Sales	15,606,000
Annual Costs	(3,790,285)
Depreciation	(1,380,440)
Income Tax	(2,400,113)
Net Earnings	8,035,162
Total Capital Investment	18,878,949
ROI	42.56%

To expand beyond this base case, a sensitivity study was conducted to investigate two key factors simultaneously: the price earned per tablet produced and the yearly demand. The same profitability analysis was performed but with different numbers for the days of continuous operation per year, operator wages (to correlate with what percentage of the year they worked), number of tablets produced per year, and price per tablet. For the hybrid process, the results were tabulated below in Table 20.1. Please note that any ROI values are for the third production year.

Table 20.1.1: Sensitivity Analysis of Hybrid Process with Changing Tablet Price and Demand

	Low Demand: 160M tablets/year, operate for 33 days/year	**Average Demand: 500M tablets/year, operate for 103 days/year**	**High Demand: 1.6B tablet/year, operate for 327 days/year**
$0.01 / tablet	NPV: -$18.4M IRR: “Negative” ROI: -10.6%	NPV: -$6.29M IRR: 7.70% ROI: 2.70%	NPV: $32.9M IRR: 40.5% ROI: 42.4%
$0.02 / tablet	NPV: -$12.1M IRR: -3.5% ROI: -3.66%	NPV: $13.4M IRR: 26.9% ROI: 23.1%	NPV: $96.1M IRR: 77.3% ROI: 98.1%
$0.03 / tablet	NPV: -$5.76M IRR: 8.3% ROI: 3.11%	NPV: $33.2M IRR: 41.2% ROI: 42.6%	NPV: $159M IRR: 108% ROI: 146%
$0.04 / tablet	NPV: $557,000 IRR: 15.6% ROI: 9.78%	NPV: $52.9M IRR: 53.9% ROI: 61.1%	NPV: $222M IRR: 135% ROI: 188%
$0.05 / tablet	NPV: $6.89M IRR: 21.5% ROI: 16.3%	NPV: $72.7M IRR: 65.5% ROI: 78.7%	NPV: $286M IRR: 160% ROI: 226%

As seen in the table, both factors have a significant influence on the overall profitability of the tableting plant. With an average level of demand, the venture will be successful even if the price per tablet drops to $0.02, but will not be able to sustain a price of $0.01. At low demand, the situation is worse, with the IRR barely larger than the cost of capital even at $0.04/tablet. Only $0.05 is able to turn this level of demand into reasonable profit. At high levels of demand, the plant is massively profitable in all price situations.

20.2 Batch Process Profitability and Sensitivity Analysis

Following the profitability analysis of the hybrid process, the same procedure was applied to the batch process in order to make a proper comparison. The same "base case" scenario of producing 500 million tablets per year at a revenue of $0.03/tablet was tested. Notably, the batch process had different equipment costs, utility usage, and days of continuous operation from the hybrid process. The resulting cash flow is shown below in Figure 20.2.1, followed by an ROI analysis of the third year of production (Figure 20.2.2). A subsequent sensitivity analysis of tablet price and level of yearly demand was performed, just as was done for the hybrid process, with the results found in Table 20.2.1.

Figure 20.2.1 Cash Flow Model for the Batch Process of 500 Million Tablets per Year at $0.03 per Tablet

Cash Flow Summary

Year	Percentage of Design Capacity	Product Unit Price	Sales	Capital Costs	Working Capital	Var Costs	Fixed Costs	Depreciation	Depletion Allowance	Taxible Income	Taxes	Net Earnings	Cash Flow	Cumulative Net Present Value at 15%
2023	0%		-	-	-	-	-	-	-	-	-	-	-	-
2024	0%		-	(19,312,400)	(822,800)	-	-	-	-	-	-	-	(20,135,200)	(17,508,900)
2025	50%	$0.03	7,500,000	-	(411,400)	(445,700)	(3,022,400)	(3,479,700)	-	552,200	(127,000)	425,200	3,493,500	(14,867,300)
2026	75%	$0.03	11,250,000	-	(411,400)	(668,500)	(3,022,400)	(5,567,500)	-	1,991,500	(458,100)	1,533,500	6,689,600	(10,468,800)
2027	100%	$0.03	15,000,000	-	-	(891,400)	(3,022,400)	(3,340,500)	-	7,745,700	(1,781,500)	5,964,200	9,304,700	(5,148,800)
2028	100%	$0.03	15,000,000	-	-	(891,400)	(3,022,400)	(2,004,300)	-	9,081,900	(2,088,800)	6,993,100	8,997,400	(675,500)
2029	100%	$0.03	15,000,000	-	-	(891,400)	(3,022,400)	(2,004,300)	-	9,081,900	(2,088,800)	6,993,100	8,997,400	3,214,300
2030	100%	$0.03	15,000,000	-	-	(891,400)	(3,022,400)	(1,002,200)	-	10,084,100	(2,319,300)	7,764,700	8,766,900	6,510,100
2031	100%	$0.03	15,000,000	-	-	(891,400)	(3,022,400)	-	-	11,086,200	(2,549,800)	8,536,400	8,536,400	9,300,700
2032	100%	$0.03	15,000,000	-	-	(891,400)	(3,022,400)	-	-	11,086,200	(2,549,800)	8,536,400	8,536,400	11,727,300
2033	100%	$0.03	15,000,000	-	-	(891,400)	(3,022,400)	-	-	11,086,200	(2,549,800)	8,536,400	8,536,400	13,837,400
2034	100%	$0.03	15,000,000	-	-	(891,400)	(3,022,400)	-	-	11,086,200	(2,549,800)	8,536,400	8,536,400	15,672,200
2035	100%	$0.03	15,000,000	-	-	(891,400)	(3,022,400)	-	-	11,086,200	(2,549,800)	8,536,400	8,536,400	17,267,700
2036	100%	$0.03	15,000,000	-	-	(891,400)	(3,022,400)	-	-	11,086,200	(2,549,800)	8,536,400	8,536,400	18,655,100
2037	100%	$0.03	15,000,000	-	-	(891,400)	(3,022,400)	-	-	11,086,200	(2,549,800)	8,536,400	8,536,400	19,861,600
2038	100%	$0.03	15,000,000	-	-	(891,400)	(3,022,400)	-	-	11,086,200	(2,549,800)	8,536,400	8,536,400	20,910,600
2039	100%	$0.03	15,000,000	-	-	(891,400)	(3,022,400)	-	-	11,086,200	(2,549,800)	8,536,400	8,536,400	21,822,900
2040	100%	$0.03	15,000,000	-	-	(891,400)	(3,022,400)	-	-	11,086,200	(2,549,800)	8,536,400	8,536,400	22,616,100
2041	100%	$0.03	15,000,000	-	-	(891,400)	(3,022,400)	-	-	11,086,200	(2,549,800)	8,536,400	8,536,400	23,305,900
2042	100%	$0.03	15,000,000	-	-	(891,400)	(3,022,400)	-	-	11,086,200	(2,549,800)	8,536,400	8,536,400	23,905,700
2043	100%	$0.03	15,000,000	-	-	(891,400)	(3,022,400)	-	-	11,086,200	(2,549,800)	8,536,400	8,536,400	24,427,300
2044	100%	$0.03	15,000,000	-	1,645,700	(891,400)	(3,022,400)	-	-	11,086,200	(2,549,800)	8,536,400	10,182,100	24,968,300

Figure 20.2.2 Return of Investment Analysis for the Batch Process of 500 Million Tablets per Year at $0.03 per Tablet

ROI Analysis (Third Production Year)

Annual Sales	**15,000,000**
Annual Costs	**(3,913,759)**
Depreciation	**(1,544,991)**
Income Tax	**(2,194,487)**
Net Earnings	**7,346,762**
Total Capital Investment	**20,958,064**
ROI	**35.05%**

Table 20.2.1: Sensitivity Analysis of Batch Process with Changing Tablet Price and Demand

	Low Demand: 160M tablets/year, operate for 38 days/year	**Average Demand: 500M tablets/year, operate for 115 days/year**	**High Demand: 1.6B tablet/year, operate for 351 days/year**
$0.01 / tablet	NPV: -$20.6M IRR: "Negative" ROI: -11.0%	NPV: -$9.91M IRR: 3.27% ROI: 0.45%	NPV: $24.7M IRR: 34.5% ROI: 35.0%
$0.02 / tablet	NPV: -$15.0M IRR: -9.38% ROI: -5.02%	NPV: $7.53M IRR: 21.8% ROI: 18.1%	NPV: $80.5M IRR: 68.5% ROI: 84.1%
$0.03 / tablet	NPV: -$9.40M IRR: 3.93% ROI: 0.84%	NPV: $25.0M IRR: 35.1% ROI: 35.1%	NPV: $136M IRR: 97.0% ROI: 127%
$0.04 / tablet	NPV: -$3.81M IRR: 11.0% ROI: 6.59%	NPV: $42.4M IRR: 46.7% ROI: 51.2%	NPV: $192M IRR: 122% ROI: 165%
$0.05 / tablet	NPV: $1.77M IRR: 16.7% ROI: 12.3%	NPV: $59.8M IRR: 57.4% ROI: 66.7%	NPV: $248M IRR: 145% ROI: 199%

The profitability of the batch process appears to be slightly worse than the hybrid process. The batch process will not be successful in low demand unless the tablet price increases

significantly to $0.05, and even then the IRR of 16.7% is only slightly larger than the 15% cost of capital. The batch process does remain profitable in all other cases except when demand is average and tablet price is $0.01, just like the hybrid process. However, the extent of profitability in all of these scenarios is lower than the hybrid process. Examining the “base case” specifically, we see that hybrid yields an NPV of $33.2M while batch produces an NPV of $25.0M, where hybrid offers 33% more value. This trend is consistent across the scenarios, increasing the appeal of the hybrid process.

Section 21: Conclusions and Recommendations

As demonstrated by the profitability and sensitivity analysis, the hybrid process offers a greater return in all cases as compared to the batch process. In a standardized example with a cost of conversion of $0.03 per tablet and an average demand of 500 million tablets per year, the hybrid process had an NPV of $33.2M and an IRR of 41.2%, while the batch process had an NPV of $25M and an IRR of 35.1%. This occurrence is likely due to the hybrid process requiring less capital investment. In particular, the need of the batch process to include three tablet presses rather than two was a significant factor, as those equipment pieces were some of the most expensive and heavily drove the overall cost. By obtaining more financially accurate information about the tablet presses via a reasonable quote and more specific bare module factor, the profitability analysis may change drastically. The hybrid process is also advantageous in that it automates much of the tableting process, requiring less frequent small-scale maintenance and cleaning, and as such, putting less strain on the operators and logistics of running the plant.

When the plant is consistently run at low demand, it struggles to remain profitable unless the price per tablet earned increases significantly. This is true for both the hybrid and batch process, but more so for batch. However, with an average demand of around 500 million tablets per year, the plant is fairly adaptable to fluctuations in tablet price, so long as they do not decrease to $0.01 per tablet. One of the key factors that allowed for the plant's profitability across a variety of scenarios is the assumption that it is built as part of an existing company facility. With utility infrastructure already established, negligible cost of land, and no cost for raw materials or transportation, many complications are already accounted for. Additionally, operators employed by the company can be reassigned to other processes once the yearly Albatol demand is reached, allowing us to more easily run production for only a portion of the year

without constantly hiring and letting go of employees. This factor also helps justify our capital expenditure, since our equipment can be repurposed by the company after Albatol requirements for the year have been met, which is a large percentage of time during average or low demand.

One likely scenario is that the first 2-3 years of production are met with low demand as Albatol first launches. Then, as the drug establishes itself and becomes more familiar to potential customers, the demand rises to average or above-average levels for the remainder of the plant's operation. Based on the results in Table 20.1.1, it is reasonable to assume that the hybrid plant would still manage to turn a profit in this case. If the company obtains better, more narrow estimates for demand, and the estimates appear to indicate an average or above-average demand for Albatol, the hybrid process can be confidently recommended. If no refined estimates can be obtained, we still recommend the development of the hybrid process, but with yearly predictions of demand and with frequent evaluations of whether the plant would be more profitable by repurposing it for alternative company use.

Section 22: Acknowledgements

We would like to thank all the industrial consultants who have taken the time of their day for that valuable expertise and advice throughout the project. We extend our appreciation to Steve Post and Lee Tassoni, of Leistritz Extrusion and Quadro Engineering respectively, for providing us with reliable quotes. We would like to show our gratitude to our project advisor, Dr. Wattenbarger, for her guidance and dedication in helping us succeed in completing the project. We would also like to thank Dr. Alex Marchut for allowing us to embark on a challenge, providing us with his expertise, and answering our questions in a timely manner. Lastly, we would also like to thank Professor Vrana for his time and dedication for coordinating the senior design projects, weekly meetings with the consultants, and lectures and providing us with the necessary tools for a successful completion of the project.

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Section 24: Appendix

Section 24.1 Energy Balance Calculations for the Batch and Hybrid Process

24.1.1 Energy Balance for Blending

The energy balance for blending can be represented by the following equation:

$$\Delta H + \Delta KE + \Delta PE = Q - W \quad \text{(Eqn. 24.1.1)}$$

where ΔH is the internal energy, ΔKE is the kinetic energy, ΔPE is the potential energy, Q is the heat in the system, and W is the work done by the system.

The kinetic energy is further represented as the rotational kinetic energy due to the stirring to uniformly combine the API and the excipients together. The equation is defined as:

$$\Delta KE = \frac{1}{2} I w^2 \quad \text{(Eqn. 24.1.2)}$$

where I is the moment of inertia of the stirring rod and w is the angular velocity.

The calculation of ΔH can be defined as the following:

$$\Delta H = m C_p \Delta T \quad \text{(Eqn. 24.1.3)}$$

Here, ΔPE is negligible for the bin blender given that the height of the powder minimally fluctuates from the blending rotation. It is also negligible for the continuous blender as the system positions horizontally.

24.1.2 Energy Balance for Granulation

24.1.2.1 Energy Balance for a High Shear Granulator

The energy balance for a high shear granulator can be represented by the following equation:

$$Q_{air} = Q_{s,sens} + Q_{water} + \mathrm{W} \quad \text{(Eqn. 24.1.4)}$$

where Q_{air} is heat provided by the air, $Q_{s,sens}$ is the sensible heating of the solids, Q_{water} is the enthalpy provided by the water, and W is the power input.

The heat provided by the air can be defined as:

$$Q_{air} = W_a C_{p,a}(T_{a,out} - T_{a,in}) \quad \text{(Eqn. 24.1.5)}$$

where W_a is the mass flowrate of the air, $C_{p,a}$ is the specific heat capacity of the air based on the mean temperature, $T_{a,out}$ is the outlet air temperature, and $T_{a,in}$ is the inlet air temperature.

The sensible heating of the solids can be defined as:

$$Q_{s,sens} = W_s C_{p,s}(T_{s,out} - T_{s,in}) \quad \text{(Eqn. 24.1.6)}$$

where W_s is the mass flowrate of the solid particles, $C_{p,s}$ is the specific heat capacity of the solid particles based on the mean temperature, $T_{s,out}$ is the outlet temperature of the solid particles, and $T_{s,in}$ is the inlet temperature of the solid particles.

The enthalpy provided by the water can be defined as:

$$Q_{water} = W_w C_{p,w}(T_{w,out} - T_{w,in}) + W_w \Delta H_{v,w} \quad \text{(Eqn. 24.1.7)}$$

where W_w is the mass flowrate of the water, $C_{p,w}$ is the specific heat capacity of the water based on the mean temperature, $T_{w,out}$ is the outlet temperature of the water, $T_{w,in}$ is the inlet temperature of the water, and $\Delta H_{v,w}$ is the heat of evaporation of the water.

24.1.2.2 Energy Balance for a Twin-Screw Granulator

The energy balance for twin-screw granulation can be represented by the following equation:

$$Q = H + W \quad \text{(Eqn. 24.1.8)}$$

where Q is the enthalpy of the solids assuming that pressure is neglected, H is the heat transfer from the granulator jacket to the solids, and W is the power input [16].

The enthalpy of the solids can be defined as the following equation:

$$Q_{s,sens} = W_s C_{p,s}(T_{s,in} - T_{s,out}) \quad \text{(Eqn. 24.1.9)}$$

where W_s is the mass flowrate of the solid particles, $C_{p,s}$ is the specific heat capacity of the solid particles on the mean temperature, $T_{s,in}$ is the inlet temperature of the solid particles, and $T_{s,out}$ is the outlet temperature of the solid particles.

The heat transfer from the granulator jacket can be represented by the following equation:

$$H = h(T_{in} - T_{out})A \quad \text{(Eqn. 24.1.10)}$$

where h is the conductivity of the granulator jacket and A is the surface area of the inner granulator jacket.

24.1.3 Energy Balance for Drying [17]

The energy balance for convective drying can be represented by the following equation developed by Kemp and Gardiner (2001):

$$Q_{heater} = W_s(X_{in} - X_{out})\Delta H_v + Q_{s,sens} + Q_{loss} \quad \text{(Eqn. 24.1.11)}$$

where Q_{heater} is the heat provided by the hot air, W_s is the mass flow rate of the solid particles, X_{in} is the inlet moisture percentage of the particle, X_{out} is the outlet moisture percentage of the particle, ΔH_v is the heat of evaporation of hot air, $Q_{s,sens}$ is the sensible heating of the solids, and Q_{loss} is the heat lost from the drying body.

The heat provided by the hot air can be defined as:

$$Q_{heater} = W_g C_{p,g}(T_{g,in} - T_{g,out}) \quad \text{(Eqn. 24.1.12)}$$

where W_g is the mass flowrate of the hot air, $C_{p,g}$ is the specific heat capacity of the air based on the mean temperature, $T_{g,in}$ is the inlet temperature of the air, and $T_{g,out}$ is the outlet temperature of the air.

The sensible heating of the solids can be determined as:

$$Q_{s,sens} = W_s C_{p,s}(T_{s,out} - T_{s,in}) \quad \text{(Eqn. 24.1.13}$$

where W_s is the mass flowrate of the solid particles, $C_{p,s}$ is the specific heat capacity of the solid particles on the mean temperature, $T_{s,out}$ is the outlet temperature of the solid particles, and $T_{s,in}$ is the inlet temperature of the solid particles.

24.1.4 Energy Balance for Milling

The energy balance for milling can be represented by the following equation:

$$\Delta H + \Delta KE + \Delta PE = Q - W \quad \text{(Eqn. 24.1.14)}$$

where ΔH is the internal energy, ΔKE is the kinetic energy, ΔPE is the potential energy, Q is the heat in the system, and W is the work done by the system.

The kinetic energy is further represented as the rotational kinetic energy due to the rotation of the conical mill. The equation is defined as:

$$\Delta KE = \frac{1}{2} I w^2 \quad \text{(Eqn. 24.1.15)}$$

where I is the moment of inertia of the truncated straight circular cone and w is the angular velocity.

The calculation of ΔH can be defined as the following:

$$\Delta H = m C_p \Delta T \quad \text{(Eqn. 24.1.16)}$$

Here, ΔPE is negligible for the conical mill given that the distance between the inlet and the outlet of the milling screen is minimal.

24.1.5 Energy Balance for Tablet Press

The energy balance for the tablet press can be defined using the first thermodynamics of law model which is defined as the following:

$$\Delta E = W - Q \quad \text{(Eqn. 24.1.17)}$$

where ΔE is the energy required by the tablet press, Q is the heat absorbed by the system, and W is the work done by the system [13, 44].

The heat absorbed by the tablet press can be defined as the following:

$$Q = W_s C_{p,s}(T_{s,out} - T_{s,in}) \quad \text{(Eqn. 24.1.18)}$$

where W_s is the mass flowrate of the solid particles, $C_{p,s}$ is the specific heat capacity of the solid particles based on the mean temperature, $T_{s,out}$ is the outlet temperature of the solid particles, and $T_{s,in}$ is the inlet temperature of the solid particles.

24.1.6 Energy Balance for Tablet Coater [6]

The energy balance for the tablet coater can be represented by the following equation:

$$Q_{heater} = W_s(X_{in} - X_{out})\Delta H_{v,a} + Q_{s,sens} + Q_{c,sens} + Q_{loss} \quad \text{(Eqn. 24.1.19)}$$

where Q_{heater} is the heat provided by the hot air, W_s is the mass flow rate of the solid particles, X_{in} is the inlet moisture percentage of the particle, X_{out} is the outlet moisture percentage of the particle, $\Delta H_{v,a}$ is the heat of evaporation of hot air, $Q_{s,sens}$ is the sensible heating of the solids, $Q_{c,sens}$ is the sensible heating of coating solution, and Q_{loss} is the heat lost from the drying body.

The heat provided by the hot air can be defined as:

$$Q_{heater} = W_g C_{p,g}(T_{g,in} - T_{g,out}) \quad \text{(Eqn. 24.1.20)}$$

where W_g is the mass flowrate of the hot air, $C_{p,g}$ is the specific heat capacity of the air based on the mean temperature, $T_{g,in}$ is the inlet temperature of the air, and $T_{g,out}$ is the outlet temperature of the air.

The sensible heating of the solids can be defined as:

$$Q_{s,sens} = W_s C_{p,s}(T_{s,out} - T_{s,in}) \quad \text{(Eqn. 24.1.21)}$$

where W_s is the mass flowrate of the solid particles, $C_{p,s}$ is the specific heat capacity of the solid particles based on the mean temperature, $T_{s,out}$ is the outlet temperature of the solid particles, and $T_{s,in}$ is the inlet temperature of the solid particles.

The sensible heating of the coating solution can be defined as:

$$Q_{c,sens} = W_c C_{p,c}(T_{c,out} - T_{c,in}) + W_w \Delta H_{v,w} \quad \text{(Eqn. 24.1.22)}$$

where W_s is the mass flowrate of the coating solution, $C_{p,c}$ is the specific heat capacity of the coating solution based on the mean temperature , $T_{c,out}$ is the outlet temperature of the coating solution, $T_{c,in}$ is the inlet temperature of the coating solution, W_w is the mass flow rate of the water, and $\Delta H_{v,w}$ is the heat of evaporation of the water in the coating solution.

Section 24.2 Residence Time Estimations and Calculations for the Hybrid Process

24.2.1 Residence Time for the Twin Screw Extruder (TSER)

The residence time of the twin screw extruder in the hybrid process (TSER, ZSE-27HP) can be approximated though estimating the bulk density changes as material is processed through the unit. Bulk densities were approximated earlier for the batch design in Table 11.1.3 and were assumed to be the same in the hybrid process. While equipment differs between the two processes, corresponding equipment between the two designs should process material in a similar manner. The bulk density of the dry mixture entering and of wet granules exiting TSER is approximately 412 kg/m^3 and 606 kg/m^3 respectively. Approximating a linear increase in bulk density ($\rho_{bulk} = [kg/m^3]$) as the material passes through TSER of length (L) 3.650 m yields the following relationship:

$$\rho_{bulk} = 412\frac{kg}{m^3} + 53.2\frac{kg}{m^4}x \qquad \text{(Eq. 24.2.1.1)}$$

where $x =$ distance $[m]$ along TSER. The following derivative describes one way to calculate residence time:

$$d\tau = \frac{dV}{Q} = \frac{Adx}{Q} \qquad \text{(Eq. 24.2.1.2)}$$

where V is the working volume of the unit $[m^3]$, Q is the volumetric flow rate $[m^3/s]$, τ is the residence time $[s]$, and A is a working cross-sectional area assumed to be constant throughout the length of TSER. The working cross-sectional area can be computed by dividing the working volume of TSER by the length. Since no mass accumulation occurs within TSER, the mass flow rate $\dot{m}$ $[kg/s]$ is constant, yielding the following relationship:

$$Q = \dot{m}/\rho_{bulk} \quad \text{(Eq. 24.2.1.3)}$$

Combing the relationships and integrating along the length of TSER computes a residence time:

$$\tau = \frac{A}{\dot{m}}\int_0^L (412\frac{kg}{m^3} + 53.151\frac{kg}{m^4}x)dx. \quad \text{(Eq. 24.2.1.4)}$$

As a result, the residence time for TSER is 15.8 minutes. The accuracy of the residence time calculation depends on the accuracy of bulk density estimations.

24.2.2 Residence Time for the Conveyor Belt Dryer (CBDR)

The residence time for the conveyor belt dryer (CBDR, DW-1.2 -8A) is directly set by the speed of the conveyor belt itself. The specifications of CBDR denote an 8 m long drying section, a 1.2 m belt width, and a recommendation for 60 mm thickness of material or less. Assuming material is not deposited on the edges of the belt, a 1 m working belt width is appropriate. Additionally, to ensure even drying, the material thickness is selected to be half the upper limit recommended, 30 mm. Thus, the cross sectional area of wet granules entering CBDR is 0.03 m^2. Given an inlet mass flow rate of 23.3 kg/hr, and assuming the wet granules entering CBDR have a bulk density of 0.606 kg / L, the inlet volumetric flow rate is 38.4 L/hr. Dividing the volumetric flow rate by the cross sectional area of wet granules at the inlet provides the conveyor speed required, 1.28 m/hr. Given that the drying section of CBDR is 8 m long, the residence time of the conveyor dryer is 6.24 hr.

24.2.3 Residence Time for the Cone Mill (COML)

The residence time within the cone mill (COML, Quadro SLS Comil PsD d90) can be approximated as zero. COML has a low residence time because it has a relatively small working

volume and high impeller tip speed (700-2800 RPM). Particles are not translated for long distances as they are in TSER and CBDR. Particles entering through COML are nearly "instantly" discharged resulting in such a low residence time to the extent that COML is recommended even for heat sensitive materials [26]. Specifically, the mean residence time in the conical mill is generally less than a second [41].

24.2.4 Residence Time for the Tablet Presses (TAB1/TAB2)

Residence time of the tablet presses (TAB1 and TAB2, Fette P1010) arises from a number of stages, including the flow of powder from the hopper to the feed frame, through the chambers of the feed frame, the filling of the dies, and ultimately, the compaction of the powder [28]. While no studies use the exact same tablet press and parameters as TAB1, TAB2, and TAB3, residence times for similar equipment and process parameters range from 5-10 minutes which is minute compared to the residence time of CBDR [29].

24.2.5 Residence Time for the Continuous Mixer (CTMR)

The continuous mixer (CTMR, Gericke GCM 250) has a residence time of approximately 1 minute. The tubular design of CTMR allows for dry granules to be continuously fed in at one end, while granules lubricated magnesium stearate are continuously withdrawn at the other. This continuous process in a relatively smaller working volume ultimately leads to a residence time of around 1 minute, which is significantly shorter than the typical residence time for batch blending, which can be as long as 20 minutes [32].

Section 24.3 Equipment Cost Six Tenths Rule Calculations

LB Bohle PM Blender 400:

Formulation of a High-Volume Small Molecule Drug Product, a UPenn Senior Design report, presents a price of $700,000 with a capacity of 4000 kg for the LB Bohle PM Blender 6000. The capacity of the PM 400 is 400 kg. The six tenths rule is thus as follows:

$700,000*(400/4000)^{0.6} = 175,832 \approx \$176,000$ each.

HuaMao DW Series Conveyor Dryer:

On Alibaba, KODI Machinery presents a price of $56,800 with a max drying strength of 160 kg/h for their DW-1.2-8 Mesh Belt Dryer. The max drying strength of the HuaMao DW Series is 30 kg/h. The six tenths rule is thus as follows: $56,800*(30/160)^{0.6} = 20,804 \approx \$21,000$ each.

Gericke Group GCM 250:

Formulation of a High-Volume Small Molecule Drug Product, a UPenn Senior Design report, presents a price of $1,000,000 with a max capacity of 500 kg/h for the Gericke Group GCM 450. The max capacity of the GCM 250 is 25 kg/h. The six tenths rule is thus as follows:

$1,000,000*(25/500)^{0.6} = 165,723 \approx \$166,000$ each.

Fette P1010 Tablet Press:

Sabrina Green, a consultant and Associate Scientist at Merck, presented a price of $1,300,000 with a max capacity of 626,000 tablets/h for the Fette FE 55 Tablet Press. The max capacity of the P1010 is 230,400 tablets/h. The six tenths rule is thus as follows:

$1{,}300{,}000*(230{,}400/626{,}400)^{0.6} = 713{,}381 \approx \$713{,}000$ each.

NCD 50 M Mixing Vessel:

Ando Equipment, a company that produces food-grade stainless steel tanks and processing equipment, presents a price of $15,500 for their 50 Gal/189 Liter ANCO Stainless Steel Process Tank. The capacity of the NCD 50 M is 53 liters. The six tenths rule is thus as follows: $15{,}500*(53/189)^{0.6} = 7{,}228 \approx \$7{,}200$ each.

Thomas Engineering Flex 500 60B Coater:

Formulation of a High-Volume Small Molecule Drug Product, a UPenn Senior Design report, presents a price of $500,000 with a max capacity of 190 liters for their Thomas Engineering Accela-Cota 48B. The max capacity of the Flex 500 60B Coater is 460 liters. The six tenths rule is thus as follows: $500{,}000*(460/190)^{0.6} = 849{,}909 \approx \$850{,}000$ each.

Industrial Factor Vacuum Tray Dryer 72:

On Alibaba, Shiv Shakti Process Equipment presents a price of $5,000 for a pharmaceutical-grade vacuum tray dryer with 6 trays. The six tenths rule applied to the number

of trays to price a vacuum tray dryer with 72 trays is as follows: $5{,}000*(72/6)^{0.6} = 22{,}206 \approx$ $22,000 each.

Glatt TDG 600 Granulator:

On Alibaba, Yichun Wanshen Pharmaceutical Machinery presents a price of $500,000 for a cGMP grade pharmaceutical wet type high shear mixer granulator SHLG-800 that handles a capacity of 800L. To price the Glatt TDG 600 Granulator, the 6/10th rule is applied as follows:

$500{,}000*(600/800)^{0.6} = 420{,}733 \approx$ $420,000 each.

Section 24.4 Equipment Technical Brochures and Specification Sheets

24.4.1 L.B.Bohle PM 400 Bin Blender

Pharma Blender **PM**

No. 1 in Blending

The range of Bohle blending systems shows the flexibility of our engineering and manufacturing departments. Bohle blenders can be adjusted and used in any imaginable pharmaceutical production situation. No matter what kind of container you use, round and square, Bohle blenders can handle them with excellent blending results.

Bohle Provides Blenders Featuring a Variety of Different Load Bearing Capacities:

- Standard arm connection and clamps
- Round forks on the lift arm
- Lift arm with eccentric, power and hydraulic clamps

PM is Capable of Advanced Processes – Blending, Chopping and Liquid Addition:

- Closed system, therefore optimal for containment applications
- No cleaning between batches
- Rotates up to 6 rpm
- Speed increase optionally possible after technical clarification
- Gentle product movement
- Blending baffles in Intermediate Bulk Container (IBC)

Blending elements

- Square or round containers
- Just rotation, no tumbling
- 20 % to 85 % fill level

Chopper System

- Chopper is inserted into the 315 mm standard opening of the blending lid
- Chopper is able to intensify blending movement and to break lumps (optimal for very small amount of ingredients)
- Chopper speed approx. 750 rpm
- Automatic coupling for PM 400 – PM 2400

24.4.2 Glatt TDG 600 High Shear Granulator

Universal Applications

TDG PRO 600 with top driven agitator and chopper, process vessel lowered

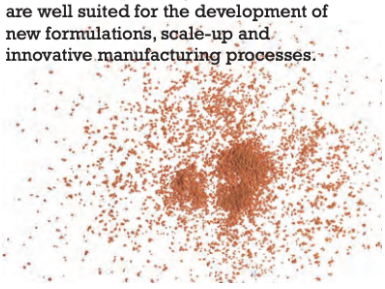
Main Features

- Flexible and efficient high shear mixer and granulator
- Total Containment and GMP compliant design
- Use of aqueous and organic binder liquids
- Top driven agitator blades and chopper
- Process-optimized gap between vessel wall and agitator blades
- Chopper fully adjustable in height respective to the process and removable from the product bed
- Product bowl lowers for access
- Improved cleaning of all product contacting parts
- Space-saving by the through-the-wall installation design
- User-friendly EcoView or MegaView PLC panel
- Camera monitoring (optional)
- Single pot technology with short drying sequences (optional)
- Production units in 12 bar PRO version(optional)
- CIP-able in SC Superclean design (optional)
- Charging by gravity or vacuum (optional)

Design:
High shear mixer represent in the history of granulation one of the oldest and best established process technologies in the pharmaceutical and life science industries.
In comparison with normal high shear mixers, the Top Drive Granulator adopts a different design concept with the mixer bearing and drives for the agitator and chopper positioned above the process vessel, and separated from the clean room.
The design completely overcomes the usual design shortcomings of difficult to clean apertures and undercuts in the product bowl.
If required, the chopper can be raised or lowered to different heights of the product according to the product and process specific requirements of the application.
Furthermore the working vessel can be lowered and allows for easy manual charging and/or cleaning and inspection.
The finished granulates are emptied into the swivelling discharge port with the option to connect to an in-line wet mill.
The TDG is available in eleven nominal sizes starting with the small lab unit through to the production size machines.
The PRO option (12 bar pressure shock resistance) is available for the production units from the TDG 100 through to the TDG 1500.

Technologies:
In addition to classic wet granulation, further process variations are possible, including hot-melt granulation, pellet production or single pot processes with solvent recovery.

TDG units, depending on machine size, are well suited for the development of new formulations, scale-up and innovative manufacturing processes.



Flexibility in Application

Production of solid particles from powder.

In wet granulation, powder is charged into a TDG process vessel and the product is vigorously mixed by an agitator and a chopper.
As mixing continues while it is then wetted or sprayed with a melt. Maximum efficiency is achieved by adjusting the gap distance between the rotor and the product bowl, thereby ensuring an optimal wet mixing process.
In many cases the granules are discharged into a rotor sieve (e.g. a Glatt sieve) to reduce oversized particles before they are dried or cooled in a fluid bed dryer (WST).

TDG single pot version for individual batches.

If only single batches or a small number of batches, (e.g highly active substances), have to be granulated, then the drying process can also take place in a Top Drive Granulator specifically designed for this purpose: using the Glatt TDG single pot. With this design, the drying can be effected via heated wall surfaces, gas stripping and vacuum. The single pot variant is a popular choice, where small and medium sized batches exist which are frequently changed.

Quick and efficient granulation and drying in integrated granulation lines.

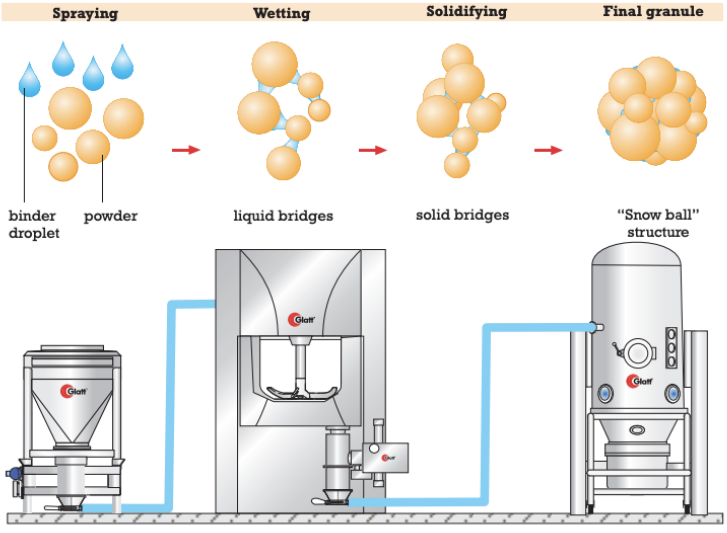
An efficient standard design for mass produced products can be achieved by the coupling together of the Top Drive Granulator with fluid bed units, vacuum conveying and/or container systems.
The Glatt group can supply all necessary core technologies for granulation and tablet production, with a wide range of equipment including fluid bed processors, coaters, systems for product handling as well as total containment equipment for processing of highly potent and critical / demanding products.
Depending on specific product requirements, a TDG may be configured with different design options in order to ensure the highest levels of operator protection and plant safety.
Total containment features help to ensure compliance with operator exposure OELS and the 12 bar (PRO) design provides maximum safety in cases where explosion risks may be present in the system.

Main Features of "Glatt"s wet granulation lines:

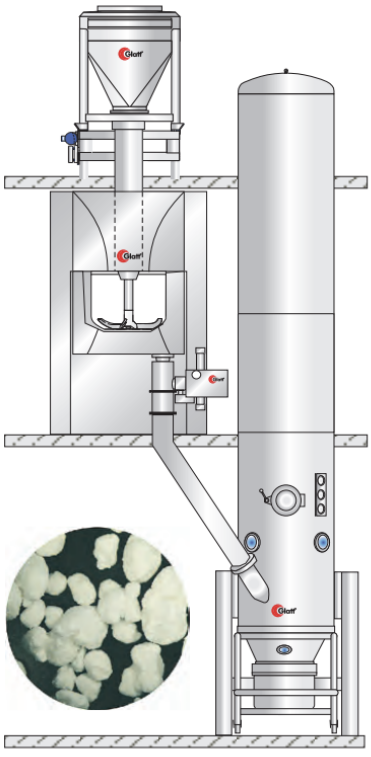
- Manufacturing of dust free granulates with excellent flowability.
- Granulates with narrow particle size distribution.
- High product yield rate.
- Excellent cleaning efficiency (CIP able).
- Total containment solutions.
- 12 bar pressure shock resistant design

Applications for wet granulates:

- Pharmaceutical
- Cosmetics.
- Fine Chemicals.
- Bio Technology.

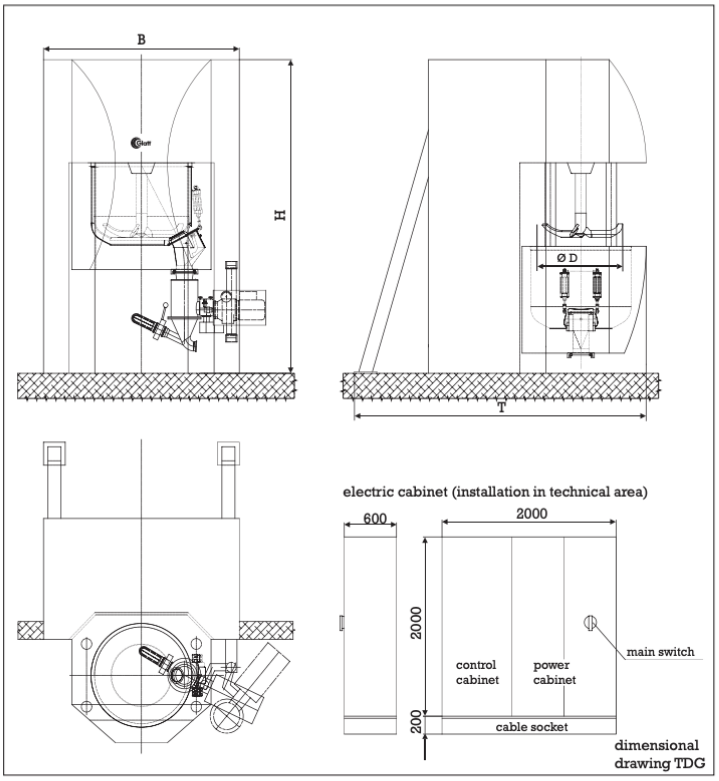


Horizontal granulation line consisting of a TDG and a Fluid bed Dryer WST (G)


Vertical granulation line with TDG and WST (G)

Technical Data / Addresses

(technical data subject to change)



TDG100 with through the wall installation

TDG type		Dim.	Lab units		TDG 100 TDG^{PRO}100	TDG 200 TDG^{PRO}200	TDG 400 TDG^{PRO}400	TDG 600 TDG^{PRO}600	TDG 800 TDG^{PRO}800	TDG 1000 TDG^{PRO}1000	TDG 1200 TDG^{PRO}1200	TDG 1500 TDG^{PRO}1500
			TDG 25	TDG 65								
Process vessel	Nominal volume	dm^3	24	64	114	231	464	710	946	1198	1499	1853
	Process volume	dm^3	6 - 20	16-52	25-80	50-160	100-320	150-480	200-640	250-800	300-960	375-1200
	Diam. anchor rotor	mm	326	446	576	726	920	1068	1168	1264	1364	1464
Drives	Anchor rotor speed	r.p.m.	30 - 600	25-500	12-250	10-200	8-160	8-150	6-130	6-110	6-110	5-100
	Motor power	kW	5.5	7.5	15	22	30	37	45	45	55	55
	Chopper speed	r.p.m.	300 - 3000		300 - 3000				150-1500			
	Motor power	kW	0.75	0.75	1.5	4	4	4	5.5	5.5	7.5	7.5
Dimensions	Width B [ca.]	mm	1400	1400	1790	1950	2050	2250	2450	2700	2700	3000
	Height H [ca.]	mm	2000	2000	2600	3000	3200	3700	3915	4300	4300	4500
	Depth T [ca.]	mm	1500	1500	2800	2800	3000	3700	3700	3960	3960	3960

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24.4.3 Twin Screw Extruder

Leistritz Extrusion Background and Overview

Leistritz Extrusion manufactures twin screw extruders and systems with screw diameters from 12 mm to 260 mm. Applications include compounding, devolatilizing, reactive processing, and direct extrusion. Established in the USA in 1976, Leistritz Extrusion is a subsidiary of Leistritz AG, originally founded in Nuremberg, Germany in 1905. Leistritz also provides a full range of technical services including field service, a fully equipped process laboratory equipped with six (6) twin screw extruders, and ongoing training seminars.

1.0 ZSE-27 DESCRIPTION AND SPECIFICATIONS

The ZSE-27 HP utilizes building block construction, including segmented screws programmed on high torque splined shafts, and modular barrels with a quick-change flangeless assembly design. The ZSE-27 is ideal to perform research, small-lot production and customer sampling.

Mobile, Stainless Steel Base Cabinet: The ZSE-27 is provided on a heavy-duty mobile base cabinet which supports the extruder and houses the system electricals and controls. The base cabinet includes the following features:

- Base cabinet fabricated of 304 stainless steel
- Removeable cabinet doors of polished 304 stainless steel
- Provided on four (4) heavy-duty locking casters with threaded screw jack-type leveling feet
- Dove-tail mounting plate to facilitate varying process lengths while still providing cantilevered front-end

High Torque Gear Assembly: The gearbox is directly driven from its motor to a reduction section through to a high torque distribution section. The following exceptions apply:

- The machine is supplied at 600 rpm in co-rotation with a 25-hp TEBC AC motor, with variable speed AC drive. The drive supply voltage is delivered at 460/3/60 hook-up.
- An electronic current limit is provided for over torque protection. In addition, a mechanical torque overload coupling is provided for redundant over-torque protection. All drive train parts are designed for long life.

Segmented Screws System: The screw set is built up as segments on high torque **splined** shafts for supporting varied screw designs and good general maintenance.

- The specific screw elements and staging will reflect the products you plan to process, and your planned practices.
- The screw elements will consist of feeding, venting, mixing and pumping elements.
- The screws will be constructed of our 400-series hardened stainless steel metallurgy, type VSA3.

Flangeless, Square, Modular Barrels: The barrels are 4 diameters in length each and are configured for electrical heating via high wattage cartridge type electric heaters for up to 250° C operation, and cooling through longitudinal bores situated near the barrel walls from the machine mounted solenoid system

- Total L/D is 40 to 1. The barrels may be reconfigured as your process changes in the future or as warranted based on further discussions and/or process development results.The feed barrel is equipped with a water-cooling assembly.
- Barrels segmentation is flangeless, held together via four strain bars to accommodate quick reconfiguration.
- Each zone is complete for operation, utilizing a PID temperature control loop for every heated barrel section.
- Barrel cooling is activated by the controller through a solenoid valve arrangement. The delivery includes input and output headers that are ready for connection to compressed air or a tempered coolant source.
- The barrels will be supplied as bi-metallic, type VSA 3, a hardened 400-series stainless steel with adequate abrasion and corrosion resistance for the intended application. VSA 3 is our standard offering for food, medical device, and pharmaceutical installations.
- The barrels layout will be provided as follows:

Pos.	Description
#1	Main feed w/ feed flange and regulated cooling
#2	Plain/solid
#3	Top open, with insert and injector
#4	Plain/solid
#5	Plain/solid
#6	Plain/solid
#7	Plain/solid
#8	Plain/solid
#9	Top open/vented, with vent insert, and closure
#10	Plain/solid
#11	Die

System Electricals and Controls; Allen-Bradley PLC with PanelView Plus HMI: The system will utilize an Allen-Bradley CompactLogix series programmable logic controller (PLC) to control all functions of the machine system, and will communicate via Ethernet to the PanelView Plus Human Machine Interface (HMI).

- The PLC will control barrel and die temperature zones using internal PID algorithm loops with J-type thermocouple inputs.
- PanelView Plus is ideal for applications with a need to monitor, control, and display information graphically, allowing operators to quickly understand the status of their application.
- The controls system will offer the following features:
  - Multi-vendor communications
  - Trending

    - Expressions
    - Data logging for activity logs, alarm logs, and data logs
    - Animation
    - Operator controls for all applicable devices
    - Indication of actual values for all applicable devices
    - Alarm messages, banners, and alarm history
    - Recipes (only limited by memory)
    - Three security levels (operator, supervisor, engineer)
    - Soak Timer
    - Manually tune gain parameters of each temperature zone
    - Temperature control screens
    - Extruder enable diagnostic screen
- The operator interface will be mounted in the front door of the electrical enclosure, and will include: PanelView Plus 12" color touch screen, E-stop, reset, extruder hour meter, and audible alarm horn w/ beacon.
- System electricals mounted in modified NEMA 12 stand-alone enclosure, (modified with blower & filter) including line reactor, contactors, branch circuit breakers, control transformer, and 24vdc power supply
- Yaskawa Digital AC Drive, 460vac
- AB CompactLogix PLC with Ethernet communications to HMI screen & drives
- VPN router for remote access
- 16 Port managed Ethernet switch
- One (1) melt pressure, one (1) melt temperature
- Nine (9) TSE heat /Cool zones SSR, fuses, heat sinks, 460/3/60, 115v cooling voltage
- Two (2) downstream heat only zones for adapters, die, etc.; including SSR's, fuses and heat sinks, 230/1/60
- Isolation transformer, NEMA 4X, mounted to side of enclosure, 460-to-230V to feed 230v equipment

Adapter/Breaker Plate/Die Assembly: A strand die (dimensions TBD) is provided with a vertical delivery to delivery melt to Buyer's chill roll unit. Front end includes provision for breaker plate and through ring. All components constructed of 1.4112 or 316 stainless steel, as warranted for the specific usage.

Manuals: One (1) set of electronic operating manuals, in English, will be included in the scope of delivery. Manuals will include the following items:

- Line drawing/floor plan (depicting space and utility requirements)
- Operation and maintenance manuals for all major and sub-components
- Complete mechanical and electrical schematic drawings

Tools Kit: A tools kit is supplied as required. The following items will be included:

- Screw extractor/puller
- Tip wrench
- Metric hex keys & open end wrenches
- Brass scraper
- Screwdrivers

2.0 Auxiliary Equipment for ZSE-27HP (GMP Format)

2.1 Granulation Chamber: Stainless steel chamber mounted at discharge end of extruder funnels granules to discharge chute for collection including**:**

- Inlet face plate and bushing secures position of protruded screws
- Hinged top plate with lexan viewing window allows access for cleaning
- Safety interlock prevents top plate from being opened while in operation
- Inlet pipe with flange for buyer's make-up air

2.2 TCU/Barrels Heat Exchanger

The water-cooled barrels of the twin screw extruder require a constant supply of tempered, treated water from a closed-loop supply. Treated water prevents mineral deposits, scaling, and corrosion associated with untreated tower water. The following specifications apply:

- Model TCU-ZSE-27 with 1-hp pump
- Brazed plate heat exchanger
- Includes stainless steel reservoir
- Pump discharge pressure gauge
- Carbon steel cabinet, finished in STEEL-IT paint
- AC starter, 460/3/60

2.3 Stainless Steel Vacuum/Devolatilization System

The custom vacuum system is configured to pull vapor from the vacuum/vent assembly on the ZSE-27HP extruder. System includes one (1) model A-10 liquid ring system. An inlet knockout pot assembly is included. The following specifications apply:

- Includes one (1) Atlantic Fluidics stainless steel water ring vacuum pump with mini sediments trap assembly. The high capacity, water sealed vacuum system is provided, complete with electrical pre-connection, fittings, control valve, and check valve.

- Vacuum/devolatilization system is supplied with instrumented vacuum level transducer, and includes digital indicator, stainless steel braided Teflon lined vacuum hose, and Tri-clover sanitary quick disconnect fittings wherever applicable.
- Power requirements: 460/3/60

2.4 K-Tron Twin-Screw Digital Loss-in-Weight Feeder

One (1) twin screw loss-in-weight feeder will be provided to set and control the rate to the main feed throat. All product contact components will be constructed of 316L stainless steel. The feeder's gearbox and motor will be finished in STEEL-IT paint. The following specifications apply:

- K-Tron model K-ML-D5-KT20 twin screw loss-in-weight feeder
- Complete with on-board K-Tron KCM single-unit display/controller
- Specified for feed rates of 2.0 - 20 kg/hr
- 20 mm diameter twin screw augers
- 0.29 ft^3 cylindrical hopper with internal agitator
- 12 Liter extension hopper
- Vertical discharge with flex connection
- Supplied with safety grill and manual refill cover
- 230V/1PH/60HZ electricals, powered via extruder base cabinet, including Harting quick-disconnect plug and 6' power cable
- Feeder supplied on mobile, height adjustable, stainless steel stand

2.5 Loss-in-Weight Liquid Additive Injection System – Ambient

The liquid additive injection system has been specified to provide accurate and repeatable metering of liquid into the extruder barrel. System includes a precision metering piston-style pump, closed loop vector AC motor/drive package, stainless steel reservoir mounted on a precision platform scale, and transfer lines. Liquid injection system controls will utilize loss-in-weight feedback and be controlled via on-board digital interface, fully integrated with the AC vector drive for closed-loop control. The following specifications apply:

- Piston (or diaphragm)-type pump, sized to the process
- Fully adjustable stroke length
- Stainless steel reservoir, sized accordingly, with removeable lid and drain valve
- Reservoir mounted on precision platform L-I-W scale
- 1/2-hp AC motor, with encoder for closed loop vector control
- Pump, motor, scale, and reservoir mounted on a common SS cart with locking casters
- Operator controls integrated with main operator PLC-based controls panel/HMI
- 8' transfer line from pump to injection nozzle, supplied w/ swagelock fittings

2.6 Factory Acceptance Test, IQ/OQ Documentation, and Validation Support

Factory Acceptance Testing (FAT), validation documentation and execution support are available. Included is a system inspection and functionality checkout performed at the Leistritz facility. Corresponding documentation is generated, maintained, and supplied upon completion. The following documentation and services are included:

Documentation:

- General arrangement view/line drawing of entire system
- Barrel/screw layout drawing
- Utility/line drawing for electrical, water, and compressed air requirements
- Certificate of materials for product contact surfaces
- Wiring diagrams for extruder, and all applicable auxiliary equipment
- All sub-vendor mechanical, electrical, and installation drawings
- Calibration certificates for all applicable devices
- MSDS sheets for all oils, and lubricants
- Complete operational manual for extruder
- Operation manuals for all auxiliary and sub-system components

FAT (Factory Acceptance Test) including:

- Visual inspection and identification of system components
- Review of control panel layout
- Documentation of model, serial numbers, and pertinent specifications of all components
- Inspection of electrical devices and corresponding wiring
- Confirmation of tagging and labeling
- Heat zone check-out
- Identification/verification of product contact materials and surface finishes
- Overview and demonstration of power-up procedure
- Verification of temperatures, speeds, and other indicated values
- Complete system dry test
- Generation, recording, and compilation of FAT documentation

IQ (Installation Qualification), including:

- Visual inspection and identification of system components
- Verification of all utility connections
- Inspection of electrical devices and corresponding wiring
- Heat zone check-out
- Overview and demonstration of power-up procedure
- Verification of temperatures, speeds, and other indicated values
- Complete system dry test
- Generation, recording, and compilation of IQ documentation

OQ (Operational Qualification) including:

- Review of FAT and IQ documentation
- Review of customer-generated SOP's (SOP's not included in Leistritz' scope)
- Verification of all safety devices and system interlocks
- Equipment operation conformity check-out
- Generation, recording, and summarization of OQ documentation

All FAT and validation support services are performed at Leistritz Extrusion. Any/all additional on-site service/assistance will be invoiced separately at our prevailing service rates.

3.0 Pricing

The equipment is offered FOB Somerville, New Jersey, skidded and ready to load onto the carrier of your choice.

Ref.	Item	
1.0	**ZSE-27HP (GMP) Co-Rotating Intermeshing Twin Screw Extruder:**	**$435,000**
2.1	**Granulation Chamber**	**$ 28,500**
2.2	**TCU/Barrels Heat Exchanger**	**$ 18,500**
2.3	**Stainless Steel Vacuum / Devolatilization System**	**$ 32,000**
2.4	**One (1) K-Tron Twin Screw Digital Loss in Weight Feeder**	**$ 94,000**
2.5	**One (1) LIW Liquid Diaphragm Pump**	**$ 58,000**
2.6	**FAT/SAT, IQ/OQ Documentation Package**	**$ 40,000**
2.7	**Spare Set of Screws (1.4112 Stainless steel)**	**$ 45,000**
	Total	**$751,000**

24.4.4 Industrial Factor Vacuum Tray Dryer IFVTD 72

Industrial fabricators is a leading and a prominent manufacturerof highly efficient and best qualityequipmentfor various industries including chemicals & pigments, pharmaceuticals & API, plastic and raisins, food, engineering, defense etc. One of our highly esteemed products making waves all overis Vacuum Tray Dryer.

Product Introduction & Application:

Product Introduction and Application: Vacuum Tray Dryers also abbreviated as VTD is designed by the expert engineersand fabricated by a team of well-trained technicians has the advanced features of being used with ease and maximum efficiency.Vacuum tray dryers are specifically designed to serve the purpose of drying ofhigh-quality materials with a precisely controlled temperature under vacuum and indirect heat. Many valuable but extremely sensitive products in Pharmaceutical, API, Bulk Drug, Food etc. industries need careful drying and Industrial Fabricators VTDâ€ s are specifically designed for such products. Some hygroscopic products are extremely heat and weather sensitive and needs to be dried at remarkably low temperature, Industrial FabricatorsVacuum tray dryersare perfectly capable of handling such sensitive products. Largely regarded in commercial production units, we have a strong presence in the small laboratory scale units with inbuilt heating systems.

Design characteristics

Industrial Fabricators make Vacuum Tray Dryers are crafted and engineered by fabrication of Stainless-Steel sheets adequately supported by heavy duty structure. Entire internal cabinet is dully argon welded.The Vacuum Tray dryer designed and fabricated by us has a unique feature which support the Clean in Place (CIP) application specifically for Pharmaceuticals, API and Food industries, as well as helps in achieving best efficiency. The special folding design enables us to have an upper hand in terms to clean the entire system and more importantly conducting maintenance if any.

Entirely constructed to withstand high pressure (Vacuum levels up to 760 mmHg), the drying chamber is hydraulically tested and comes with various utilities like oil lubricated vacuum pump, Digital control panel, receiver, condenser, cyclone separator etc. The assembly comes as an option and customer can pick one or all based on their specific requirements.

∗IFHWG & IFHOG systems offered by Industrial Fabricators can be coupled along with the system as heating media. IFHWG and IFHOG are uniquely designed utilities to generate hot water or thermic fluid oil which can be circulated within the VTD for precise and accurate and extremely economic operations. Our Vacuum Tray Dryers are proudly bifurcated in two segments lab to med sized systems & Medium to large commercial sized systems.

TECHNICAL SPECIFICATION (Lab to Medium Size)

Model	IFVTD 36	IFVTD 48	IFVTD72	IFVTD 96
MOC	MS, MS/ SS.304, MS/ SS.316, SS.304, GMP			
Approx. Size (LXWXH)	External			
	60â€ x 42â€ x 72â€	80â€ x 42â€ x 72â€	60â€ x 72â€ x 72â€	80â€ x 72â€ x72â€
No of Tray	36	48	72	96
Tray Size	16â€ x 32" x 2"			
Type of Trays	Solid			
Tray MOC	SS.304, SS.316			
Heating	Steam, Thermic Fluid, Hot water			
Insulation	Glass wool with suitable thickness and cladding. (96% Density)			
Connection Type	3 Ph.415 V, 50 HZ			
Operating Temperature	Ambient + 5 to 80Â°C (Higher temperatures available on request, subject to type of heating media)			
Controls	Standard Semi-Automatic, Touch screen with PLC & HMI based Fully Automatic, FlameProof/Explosion proof			
Special Note.	Industrial Fabricators reserves rights to change the specifications without prior notice. The data shared are just indicative and actual data may vary. Completely customized systems with special requirements can be designed as per customerâ€ s requirements			

Special Features

- Excellent performance due to specially designed Folding type Heat Exchanger with extended Heat Surface area.
- Aero dynamic design with radius corners helps in achieving Higher Performance and Efficiency.
- Heavy Duty Construction for Zero Maintenance design enables our systems to operate uninterruptedly for years to come.
- Clean in place (CIP) design with for Hygienic Operations. Our uniquely designed system having a folding type of Heat Exchanger allows the user to ensure maximum hygiene. No sharp corners, no rough edges, no corners whatsoever.
- COMPLETE SYSTEM CAN BE WHASHED FROM INSIDE.
- Compatible with latest low emission flues/heating media.

24.4.5 HuaMao DW Series Conveyor Belt dryer

Introduction

HuaMao conveyor drier is used for continuous drying and cooling of sheet, stripe, granular and some paste materials. And the processed materials can maintain their original shapes without any deformation. The machine has other names—belt dryer and belt drying machine. With features of high speed, high evaporation strength and good quality, this conveyor drier is widely applicable for chemical, pharmaceutical, foodstuff, feeding stuff, mining, plastics and ceramics industry.

Products Can Be Produced

Conveyor drier is capable of making dehydrated vegetables, traditional Chinese medicine decoction pieces, pellet feed, chicken essence, organic pigment, synthetic rubber, acrylic acid fiber, medicines, medicinal materials, small wooden products, plastic products, electronic elements, etc.

Features

1. Belt dryer not only can dry materials but also can bake or burn them sometimes.
2. It has a simple structure and is easy to install and is long in service life. Besides, conveyor drier is convenient to maintain.
3. The machine adopts air distributing device which makes hot air spreading more uniform.
4. With a feature of flexible equipment configuration, it can use belt washing and material cooling system.
5. Belt drying machine can recycle air, thus energy saving.
6. Conveyor drier is able to employ steam, conduction oil, electricity or kerosene as its heating source.
7. The air, heating temperature, material residence time and feeding speed can be adjusted to achieve the optimum drying effect.

Technical Parameters of Conveyor Drier

Model of Belt Dryer		DW-1.2 -8A	DW-1.2 -10A	DW-1.6 -8A	DW-1.6 -10A
Quantity of Unit		4	5	4	5
Length of Drying Section (m)		8	10	8	10
Thickness of Raw Material Spreading (mm)		≤60			
Operation Temperature (°C)		50-140			
Steam Pressure (Mpa)		0.2-0.8			
Steam Consume (Kg/h)		120-300	150-375	150-375	170-470
Drying Time (h)		0.2-1.2	0.25-1.5	0.25-1.2	0.25-1.5
Drying Strength (Kg. H_2O /m^2 .h)		6-30			
Power Equipped (Kw)		11.4	13.6	11.4	13.6
Overall Dimension (m)	A	1.2	1.2	1.6	1.6
	A1	2.28	2.28	2.68	2.68
	B	8.0	10.0	8.0	10.0
	B1	9.5	11.5	9.5	11.5
	C	2.5	2.5	2.5	2.5

24.4.6 Glatt GCM 250 Continuous Mixer

GBM MINI BATCH BLENDER

The Gericke Mini Batch Blender is a semi-continuous inline approach to make continuous manufacturing suitable for low dosage, low volume, highly potent products. It combines advantages of the traditional batch and true continuous manufacturing processes to generate a simplified system. Choose between the integrated Gericke Formulation Skid GFS or standalone equipment for early phase development.

Your benefits

- Maximal mixing homogeneity (even with very low API concentrations)
- Minimum batch sizes < 1 – 3 kg
- No start-up losses
- Simple feeder start up
- Suitable for 0 – 20 kg/h without scale up
- Simple material tracking no RTD modelling
- Simple Integration of PAT, even Raman feasible
- Simple control strategy
- High containment, Wash-in-Place WIP

GCM CONTINUOUS MIXER

Gericke Continuous Mixers GCM offer the optimum combination of radial and axial mixing (dispersion), ensuring highest homogeneity with low RSD.
The shape, layout and adjustment of the Gericke mixing tools have been developed based on upon 50 years of experience in continuous mixing and in collaboration with universities. The residence time and the energy input can be adjusted easily.

Your benefits

- Starting at continuous mixing capacities of 1 kg/h
- Maximal mixing homogeneity even with very low ingredient concentrations
- Minimal start-up losses
- Interchangeable housing and mixing tool
- Minimal product residue at the end of the process, with good residue discharge
- Low space (consider footprint) requirements even with large throughputs
- Removable mixing tool and housing for fast and hygienic cleaning

SLS – SCALABLE LAB SYSTEM™
EXCHANGEABLE PLATFORM FOR BENCHTOP POWDER PROCESSING

The Fitzpatrick Company and Quadro Engineering Corp. are part of the IDEX Material Processing Technologies group, and have been trusted partners of the world's top pharmaceutical, chemical and food ingredient processing customers for a combined total of more than 120 years.

This unmatched experience is the fundamental reason why our products and people are recognized throughout the world for the highest standards of professionalism and performance.

Reduce capital investment with the SLS: four interchangeable heads on a single drive platform

The SLS – Scalable Lab System™ is a unique benchtop powder milling and screening platform that utilizes one common drive platform with a series of interchangeable heads. The SLS eliminates the costly requirement for four individual units in separate locations – ideal for R&D labs and start-ups.

Learn more, page 4.

Save development time: changeout the head for a different process

The four different heads offer a wealth of conical milling, hammer milling and security screening options. With the SLS, you can undertake a test, record the results, and quickly move on to another approach. The SLS will speed up your research and reduce material usage, as well as overall product development time.

Learn more, page 6.

SMARTdetect™ technology ensures repeatability and consistency

Our unique SMARTdetect™ functionality affords the SLS the ability to automatically set the correct RPM range for each technology. Customers now have the ideal platform for reliable and repeatable testing / research within their R&D lab or start-up, with full confidence of accurate scale-up to production-size equipment.

Learn more, page 8.

Extensive screen and impeller options to complement application requirements

Fitzpatrick and Quadro manufacture the industry's most extensive and flexible range of conical and hammer milling screens and impellers / rotors. We help you find the right solution for your application requirements.

Learn more, page 10.

Ready for production? Easily scale-up to the SDx Series™

The SLS offers the perfect path from R&D tests to full-scale production. With all parameters transferring, SLS users can now experiment in small-scale product development knowing that exactly the same results can be duplicated with the production-scale SDx Series™.

Learn more, page 14.

Distinct drive housings offer cleanability options

Available with a medical-grade thermoplastic cover or stainless steel enclosure for more rigorous cleanability requirements. Clean in-situ or remove the head to a cleaning area to further protect operators and maintain a clean lab environment.

OUR PRODUCTS AND PEOPLE ARE RECOGNIZED THROUGHOUT THE WORLD FOR THE HIGHEST STANDARDS OF PROFESSIONALISM AND PERFORMANCE

REDUCE CAPITAL INVESTMENT
FOUR INTERCHANGEABLE HEADS
A SINGLE DRIVE PLATFORM

Introducing the world's most advanced benchtop, multi-purpose powder milling and screening platform, utilizing four interchangeable heads on the same common drive. Fast changeovers between heads (rather than switching between different units) means you can experiment and reach your research goals quickly, and with a reduced investment.

The unique design and technology within the SLS – Scalable Lab System™ allows the user to:

- Substitute the requirement for several different powder processing units with a single, flexible platform
- Quickly and easily alternate between five powder processes in seconds
- Improve on-target particle size distributions (PSDs) by up to 50%
- Process samples as small as 5 grams with minimal loss – 95% product recovery for most products
- Easily scale-up from R&D tests to full production

Results are replicated for production-scale processing with the SDx Series™

Fitzpatrick and Quadro's SLS provides users with the reassurance that once they are ready to move to full production, results can simply be transferred from small sample R&D tests to full-scale production with the SDx Series™. With fully transferable parameters, users can expect to duplicate results when transferring to a production-scale environment with the SDx Series™.

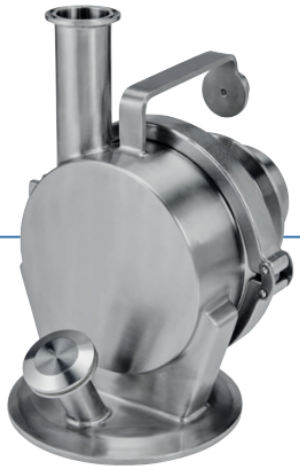
Learn more, page 14.

1. **Powder Processing / Milling Head**
2. **Common Drive Connection**
3. **SMARTdetect™ Interface**
4. **SLS Drive Control System**
5. **User Interface**


ONE
COMMON
DRIVE
FOUR
INTERCHANGEABLE
HEADS
FLEXIBLE
POWDER
PROCESSING
www.quadro-mpt.com
5

SAVE DEVELOPMENT TIME
CHANGEOUT THE PRODUCTION HEAD FOR A DIFFERENT PROCESS

The **SLS – Scalable Lab System**™ facilitates the attachment of four custom heads for five powder processing solutions that include conical milling, hammer milling and security screening. Simply choose the type of head that best fulfills your testing requirements.



COMIL® U5

Conical Milling

- Available with legacy and patent-pending high-efficiency screens.
- Consistent / repeatable results with tight granulometry.
- Improved product quality with low levels of heat, dust and fines.
- Wide range of scalable screens and impellers from which to choose.
- Fully scalable to the Quadro® Comil® U20x and Classic U20.

FITZMILL™ L1A

Hammer Milling

- High impact hammer mill for achieving finer particle sizes.
- Handles samples as small as 5 grams with minimal loss of yield or screen residue.
- Integrated feed system for optimized containment and predictability.
- Fully scalable to the D6Ax and Classic D6A Hammer Mills.

When ready to transfer results from small-sample R&D testing to full-scale production, users can quickly and efficiently scale-up to the production size SDx Series™. **Learn more, pages 14 and 15.**

COMIL® H5

High Energy Conical Milling

- High energy conical milling achieves smaller particle size distributions (PSDs).
- Primarily for APIs, finer oral solid dosage, fine chemical and cosmetic applications.
- Narrow PSDs with 30–70% more on-target.
- Integrated feed system for optimized containment and predictability.
- Fully scalable to the Quadro® Comil® Classic H20 production-scale head.

FLEXSIFT S5

Security Screening

- In-line security screening.
- High capacity for efficient testing protocols.
- Utilizes standard equipment for fast clean-down.
- Fully scalable to the Quadro® FlexSift S20x and Classic S20 production-scale heads.

UNIQUE SMARTdetect™ TECHNOLOGY SPEEDS TESTING AND RESEARCH

Our unique SMARTdetect™ functionality gives the SLS – Scalable Lab System™ the ability to operate as four different units from one single base unit. Quick and easy head changeovers allow it to be used for processes including conical milling, hammer milling and security screening.

SMARTdetect™ automatically recognizes which processing head is attached, and adjusts the platform's RPM range accordingly for the most efficient operability, thereby ensuring reliable and consistent results. With SMARTdetect™ technology and the simple clamp connectivity working together, users can change heads – and production / processing methods – within seconds. For more information on the heads available, **see pages 6 and 7**.

Operator safety is ensured with its interlock proximity switch that prevents operation if the head is incorrectly positioned.

SMART detect™

SMARTdetect™

Our SMARTdetect™ technology gives you failsafe reassurance that the correct processing method is selected automatically. With SMARTdetect™, milling and screening operations can't go wrong.

- **Unique hardware / software technology**
- **Automatically detects which processing head is selected**
- **Sets RPM for repeatable and reliable material processing requirements**

FITZPATRICK AND QUADRO'S COMBINED EXPERTISE HAS ENABLED INNOVATIVE FEATURES TO BE BUILT INTO THIS REVOLUTIONARY PROCESSING PLATFORM


www.quadro-mpt.com 9

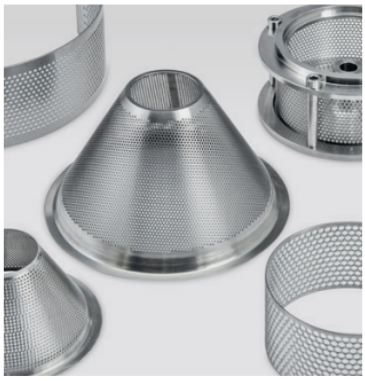
SCREEN & IMPELLER / ROTOR
OPTIONS FOR ALL POWDER MILLING AND PROCESSING APPLICATIONS

Unlimited process requirements and applications can be accommodated using a wide range of available screens and impellers. Customers now have the ideal platform for much faster testing and research within their R&D lab or start-up.

Fitzpatrick and Quadro manufacture the industry's most extensive, and flexible line of conical and hammer milling equipment available.

Customers quickly find that it is possible to directly match applications with a unique combination of screen and impeller / rotor to solve their powder processing requirements.

Our extensive knowledge of setting the optimum parameters for both milling and screening means we can handle just about any application requirement.



Range of screens

An extensive selection of screen types and sizes accommodates most particle size requirements. Screens are available with openings as small as 0.150mm (0.006"), and as large as 38mm (1.5"). Screen choices are extended further with options for round or square perforations, wire mesh or for grater or Conidur holes.

Types of Comil® impellers

Dozens of different profiled impellers can be used to suit the specific application requirements. Basic options include round arm, square arm, or beveled arm impellers. More aggressive and process-specific profiles are also available.

Configurable FitzMill™ rotor options

The wide range of rotor configurations enables us to achieve the desired particle size distribution (PSD) for your specific process. These uniquely configurable options can solve most powder processing requirements and achieve the tightest PSDs of any hammer mill manufacturer.

DELIVERING THE INDUSTRY'S MOST EXTENSIVE LINE OF API MILLING, ORAL SOLID DOSAGE AND POWDER PROCESSING EQUIPMENT

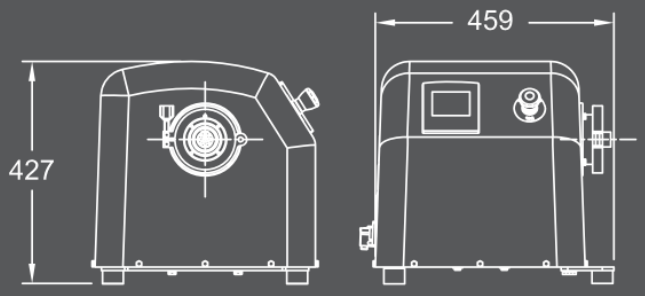
TECHNICAL OVERVIEW
FOR THE SLS – SCALABLE LAB SYSTEM™

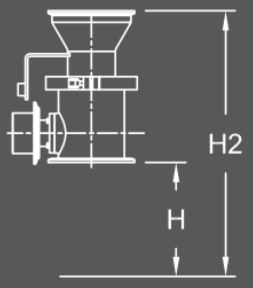
The SLS – Scalable Lab System™ has been designed with the user in mind. Simple to maintain, with fewer parts to remove during cleaning cycles, it maximizes uptime and reduces your total cost of ownership (TCO).

BENCHTOP DRIVE PLATFORM

U5

General Capacities	kg/hr — up to 50*
Speed Range	m/s — up to 28
Power	kW — 0.55
Noise	dB — 77
Height to Discharge (H)	mm — 220
Height to Inlet (H2)	mm — 513





* Capacity is dependent upon product characteristics, final PSD targets and equipment set-up. For some products, capacities may be significantly higher, or slightly lower, than those indicated above.

Simple controls for the lab environment

Integrated HMI controller with logical menu structure and simple controls is standard. Integrated feeder controls are also standard — add a VFS feeder at time of purchase or at a later date, as needed.

Unmatched screen and impeller combinations

Over 200 screen types and dozens of different impellers provide an ideal match for all applications. Comes with accessories including hand-feed hoppers and thermoplastic containers.

Maximized product recovery

Process samples as small as 5 grams with minimal loss or product retention. 95% product recovery for most products.

L1A

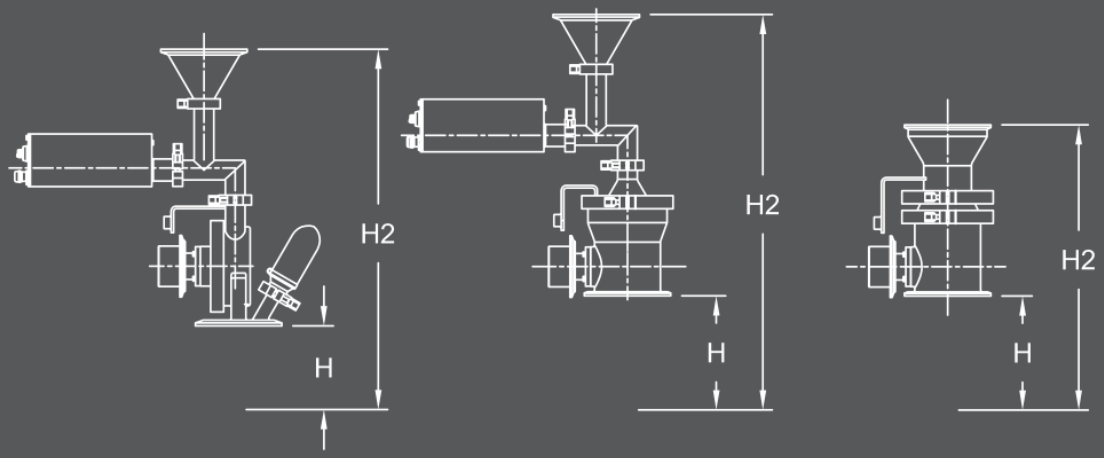
kg/hr	up to 50*
m/s	up to 85
kW	0.55
dB	95
mm	162
mm	696

H5

kg/hr	up to 50*
m/s	up to 72
kW	0.55
dB	88
mm	220
mm	763

S5

kg/hr	up to 500*
RPM	2500 - 3500
kW	0.55
dB	76
mm	220
mm	551



Accreditations

Quality ISO 9001 SAI GLOBAL

READY FOR PRODUCTION?
EASILY SCALE UP TO THE SDx SERIES™

Customers that are developing new product lines need to guarantee the easiest path from product research and development through to actual production. Fitzpatrick and Quadro now make the product development path as simple as possible with the ability to scale from testing and R&D size samples to full-scale production without the need for changes in parameters.

The material processing technologies and primary size reduction capabilities all incorporated into the SLS – Scalable Lab System™, are exactly the same as those in the larger, production-scale SDx Series™. Users developing new product lines in a benchtop environment using the SLS can now easily grow into full production with the SDx Series™ powder processing exchangeable platform.

The SDx Series™ offers robust flexibility, with fast head changeovers and SMARTdetect™ functionality. Unparalleled screen and impeller options, as well as the performance and reliability you expect from one of the world's most trusted partners make the SDx Series™ the best choice.

SMART detect™

SMARTdetect™

Our SMARTdetect™ technology provides users with failsafe reassurance that the correct processing method is automatically selected. With SmartDetect™, milling and screening operations cannot go wrong.

- **Unique hardware / software technology**
- **Automatically detects which processing head is selected**
- **Sets RPM for repeatable and reliable material processing requirements**

Main benefits of Fitzpatrick / Quadro's SDx Series™:

Unparalleled scalability:

PSD and capacity scalable with simple operating parameters transferrable from R&D testing to full-scale production.

Reduced space / power requirements:

With the interchangeable heads, the SDx Series™ replaces the need for several, dedicated machines in different locations, each with their own power source.

Widest range of sample sizes:

Process samples of up to more than 10,000 kg/hr depending on your application requirements, with minimal product loss.

Fast application conversion:

Easily switch between different powder processing solutions in seconds using SMARTdetect™ technology and standard simple clamp fittings.

Reduced need for cleaning:

With one common drive, heads can easily be removed and cleaned whilst leaving the drive unit in place for fast changeovers and minimal downtime.

24.4.8 Fette P1010 Tablet Press

Solution for many varieties and small batches

It's the third model in the P series. The suitable output, small footprint, easy clean, changeable turret, make it become one of the prior choice for your small batch production.

Support for your tablet production
We are always present where our customers are, and where they need our support.

We have five Competence Centers in Germany, India, China, Brazil and the USA, and these allow us to make comprehensive consultation, training and product trials possible.

Here again, we are starting with ourselves, and orienting ourselves around international standards. This begins with the guidelines for Good Manufacturing Practice (GMP), and extends through to standards for Technical Safety Management (TSM) or those of the European Union (EU). In fact our product tools even surpass these.

This is a central topic, and one for which we have achieved a lot through the development of the Competence Centers. For example, we can now offer a wide range of training courses, and these are almost identical in different parts of the world.

In other words, a pharmaceutical concern that produces globally can train its machine operatives everywhere, and knows that every worker has the same know-how.

Our service consultants actively approach customers, working together with them to see how they can optimize production.

Fette Compacting has several thousand contacts with customers globally every day in the support context alone. Each of these contacts is important to us!

Continuous improvement
Fette Compacting always pays attention to the latest developments in the pharmaceutical industry and customer needs, constantly upgrades and optimizes our P Series, provides customers with higher quality products and services.

FEATURES	BENEFITS
+ VME-bus controlled, user-friendly, high-performance rotary press	+ Excellent price/performance ratio
+ Exchangeable turrets	+ Rapid format changeover results in high annual yields
+ Productive, precise, safe and robust	+ Continuous use
+ Pressure and filling depth adjusted by servo motor	+ Outstanding format and production flexibility
+ Wide range of accessories and process equipment	+ Can be adapted for a wide range of production requirements
+ Perfect overall design of machine and terminal	+ Easy to handle and operate
+ High-quality standard Fette Compacting components	+ Conform to GMP and FDA
+ Tablet weight monitor control function	+ High automation level reduce man-power and increase the quality of the tablets

Performance and quality

Upgrade Features
+ Design & functionality
+ Full stainless steel terminal, easy to clean
+ Optimized dust collection system
+ Metal handle for easy cleaning and durability
+ System integration of deduster and in process control
+ On-line tablet weight monitor & control function
+ MES system support

Structure
+ Modular design with enclosed compression area to avoid the risk of cross-contamination, in compliance with cGMP regulations
+ High operating safety
+ Robust design ensure consistent accuracy even over long periods of high pressure
+ Quick-connect for easy disassembly of components, easy for maintenance and repair
+ Full accessibility to the compression zone – double layer window flaps on all four sides

Exchangeable Turret
+ Turret is made in Germany, super precision
+ High level of format flexibility
+ High output by selecting the suitable turrets according to different product size
+ Unique turrets can be interchanged with cams and tools
+ Signifisant reduction of down-time by using extra turret complete with cams and toolings
+ Rich options for turret changing are available

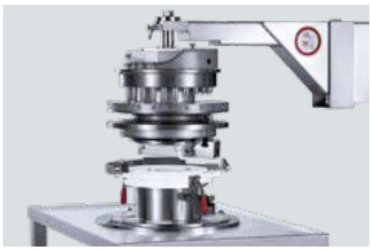
Fill-O-Matic
+ Unique three chamber filling system, more than 40 years experience on it
+ Metering wheels can increase powder flowability and uniform density
+ Filling wheels and dosing wheels can precisely fill and dose powder
+ Different options for products with poor flowability, and reduce the product loss

Compression station
+ Main compression roller and pre-compression roller are same size (250 mm, exchangeable)
+ All compression roller are independent mounted, main compression station can offer no more than 80* KN force
+ Roller is made in Germany with special material and technology, longer lifetime

Tablet discharge
+ Each discharge chute includes good tablet channel and reject tablet channel
+ Optional air sorting system, reject single tablet precisely, reduce the product loss
+ Optional sampling gate, easy to take sample and check tablet quality

Electronic control
+ Equipped with advanced VME-bus control system and top class electrical parts, faster and more stable
+ Professional software developed by Fette Compacting, verified by a lot of customers including many MNCs.
+ Ergonomical HMI consisting of a large touch screen, screen-guided interface simplify the operation
+ Structured diagnostic messages for troubleshooting
+ Support FDA 21 CFR Part 11

* Subject to product properties



Optional accessories and process equipment

The quality requirements for tablet production are constantly increasing. Process equipment from Fette Compacting ensures that your production fully complies with the applicable regulations and effectively reduces the workload of your staff. Extensive automation of all process steps reduces manual intervention and provides for excellent tablet quality.

Your advantages: more reliability, high quality and efficiency in tablet production.

Weightmaster 6.2P

+ Fully automatic measurement of tablet weight
+ Automatic feedback to Fette Compacting tablet press with stop function
+ Precise monitoring of tablet weight within freely adjustable stop limits
+ Documented tablet inspection results in your batch report
+ 21 CFR Part 11 compliant operation via the operator and password management on the Fette Compacting HMI (Human Machine Interface)
+ GMP-compliant design

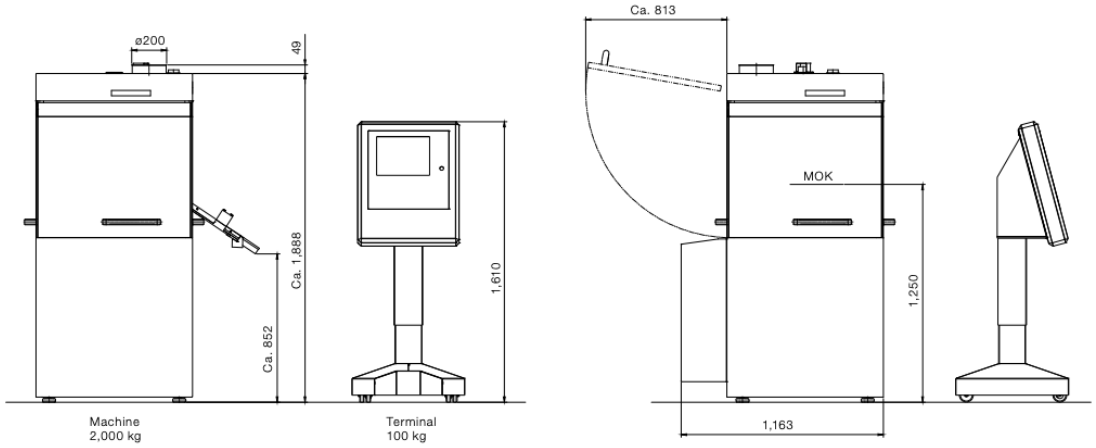
Handling system

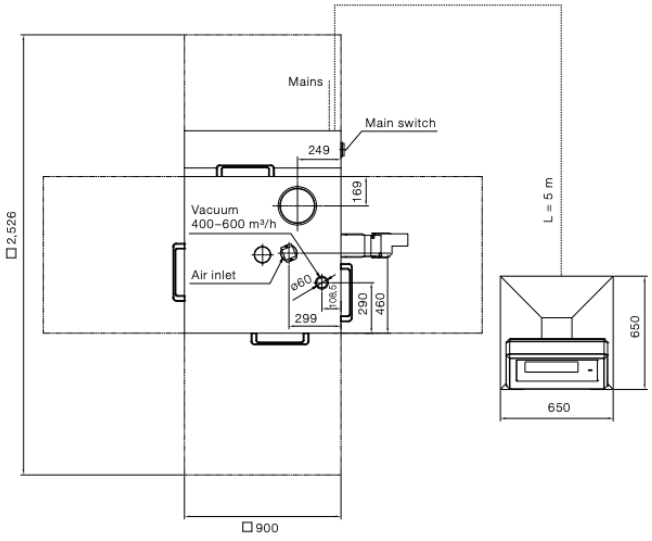
Deduster stand-alone or with metal detector

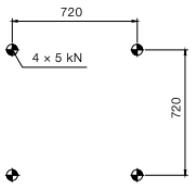
PKB-II

Tableting Tools

Dimensions







Foundation loading

Main
380–480 V ~50–60 Hz

Connection
4 × 6 mm² – on floor
4 × 10 mm² – cable conduit

Technical Data

Die (D)		D	D	D	D
Number of punch stations		32	30	24	20
Punch type		EU19 FS / EU19 TSM19 BBS	EU19 FS / EU19 TSM19 BB	EU19 FS / EU19 TSM19 B	EU1"/EU1"-441 TSM 1" D
Tablet output/h	min.	28,800	27,000	21,600	18,000
	max.	230,400	216,000	172,800	120,000
Max. compression force	kN	80*	80*	80*	80*
Max. pre-compr. force	kN	60	60	60	60
Max. tablet diameter	mm	11	13	16	25
Max. filling depth	mm	18	18	18	18**
Max. tablet thickness	mm	8.5	8.5	8.5	8.5
Pitch circle diameter	mm	280	280	280	280
Die table rotation speed	min^{-1} min.	15	15	15	15
	min^{-1} max.	120	120	120	100
Die diameter	mm	22	24	30.16	38.1
Die height	mm	22.22	22.22	22.22	23.8
Punch shaft diameter	mm	19	19	19	25.35
Punch length Upper/lower punch	mm	133.6 (133.35)	133.6 (133.35)	133.6 (133.35)	133.6 (133.35)
Upper punch insertion depth	mm	1–4	1–4	1–4	1–4
Dimensions	mm	900 × 1,163 × 1,888			
Weight		Tablet press approx. 2,000 kg, operating terminal approx. 100 kg			
Electrical supply parameters		Operating voltage 380 – 480 V, 50/60 Hz, power consumption 10 kW			

Theoretical values or technical limits: These can vary in practice, according to product and application.
Tablet thickness is a size dependent on product and can strongly vary.
* Subject to product properties
** Special filling depth available on request

24.4.9 Thomas Engineering Flex 500 60B Tablet Coater

THOMAS SPRAY BAR (TSB)

THE PATENTED THOMAS SPRAY BAR (TSB) IS A MODULAR SPRAY MANIFOLD. THE NUMBER OF SPRAY GUNS CAN EASILY BE ADJUSTED BY ADDING OR REMOVING SPRAY BAR SECTIONS.

The modular design eliminates the need for multiple complete spray manifolds. The TSB is designed to eliminate unnecessary parts from the process airflow path, reducing turbulence and improving spray performance. The solution and compressed air lines inside of the spray bar eliminate tablet entrapment areas and create a smooth profile. In the rare event of a clogged spray gun, the fluid nozzle can be removed and cleaned from the gun while the bar is primed and solution is in recirculation. Clearing a spray gun clog takes less than 10 minutes.

All Thomas tablet coating systems feature the TSB. The solution delivery system is engineered to deliver a consistently better performance compared to conventional manifolds, resulting in easily validated, repeatable tablet coating processes.

THOMAS ACCELA-SPRAY PRO

- A peristaltic pump with VFD controller
- Solution and pneumatic lines and fittings
- Solution recirculation system
- Independent pneumatic controls for atomizing, pattern, and trigger air
- Solution totalizer system
- Volumetric or mass flowmeter for solution flow rate control

THOMAS SPRAY BAR (TSB) PARTS CART

- Designed Delrin trays to hold individual parts
- Capable of holding fully assembled bar sections
- Prevents parts from touching to reduce damage
- Provides operators with a workstation for assembly and disassembly
- Eliminates downtime and part-searching

QUICK DISASSEMBLY AND EFFICIENT CLEANABILITY

- Toolless assembly for quick changeover
- Indexable mounting hardware for repeatable positioning
- Sanitary tri-clamp solution feed and recirculation connections
- Schlick spray gun components
- Independent pattern and atomizing air control
- TSB made of FDA approved PEEK thermoplastic

- A streamlined sanitary design
- Easy cleanability and minimum downtime
- Efficient product changeovers
- Lightweight sections for easy handling
- Hardware that meets GMP requirements
- Innovative external gun positioning

CONTROL SYSTEMS

COMPU-COAT

Our integrated COMPU-COAT operating system features touch screen capability mounted on the front of the coating system. With unparalleled accessibility, operators are granted a high degree of control with user-friendly controls. It is available in different platforms and comes with multi-language functionality. The large color touch interface raises awareness and clarity for the operation of your tablet coating system.

COMPU-COAT ELITE

Developed to meet the strict requirements of the pharmaceutical industry, the all new COMPU-COAT ELITE is the most powerful, feature rich and customizable control system we have designed. The large storage capacity will store hundreds of recipes and thousands of batch reports. COMPU-COAT ELITE is the most sophisticated control system we have ever created.

The fully customizable platform allows our team to tailor each system for our customers exacting needs. Customization includes integration with plant-wide MES, custom controls for material handling and solution preparation, automatic export of batch records an external server and automatic software back up.

The large 21" wide screen touch screen monitor clearly displays the entire coating process.

- GAMP 5 Compliant
- 21 CFR Part 11 Compliant
- Electronic Batch Records and Signatures
- Integration with material handling and solution preparation equipment
- Integration with MES Systems
- Siemens or Allen Bradley PLC
- Historical Trending
- Automatic batch report export to external server

COMPU-COAT PRO+

COMPU-COAT PRO+ is a recipe-based control system.

- 21 CFR Part 11 Compliant
- GAMP 5 Compliant
- 100 Recipes
- Large HMI
- Animated process screen
- Intuitive graphical user interface
- PID loop control for all process parameters

FLEX 500

The Thomas Processing division FLEX 500 is a highly efficient tablet coating system designed for the special needs of the pharmaceutical industry, which features our patented exchangeable drum design. Standard configuration allows for all aqueous tablet coating processes including film, sugar, functional, and active multi-layer coatings. Optional features allow for organic solvent coating and various OEL containment levels for potent compound processing. The Thomas patented exchangeable drum design allows each coating drum to be easily removed and can be immediately exchanged with any of the eight (8) available drum configurations.

FLEXIBILITY

- 8 exchangeable drum configurations available
- Process batch loads from 25% to 100% of drum capacity
- Dedicate drums to product classes or to contract manufacturing clients
- Easy to use graphic HMI with multiple languages
- Adapt easily to future needs

INNOVATION

- Enhanced coater utilization
- Removable drum for inspection and cleaning
- Exchangeable drums for unmatched flexibility
- Interchangeable mixing baffles
- Patented Thomas Spray Bar

DRUM EXCHANGE

Thomas Processing is the originator of the fully perforated side-vented drum. Today, Thomas continues our legacy of imaginative and practical coater design with the FLEX 500. The compelling simplicity of the design makes routine drum exchange fast and easy.

- Choose a drum configuration and mixing baffles to best suit requirements of the process
- Dedicate drums to specific drug compounds or to individual clients
- Reduce risk of cross-contamination
- Faster cleaning and product changeover for enhanced utilization
- Reduce facility improvement costs and operating expenses - build and staff one coating suite for the FLEX 500 instead of two or more suites for ordinary tablet coaters

FLEX 500

FLEXIBILITY

- Routine exchange of drums within the coating suite
- Wide turndown volume of 40 to 920 liters in same machine - 8 drum sizes available
- Process batch loads from 25% to 100% of drum capacity
- Externally position spray bar for optimal angle and distance to bed
- Exchangeable mixing baffles
- Install Through-the-Wall, Front or Rear Flush, or Free Standing
- Adapt easily to future manufacturing needs

SOLUTION DELIVERY

- Peristaltic pump with single or dual element head
- Recirculation to reduce settling of solids in solution lines
- Choice of volumetric or mass flowmeter
- Automated solution switching

CLEANABILITY

- "Total Access" design for swabbing and routine inspection
- Optimized chamber design for enhanced cleanability
- Continuously welded interior with rounded corners
- Smooth chamber surface finishes throughout
- Water-tight inflatable seals on access doors

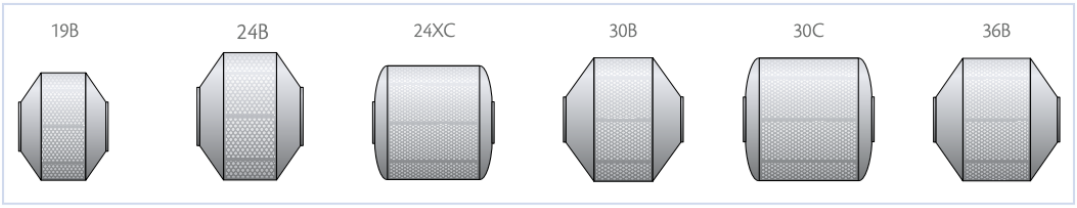
INTEGRATED PERIPHERALS

- Range of affordable WIP executions
- Solution preparation equipment and delivery tanks
- Optional devices for assisted loading using IBCs or drums
- Purpose-built dollies for drum exchange and storage

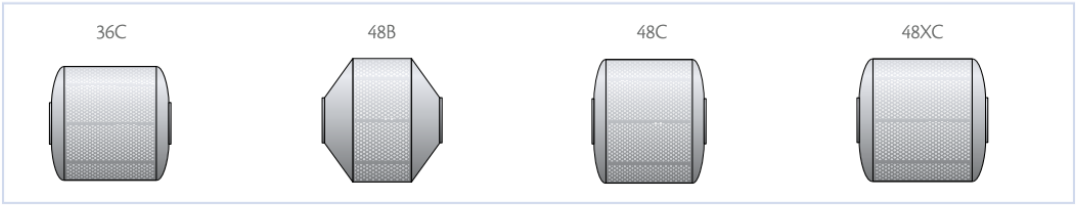
MIXING BAFFLES

- Exchange and select baffles to best suit a process
- Designed for tool-less removal and assembly
- Choice of Thomas helical or plow baffles

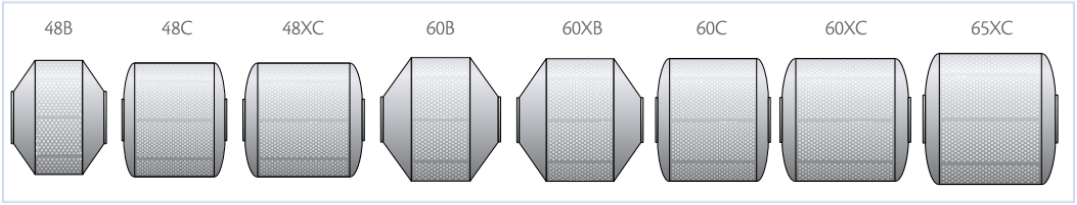
TECHNICAL DATA



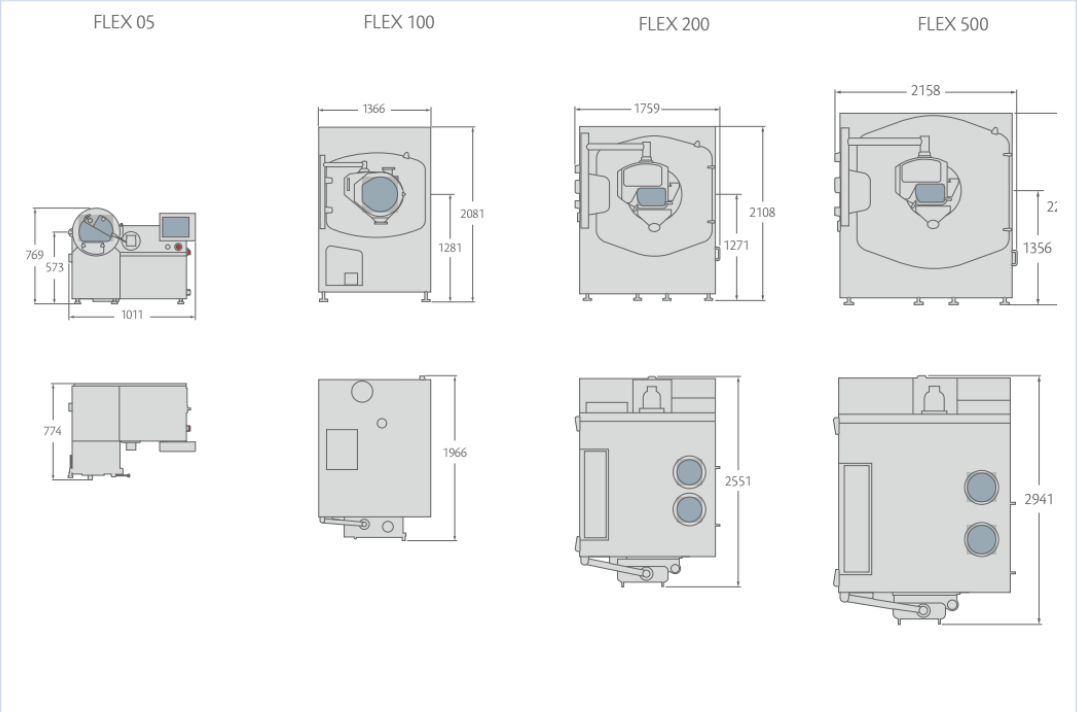
FLEX 100	19B	24B	24XC	30B	30C	36B
Drum Diameter Iches, (mm)	19" (440 mm)	24" (610 mm)	24" (610 mm)	30" (760 mm)	30" (760 mm)	36" (915 mm)
Drum Capacity	8 liters	25 liters	75 liters	75 liters	125 liters	110 liters



FLEX 200	36C	48B	48C	48XC
Drum Diameter Iches, (mm)	36" (915 mm)	48" (1,220 mm)	48" (1,220 mm)	48" (1,220 mm)
Drum Capacity	110 liters	190 liters	290 liters	325 liters



FLEX 500	48B	48C	48XC	60B	60XB	60C	60XC	65XC
Drum Diameter Iches, (mm)	48" (1,220 mm)			60" (1,525 mm)				65" (1,650 mm)
Drum Capacity	190 liters	250 liters	325 liters	460 liters	530 liters	530 liters	750 liters	920 liters
Raccomended Airflow CFM, (m^3/hr)	2,500 (4,250)		4,000 (6,800)				7,000 (11,900)	
Width	60"			72"				
Height	80"			86"				
Depth	90"			100"				
Net Weight	4,125 lbs			5,500 lbs				

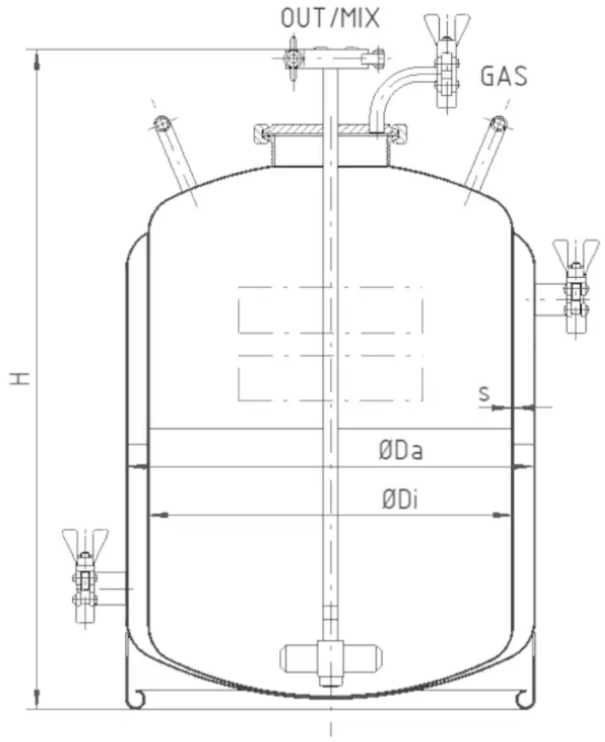


MODEL	FLEX 05	FLEX 100	FLEX 200	FLEX 500
Minimum/maximum capacity (l)	0.5-5 100 ml w/ divider plate	8 (2-8) 25 (6-25) 75 (19-75) 75 (19-75) 110 (28-110) 125(32-125)	110 (30-110) 190 (40-190) 250 (60-250) 325 (80-325)	190 (40-190) 250 (63-250) 325 (80-325) 460 (115-460) 530 (133-530) 500 (125-500) 750 (187-750) 920 (230-920)
Pan Diameter mm (inches)	305mm (12")	440 (19") 610 (24") 610 (24") 760 (30") 760 (30") 915 (36")	915 (36") 1,220 (48") 1,220 (48") 1,220 (48")	1,220 (48") 1,220 (48") 1,200 (48") 1,525 (60") 1,525 (60") 1,525 (60") 1,525 (60") 1,650 (65")
Pan mouth diameter mm (inches)	254 (11.5")	254 (10") 406 (16")	483 (19")	
Process air delivery m^3/hr (CFM)	170 (100)	1700 (1000)	4,250 (2,500) 6,800 (4,000)	4250 (2,500) 6,800 (4,000) 11,900 (7,000)

24.4.8 NCD 50 M Stirring tank with double jacket

Tempering & Mixing Vessel

Stirring tank with double jacket



Type	Vol	Material	Finishing	M	H	D	s	Pressure
NCD 50 M	53	1.4404 (316L)	electropolished	28	700	363	1,5	-1/+5

Vol = Volume (in litres), **D** = Diameter (in mm), **d** = Inner diameter (in mm), **H** = Height (in mm), **s** = Wall thickness (in mm), **M** = Mass (in kg)

Description | Equipment | Advantages

Material
1.4404 (316L)

Finishing
electropolished inside and outside

Volumes
0.1 to 200 liters (see **type overview**)

Gaskets
EPDM, silicone or PTFE

Pressure
-1/ 5 bar

Other
GMP-compliant **documentation**

Description | Equipment | Advantages

Central Tri-Clamp nozzle with:

- **OUT/MIX** immersion tube with PTFE-coated double magnetic stirrer
- Tri-Clamp connection
- **GAS** pipe bend with Tri-Clamp connection

Above cylindrical part and bottom:

- **DOUBLE MANTLE**

Description | Equipment | Advantages

- GMP-compliant design and documentation
- Aseptic product room
- Pressure and vacuum resistant (CE)
- Sterilizable and autoclavable (SIP)
- No dead spaces, easy to clean (CIP)
- Customisable modular system