Mini-Monoplant Technology for Pharmaceutical Manufacturing

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ABSTRACT: Pharmaceutical production has historically relied on multipurpose batch vessels in order to produce material through scheduled production campaigns. Although this method is flexible, it is becoming less effective in addressing the changing landscape of pharmaceutical production, where more complex and potent molecules are required to be produced more rapidly and can have fluctuations in their demand. This article describes a method for developing intensified and dedicated pharmaceutical processes, known as mini-monoplants. Key value-generating aspects are described at each stage of development, from lab-based development of best-in-class processes to factory-based development for an accelerated time to market and finally to mini-monoplant technology for production at commercial scale.

KEYWORDS: pharmaceutical manufacturing, process intensification, continuous flow design, scale-up, FlowPlate

1. INTRODUCTION

The class of bulk chemicals generally comprises two divisions of chemical production, namely, the production of approximately 20 base chemicals and 300 intermediates. About 85% of all chemicals are produced through modifications of the base chemicals, with the first level of transformations leading to the intermediate chemicals. The value of these chemicals is relatively low compared with those that are more advanced and require more complex transformations, but their immense volume and necessity as feeds for other processes allow them to maintain a significant share of the chemical market, accounting for 60% of chemical sales in the EU in 2018 (excluding pharmaceuticals).\(^1\) The large production requirements of these chemicals lead to dedicated continuous processes that are run over long periods of time, a processing mode that is known to be more economical when flexibility in the reactions, capacity, and equipment is not required.\(^2\) The cost efficiency of these plants is dependent on their being large and long-operating because of the economy of scale, which tends to lead to larger and riskier investments.\(^3,4\)

Conversely, processes in the pharmaceutical and fine chemical industries typically require a high degree of flexibility because of their short lifetimes and a constantly changing product market. The scale of these processes is significantly smaller than in the bulk chemicals industry and is usually on the order of a few kilograms to 100 tons per year.\(^5\) As a result, these chemicals are most often produced in modular and/or multipurpose plants that utilize primarily batch or semibatch stirred tank reactors. These reactors are often not optimized for any specific reaction but rather are able to accommodate a wide range of phases and reaction rates relatively easily. This flexibility allows for production of different chemicals through a schedule of campaigns that can last as little as a few days or as long as a few months, making it possible to produce tens of different products annually in a single train.\(^6,7\) This flexibility does not come without cost, however, as batch vessels tend to have reduced performance as their scale increases. Most products in this industry are developed at the lab scale in the drug discovery stage and are primarily scaled up by increasing the vessel size while maintaining a similar geometry. However, the increase from a lab-scale flask to a production-scale vessel imparts a drastic reduction of the reactor surface-to-volume ratio and a significant resulting decrease in the heat transfer performance of the system. In the interest of safety, these reactions are then usually run diluted or semibatchwise. Reactions run under such conditions are slower and inherit poor mass transport because of the reduced concentrations and small interfacial areas in large multiphase systems. Furthermore, this dilution requires an excessive amount of solvent—a situation that should be avoided because of the amount of waste and the environmental impact of its disposal. As a result, production-scale pharmaceutical processes are often run (semi)batchwise at suboptimal efficiency with a large E-factor (defined as the mass of waste per unit mass of product)\(^8\) and relatively low space-time yield, both of which afford opportunities for process intensification.\(^9−12\)

In this article, a model for pharmaceutical process design based on principles already in use in the bulk chemical industry is proposed. While it is generally accepted that both industries possess the potential to benefit from process intensification, there exist specific barriers and challenges for each that need to be addressed and evaluated on a case-specific basis. Specifically...
in the pharmaceutical industry, the batch campaign approach to production represents a key area where value may be generated through a shift to alternative methods of processing. For those campaigns that are longer with production quantities approaching the range of bulk chemical production, dedicated processes that more closely resemble those found in the bulk chemical industry should be considered. The goal of this article is thus to provide a pragmatic perspective on pharmaceutical process design that utilizes a set of established technologies to select the most optimal design given a particular reaction environment. Challenges and developments pertaining to process intensification within the pharmaceutical industry are presented, leading to a model for the development of dedicated, intensified pharmaceutical processes from early lab-scale to commercial production via mini-monoplant technology.

2. PROCESS INTENSIFICATION

Process intensification is a well-established concept for improving the efficiency and economics of chemical production while reducing its environmental impact. This has traditionally been proposed as a reduction in process equipment volume in order to allow more intensified reaction temperatures and pressures, but it may also include methods of combining multiple unit operations into one device or module and bringing them physically closer to each other. In both cases, limitations in mass and heat transfer are reduced as well as solvent holdup and distances between unit operations. The definition of process intensification has been extended by Stankiewicz and Moulijn to include “the development of novel apparatuses and techniques that, compared to those commonly used today, are expected to bring dramatic improvements in manufacturing and processing, substantially decreasing equipment-size/production-capacity ratio, energy consumption, or waste production, and ultimately resulting in cheaper, sustainable technologies,” with the fundamental principles of process intensification lying in the spatial, thermodynamic, functional, and temporal domains from the molecular to processing scales. Accompanying this concept of process intensification is the Industry 4.0 standard for a high degree of automation and information processing in chemical production. In this idea, various pieces of processing equipment are able to communicate with each other and their operators digitally, leading to a high level of information transparency and availability as well as the ability of machines and artificial intelligence to help with decision making and performance of physically difficult tasks. Product quality can be monitored and adjusted using process analytical technology (PAT) and real-time release testing (RTRT). A factory running autonomously in this manner is dubbed a “smart factory” and is predicted to exhibit greatly improved product quality assurance and control. Despite the known benefits of process intensification and automation, there are general barriers to its widespread implementation, such as cost, complexity, and a general hesitation to break the status quo. Thus, there is a so-called “rush to be second”, where most managers want to wait for proven full-scale evidence of process intensification before committing. The best opportunities for the implementation of new intensified technologies will therefore come from situations where new plants or processes are being developed. The barriers described above are being addressed through the establishment of various institutes or consortia, such as the pioneering Fraunhofer-Institut für Mikrotechnik und Mikrosysteme.

Figure 1. Examples of fundamental continuous reaction technologies. (a) FlowPlate rack with ultrasound unit for deplugging. (b) Coiled tube reactor. (c) CSTR. (d) Tubular reactor with static mixer inserts. (e) FlowPlate rack with ultrasound used in series with a tubular reactor with static mixer inserts.
(IMM), and followed in other countries by Continuous Manufacturing and Crystallization (CMAC), Research Center Pharmaceutical Engineering (RCPE), Synthesis and Solid State Pharmaceutical Centre (SSSPC), Maison Européenne des Procédés Innovants (MEPI), and Rapid Advancement in Process Intensification Deployment (RAPID) as well as efforts from various companies within the pharmaceutical industry.

2.1. Pharmaceutical Process Intensification. In the pharmaceutical industry, where short-lived production campaigns are primarily performed in (semi)batch reactors, the desire to miniaturize and intensify will generally require continuous processing. Continuous flow at the micro- or milliscale provides several advantages compared with typical large-scale batch production processes, including improved heat and mass transfer, lower solvent requirements, better process control, enhanced reaction homogeneity, and safer handling of hazardous materials. Productivity (defined as the amount of product generated with a finite amount of resources, including labor) comparable to that in large-scale batch operation can be achieved when the system is run continuously in a smaller-scale unit, leading to a drastically smaller footprint. Several examples of continuous pharmaceutical production have been developed and published by researchers at Eli Lilly, including high-temperature continuous crystallization and continuous active pharmaceutical ingredient (API) production under cGMP conditions, and there are also reports detailing collaborations and technology transfer between pharmaceutical companies and contract manufacturing organizations. Of key importance to the intensification of pharmaceutical processes and due to the enhanced rates of heat and mass transfer is the ability to perform reaction chemistries that would normally be considered “forbidden” under standard batch operation. Intensified reactions run at high temperature, pressure, and concentration result in higher reaction rates and larger productivities, especially with the implementation of automation and RTRT. In addition, higher-energy reagents may be employed, which can facilitate more direct synthesis routes with fewer steps and higher-purity products. For example, microreactors have previously shown success in the generation of explosive nitroglycerin and can significantly broaden the safe operating window with explosive substances. The selection of the appropriate continuous reactor technology depends on the reaction phases, kinetics, and reaction network, and these technologies may be broadly divided into three fundamental categories: plates, coils, and continuous stirred tank reactors (CSTRs). Plate reactors are generally applicable to reactions containing liquid and/or gas phases and when more plug flow is desired with rapid micromixing and/or heat transfer. Coil-type reactors can be applied to plug flow reactions with slower kinetics that require longer residence times and less intensive heat transfer and can be extended to handle solids when oscillation is applied to the reaction medium. For perfectly mixed reactions, one CSTR can be implemented for reactions with a specific network or a cascade of CSTRs to handle a wide range of reactions, kinetics, and phases. Some specific continuous and intensified examples (shown in Figure 1) and applications of these (and related) reactor categories include plate microreactors, coiled flow reactors, oscillatory flow reactors, micro packed bed reactors, plug flow reactors with static mixer inserts, mixed-suspension mixed-product-removal (MSMPR) crystallizers, and miniaturized CSTRs. Thus, pharmaceutical processes may be intensified through these three targets:

1. intensification of the synthesis route via more direct and higher-yield pathways;
2. reactor technologies, often miniaturized, with high surface-to-volume ratios and reduced transport lengths that facilitate the use of the intensified reactions in target 1;
3. increased productivity through continuous processing with a high degree of automation and RTRT.

When all three targets are incorporated into the design of a pharmaceutical process, the result is a higher-yield, higher-productivity continuous process that can run relatively autonomously and with a smaller footprint than typical batch or semibatch processes. Specific benefits of optimizing these targets may be illustrated by comparing two cases: a non-GMP (early) intermediate and an API/late intermediate under GMP. In the first case, production costs are driven primarily by throughput (defined as the mass of product per unit time) and productivity and would benefit from increasing the amount of automation in the process. In the second case, the production costs of the more complex API are governed by the yield and selectivity, parameters that may be improved through the use of more intensified synthesis routes permitted by miniaturized reactor technologies. For example, Monteiro et al. showed continuous synthesis (with 98% conversion and 85% selectivity) of a complex API via trifluoromethylation in a rack of FlowPlates followed by a CSTR for quenching. However, the downside to continuous processing in this manner is the obvious and significant loss of flexibility that is usually desirable in these industries. It can become difficult to handle the constant changing influx of reactions in less versatile continuous reactors, especially when there is a solid phase present in a miniaturized channel. Additionally, using a new or redesigned dedicated continuous process for each separate campaign can incur significantly higher development and implementation costs that may outweigh the value of the production campaign itself. These costs are generally manifested where new technologies need to be developed, especially in the cases of particularly slow reactions and workup stages, where the choice to either invest in such technologies or simply use batch for these steps becomes a comparison of capital expenditure (CAPEX) and solvent usage depending on the stage of product development (i.e., in clinical phases or commercial production) and efficiency of technology.

2.2. Keeping Pharmaceutical Processing Flexible through Modularity. Ideally, pharmaceutical production technology should be intensified, continuous, and flexible enough to optimally produce a wide range of potential products; however, a perfect solution to obtain all three may not exist. The development of modular systems to achieve a balance among these three targets has been ongoing, and an early adoption of such a modular microreaction system developed by Ehrfeld Mikrotechnik was described in 2005. More recently and in the same vein, two modular platforms that aim to address these requirements have been developed at MIT. The first is a self-contained continuous manufacturing platform in a mobile cabinet that is capable of producing and purifying liquid API formulations. The second is a reconfigurable universal bay for automatic chemical reaction optimization in which several different interchangeable reactivity...
can be attached. Utilizing one of these modules is likely to be less expensive than engineering and implementing a brand-new intensified process with specialized technology. This can be particularly beneficial to smaller firms where the required capital and infrastructure are not available for extensive process development, rapid switching between production campaigns is more desirable, and/or the amount of required product is smaller. Additionally, these flexible modules can allow the production of specific therapeutic formulations that can accommodate the range of responses by patient populations. In cases where more capital is available for larger production campaigns, however, a more dedicated approach similar to that found in the bulk chemical industry may be more suitable.

3. MINI-MONOPLANT CONCEPT

As mentioned above, API production under GMP is generally driven by product yield because of the complex reaction pathways required to transform intermediate chemicals into highly specialized products. However, it can often be difficult to move into continuous production when clinical development has been completed in batch because of GMP registration constraints. This section describes an approach for the development of a continuous, intensified process at lab scale using a toolbox of established and developing reactor geometries that can be directly scaled up to production volume using established principles based on maintaining the relative transport and reaction rates upon geometrical scale-up.

In the early 2000s, a typical commercial-scale batch production campaign at Lonza could last anywhere between 4 and 8 weeks, with an average yield and throughput of around 77% and 1.5 tons/day, respectively, in the Fine Chemicals Complex (FCC) facility with a reactor size of 10,000 L (Figure 9, vide infra). The flexibility and versatility in batch processing equipment in a multipurpose plant allowed for the equipment to be cleaned after completion of the campaign and reused in the subsequently scheduled production campaign. This business model relied on multipurpose plants remaining well-occupied and having numerous vessels or facility sizes to accommodate a wide range of customers and product demand. However, the system of scheduling processing equipment cannot effectively address the changing landscape of pharmaceutical processing, where there is a focus on more complex, potent, lower-demand, and specialized drugs that require an accelerated timeline to reach the market and have uncertainty in their demand. The latter two points may be addressed via dedicated manufacturing assets for a single product in a monoplant (i.e., a production plant dedicated to a single product, with the goal of rapid and economical attainment of production capacity with the ability to adapt to market demand that can be designed in batch or continuous flow and built within an existing facility.

This concept is illustrated in Figure 2. Whereas a multipurpose plant will generally produce one large batch during a scheduled campaign, a monoplant can produce product batches year-round if required. This offers the capability to rapidly address any changes in product demand, whereas the multipurpose plant may have to wait until the equipment is available for additional production, which often results in overproduction during the launch phase of a new API. For complex molecules, it is also common to have lead times of several years from order to delivery since multiple campaigns are required for the different synthetic steps performed in a sequential manner. In addition, the cleaning and changeover steps required for multipurpose plants are time- and resource-consuming, demanding full HAZOP analyses each time and requiring a level of cleanliness that is directly proportional to the potency of the API. Thus, the use of monoplants has great potential to reduce the cost of goods compared with initial batch campaigns and to decrease the lead time from order to delivery from years down to potentially a few months, while also allowing a buffer stock of key and stable intermediates to be maintained that, in combination with the dedicated facilities, can facilitate rapid responses to fluctuations in customer demand.

When year-round monoplant batch production is employed, automation and RTRT are fundamental attributes to increase productivity. However, even further enhancements to productivity may be achieved by also addressing the first two intensification targets described in section 2.1. More desirable and novel reaction pathways are primarily enabled through...
continuous-flow processing in advanced, miniaturized reactor technologies, where dedication of such assets to production of a single product in a monoplant then results in a so-called “mini-monoplant” (Figure 3).

The use of a mini-monoplant presents three key advantages in pharmaceutical production, as shown in Figure 4. First is the opportunity to develop best-in-class processes at the lab scale, where novel synthesis routes will improve the safety, sustainability, and yield. Second is accelerated development and time to market through a streamlined scale-up to factory-based production facilities. Here the lab-scale process becomes the production setup, which may be developed further and, when required, scaled up using established geometrical scale-up methodologies in an available production cabin within the factory. The final advantage is an overall reduction in capital and operating expenditures when the mini-monoplant is ultimately built and dedicated to continuous production of a single product, effectively increasing the productivity while reducing the factory footprint and avoiding the time-consuming and costly changeover steps required in typical multipurpose plant production. In a situation when many multipurpose plants are run at capacity, the mini-monoplant then becomes attractive for new investments and allows customers to maintain occupancy of their respective production facilities.

3.1. Lab-Based Development of Best-in-Class Pharmaceutical Production Processes. The development of a mini-monoplant can begin directly in the safety of a laboratory, where innovative and novel continuous processes can be performed with a small footprint. Lab-based process development allows engineers and chemists to focus on key value-generating features for the finalized mini-monoplant, including process intensification, unit operations with advanced techn-
technologies, and full automation over a range of throughputs that may typically span from 1 to 50 kg of product per day.

An example of such a process is shown in Figure 5, with a simplified process flow diagram shown in Figure 6. Here lab-based development of a mini-monoplant was conducted within the space of three fume hoods. The system consisted of a rack of FlowPlate A6 microreactors (temperature maintained at 30 °C) in which a rapid type-A and highly exothermic nitration reaction was performed using a concentrated mixture of nitric acid and sulfuric acid. The excess acid was then quenched twice sequentially in two mixer settlers, in the first with water (to prevent excessive heat generation) and in the second with sodium bicarbonate (to quench any remaining acid in the organic phase). A film evaporator was then used to remove the organic solvent so that the slightly soluble main intermediate could undergo a saponification reaction under biphasic conditions in a cascade of three CSTRs in series. The more water-soluble product was then back-extracted into an organic solvent, a step that required an efficient multistage countercurrent liquid–liquid extractor.

The process pictured in Figure 5 had a throughput of 10 kg/day and had the capability to deliver material that was required for clinical trials. However, a bottleneck existed in this stage of development, as larger production amounts would require more than 100 L of organic solvent per day, an amount that was too large to be properly handled within a laboratory setting and necessitated larger and more capable infrastructure for further development.

3.2. Factory-Based Development for Accelerated Development and Time to Market. Upon completion of lab-scale process development, further development of the process for larger production volumes can then be moved into

Figure 6. Simplified process flow diagram for the lab-based mini-monoplant development shown in Figure 5.

Figure 7. Factory-based process development. Use of an available cabin within the existing production infrastructure allows for a reduction in development time and time to market.
an available cabin within an existing production infrastructure. As shown in Figure 7, the lab-scale process can be directly transferred to a cabin that allows for connection to all of the factory infrastructure, including large-volume storage tanks for the feeds and products. The cabin can be operated without explosion-proof equipment, as the processes are intensified, the reactive volume inside the cabin remains sufficiently small, and the cabin is well-ventilated. The objectives here are to reach a flexibility similar to that available in a laboratory and to validate the scaling approach taken. During this stage of development, various unit operations within the process can be mounted onto mobile skids and used as flexible and multipurpose modules. These may be base modules, such as dosing modules and reactor modules (Figure 8), or more advanced modules, such as a specific reactor technology (e.g., photocatalytic or electrochemical reactors) or solid–liquid-handling modules. These modules allow for rapid process assembly during factory-based development and can provide significant time savings if they are prequalified for GMP production. Additionally, the modules may be cleaned and reused for additional processes upon completion of a production campaign. It is important to note, however, that these modules may be subject to use in a campaign approach when multiple factory-based developments are occurring simultaneously.

It is during factory-based development that the first integrated process scale-up occurs. Here the flow rates can be increased when necessary to accommodate larger amounts of pharmaceutical demand that may occur during phases I to III of clinical development when the drug has not yet gone commercial. At this stage, the spatial advantages of operating a miniaturized continuous-flow process become clear, as illustrated in Figure 9. Often, when operated over time, a flow rate of 10 mL/min through a plate-type microreactor is sufficient for clinical development. The footprint of such a process is significantly smaller than the 250 L vessel that would be required for batch unit operations. It is of course assumed that a drastic intensification of the reaction conditions has been achieved and that the reaction has become mainly mass- or heat-transfer-controlled. Under such circumstances, the volume of a plate-type reactor is in the range of milliliters, while the volume of a CSTR is in the range of 1–2 L. If the reaction is inherently slow and kinetically limited, larger reactors (i.e., coiled tubes or stirred tanks) may be required. With respect to scaling, the flow rates and reactor sizes included in Figure 9 have scaling factors (i.e., multipliers of the bulk flow rate or CSTR volume) ranging from 1 to 60, with the first approximately 5-fold scale increase often occurring during laboratory-based development and the remaining occurring during factory-based development. With the use of modular equipment and GMP-ready modules (as shown in Figure 8), two sets of equipment will be enough to cover the required scales during factory-based development, where one set is for low flow and the other is for high flow. In a dosing module, for example, a pump and flow controller can adequately span a 10-fold scale in flow rate, allowing a set of two dosing modules to readily handle the entire scaling range shown in Figure 9. With respect to the reactor technology, a modular system with easily interchangeable reaction volumes is desirable (e.g., FlowPlate technology with a range of swappable plate sizes, geometries, and volumes). Acquisition of an available pool of flexible process technologies requires a certain initial cost but has long-term benefits as additional and more effective options become readily available to engineers and chemists during process design and implementation.

With respect to scale-up methodologies, reactor dimensions are increased while maintaining geometric similarity and transport phenomena as allowable within the specific micro-mixing requirements of a given reaction, permitting the use of a single larger channel rather than multiple smaller channels in parallel. Moving to a factory-based setting is a pivotal stage of development, as it allows testing of long-term process stability to occur with solvent capacities that would otherwise be limited within a laboratory setting. During this stage of development, the process and factory must be designed with contingency methods of cleaning and deplugging, which can include automated solvent switching and the use of ultrasound.

In an example toward factory-based development, 2-nitroethanol (3), which is an early intermediate required for an alternative synthesis of aliskiren, was produced in a lab-based miniplant via a Henry reaction between formaldehyde and nitromethane (Scheme 1). The reaction is relatively fast, reaching around 50% conversion after 25 s. In this reaction, the molar ratio of nitromethane to formaldehyde has a significant impact on the selectivity of the reaction, as the product 3 can react further with formaldehyde to form 4 and 5 as byproducts. The higher the relative amount of nitromethane, the higher of the selectivity of the reaction toward 3, and subsequent recycling of the excess nitromethane after completion of the reaction is essential for safe operation to considerably reduce...
its holdup and consequently its potential as an explosion hazard.

A simplified process-flow diagram of the miniplant setup is shown in Figure 10. The formation of 2-nitroethanol took place in a series of A5 plate-type microreactors at 30 °C, which included an initial SZ mixing plate followed by a series of residence time plates. The Henry reaction occurred under basic conditions, and in a crucial safety step, the reaction mixture was then acidified in a CSTR because the removal of nitromethane from a basic mixture has the potential to become explosive. A filter was implemented downstream of the CSTR in order to handle the solids generated by the acid−base reaction (salt formation). The resulting mixture of 2-nitroethanol and nitromethane was separated by a wiped-film evaporator, generating crude 3 and allowing the excess nitromethane to be recycled, thereby reducing its holdup in the laboratory and removing any feed impurities that would have otherwise led to the formation of precipitates and caused
The synthesis route could be employed because of the intensification of the processing environment that will occur in larger-scale production units, allowing for the identification and correction of any potential problems or instabilities early in development.

The scale-up of this process was achieved in a nearly identical setup utilizing the same pumps by adjusting the number and volume of plates and using a larger wiped-film evaporator. The throughput was quadrupled to 1 kg of crude 2-nitroethanol per day, and more than 5 kg was produced intermittently over 5 days. In fact, depending on the need, the flow rate could have been tuned from 1 up to 40 kg/day with a further increase in the capacity of the wiped-film evaporator—an investment that would be required upon a request for additional product. Although larger, this equipment would not have substantially increased the holdup of crude 2-nitroethanol at 70 °C, as its quantity would remain relatively small within the film. This system exemplifies the three targets of pharmaceutical intensification described above, where a novel synthesis route could be employed because of the intensified reactor and workup unit operations, and a range of throughputs and productivities were possible by adjustment of the flow rates in the fully automated process.

In the example above, intensified workup in the wiped-film evaporator was essential for safe operation of the process. Oftentimes, however, intensified units for the workup stages of a miniplant may not yet be commercially available, as is especially the case when there is a solid phase present in the mixture. Other times, intensification of the workup stages may not be economical when the solvent is not inherently dangerous and is used in relatively small amounts (e.g., in production of a product for clinical trials) compared with the cost of developing miniaturized workup units. If no intensified modules are available for the workup stages during factory-based development, then the decision of whether to continue using batch at production scale or to transition into new continuous technologies should be evaluated on a case-specific basis through a comparison of the amount of solvent and/orCAPEX required for each.

In a process containing a solid product, as shown in Figure 11, the filtering, washing, and drying of the solid product are performed in a batch filter dryer vessel where two potential routes may be taken. In the first, two filter dryer vessels are operated intermittently, one of which performs the cake washing and drying of the solids while the other is filtering. In the second method, a surge tank is implemented upstream of a larger filter dryer vessel in order to buffer the feed and allow the filter dryer vessel to be periodically emptied. In the first case, the cost of purchasing two filter dryer vessels is substantially larger than in the second case, where the purchase of a surge tank and a single larger volume filter dryer vessel will ultimately cost less, as volume gain is relatively inexpensive in vessels. The size of this vessel should be big enough to enable a complete cycle of the filter dryer while allowing for some additional buffer time. In this example, the transition between

3.3. Mini-Monoplant Production Technology at the Commercial Scale. Once the factory-based development has been completed and the product has gone commercial, the process can then be installed in a dedicated production area within the plant. It is during this final stage of development that the temporal integrated process scale-up occurs, i.e., in the operational time of the process, which may be run year-round when required. At this stage, complete automation is a prerequisite to increase the productivity as the production is extended over time. It is also important to consider the cost and resulting value of developing and implementing RTRT in order to increase the overall productivity of the process. If the entire process including workup is intensified and continuous (see Figure 10), then installation becomes a matter of simply transitioning the factory-based process into production via the acquisition of new, dedicated production assets. If steps within the process, including reactions and/or workup, were run in batch using the campaign approach during factory-based development, then the decision of whether to continue using batch at production scale or to transition into new continuous technologies should be evaluated on a case-specific basis through a comparison of the amount of solvent and/orCAPEX required for each.

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continuous and batch operation is well-defined, and such transitions are an important consideration during process design because they will increase the complexity of the process.

The previously described system with the surge tank and single filter dryer is the planned approach for a mini-monoplant for commercial production of a tetraalkylphosphonium salt (Scheme 2), to be implemented according to the overall process description below. Under the employed reactive conditions, the reaction has an adiabatic temperature rise of 118 °C with heat accumulation, with the onset of the first exotherm occurring at 100 °C. Thus, the reaction requires very tight temperature control in order to prevent thermal runaway. In batch using a vessel size of 160 L, the temperature is controlled via dosage of 6 at 40 °C over the course of 30 min (for 5 kg of 8). In the flow system shown in Figure 12, the FlowPlate A6 allows for intensified reaction conditions and nearly full conversion to be reached after 2.5 min at 70 °C and 3 bar. Reactants 6 and 7 are first combined in an SZ-type mixing structure to allow for rapid mixing, followed by a series of residence time plates, of which the quantity can be adjusted in order to accommodate the necessary residence time at a given flow rate. The two liquid feeds are not preheated because of thermal instability of the reactants. The resulting mixture is then cofed with an antisolvent into a stirred precipitation vessel run continuously with a jacket temperature of 10 °C. Once the precipitation vessel reaches a designated fill volume, the suspension is transferred to a surge or buffer tank via a suspension transfer module. The suspension from the surge tank is then transferred to a filter dryer, where the solid product is separated from the mother liquor, washed, and dried. After discharge of the dried product, the filter dryer is then ready to receive new suspension from the surge tank, which has been refilled in the meantime. The reactor plates do not require intensive cleaning cycles, as the quantity of formed phosphonium salt remains soluble in the reaction mixture at 70 °C, while those sections of the process containing a precipitated solid suspension can be rinsed with the process solvent. The primary heel of the filter dryer is removed periodically on the basis of the stability data of the product.

Logistically, installation of a mini-monoplant would occur in a complex within a plant containing “monosuites” for every new product. The complex would be designed with service infrastructure (i.e., solvent tank farm, cooling/heating systems, waste management, etc.) analogous to that normally available in a multipurpose plant. Direct lines to solvent or water tanks/containers will be included, as well as lines to containers with standard concentrations of acids or bases when required. Such an approach is currently being taken at Lonza for biologics manufacturing, where significant investment has been initiated into a manufacturing complex called Ibex.92,93 For small molecules, monosuites can be retrofitted into existing multipurpose facilities in order to limit investment.

The monosuite itself would encompass cabins or rooms that include space for head tanks for solution preparation when required. At this stage, it is important to mention that these tanks or containers are by no means the equivalent of a multipurpose batch reactor in terms of both technological complexity and investment. Such tanks are significantly less expensive and can also consist of single-use plastic containers. Some of them may require cooling or heating capacities depending on the contained solution’s stability, viscosity, or liquefaction. It is also assumed that when the reactions are run under intensified conditions in miniaturized technologies, the solvent requirements (and their associated footprints) will be smaller than in an unintensified batch process with an equivalent production quantity. In addition, the monosuite would require solid isolation capacity. The example given above (Figure 12) shows solid isolation via filter dryer operation, but this could also be approached in a different manner.

The monoplant strategy is already in use for batch technology.94 The main driver behind the widespread

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Scheme 2. Reaction between Allyl Bromide (6) and Trialkylphosphine (7) to Form Tetraalkylphosphonium salt (8)

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![Figure 12. Intensified reaction with automated batch workup, here applied to the production of a tetraalkylphosphonium salt.](https://dx.doi.org/10.1021/acs.oprd.0c00207)
development of monoplants arises from the reduction of investment costs via the use of intensified continuous technologies. When batch technology is used in solid handling, for example, the investment costs and space requirements are similar to those needed in a multipurpose plant with comparable equipment size. The cost and space advantage is therefore manifested in the compact system design and year-round operation. Technological development in solid handling and crystallization is an important ongoing research topic and will determine the extent to which this aspect of a process will be amenable to process intensification and continuous operation. For example, solid dosage and automatic feed preparation with solid substrates are now possible under continuous operation, and this approach is also valid for workup unit operations. Implementation of such technologies will occur when they bring sufficient advantages that supersede the investment needs.

4. CONCLUSIONS

Pharmaceutical production has historically relied on multipurpose batch vessels utilized through a campaign approach. Although these vessels are flexible and can accommodate a wide range of reaction phases and kinetics, they are becoming less effective in their ability to address recent developments in pharmaceutical production, where more complex, potent, and specialized drugs are becoming increasingly desirable with accelerated times to market and uncertainty in their demand. As seen in the bulk chemical industry, rapid changes in product demand can be addressed through dedication of production assets to a single product in a monoplat. The more specialized products desired by the pharmaceutical and fine chemical industries can be produced though miniaturized and intensified production assets that allow for the use of previously “forbidden” chemistries in a miniplant. When applied in combination with the development of a pharmaceutical production process, the result is a mini-monoplant that is dedicated, highly intensified, and able to operate year-round to respond to fluctuations in product demand.

The road to development of a mini-monoplant for pharmaceutical production occurs through three main stages, namely, lab-based development, factory-based development, and mini-monoplant production at the commercial scale. In lab-based development, miniplant process development occurs within the safety of a laboratory, where chemists and engineers can focus on value-generating features such as novel reaction pathways, intensified reactors, automation, and dedication. Here, novel and innovative continuous processes can be developed with a small footprint with throughputs that can span from 1 to 50 kg of product per day. Upon completion of the lab-scale development, the miniplant can then be moved to an available cabin within the existing plant infrastructure, allowing for access to large-volume feed and product storage tanks. This provides a similar flexibility as was available in the laboratory, and the usage of predesigned (and potentially GMP-qualified) multipurpose unit operation modules can greatly reduce the development time and time to market for introducing new technology into the pharmaceutical production process. The first stage of process scale-up occurs in factory-based development, where throughputs can be increased to meet the demands of clinical trials. Finally, when the product has gone commercial, dedicated production assets can be acquired, and the process can be installed in a designated area within the plant. It is at this stage that the process can be considered a mini-monoplant, and the final temporal scale-up occurs with respect to the overall operating time of the process, of which dedication allows year-round operation if required in order to meet fluctuations and uncertainty in product demand. In line with the ongoing paradigm shift toward continuous manufacturing in pharmaceuticals, process development via mini-monoplant technology is a pragmatic approach to pharmaceutical production using carefully selected processing units that are currently available to chemists and engineers. As this processing mode becomes more commonly adopted, it is expected these technologies will develop and become more readily available, especially when/if regulatory and tax incentives that can help address the financial hesitation toward widespread adoption of novel technologies become available.

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■ ABBREVIATIONS

API = active pharmaceutical ingredient
PAT = process analytical technology
RTRT = real-time release testing
GMP = good manufacturing practice
CAPEX = capital expenditure
HAZOP = hazard and operability
CSTR = continuous stirred tank reactor  
SSP = small-scale plant  
LP = launch Plant  
FCC = fine chemicals complex

REFERENCES