Achieving Continuous Manufacturing for Final Dosage Formation: Challenges and How to Meet Them

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ABSTRACT

We describe the key issues and possibilities for continuous final dosage formation, otherwise known as downstream processing or drug product manufacturing. A distinction is made between heterogeneous processing and homogeneous processing, the latter of which leads to the full value of continuous manufacturing. We also give the key motivations for moving to continuous manufacturing, some of the exciting new technologies, and the barriers to implementation of continuous manufacturing.

Keywords: upstream, downstream, drug substance, drug product, mixing, solution, dispersion, heterogeneous, homogeneous

1. Introduction to Continuous Manufacturing for Final Dosage Formation

As discussed in the Introduction of this volume, "continuous manufacturing" means integration, a systems approach, and a model-based control within a flow process. Thus, since a continuous process is designed as a whole, the distinction between upstream and downstream, or drug substance and drug product, as currently used, is potentially eliminated. The disappearance of these terms corresponds to a change in mindset, which itself would lead to the adoption of new terms. However, there is clearly still the need for expertise in chemical synthesis, reaction engineering and work-up on the one hand, and material understanding, formulation development, and formulation process engineering on the other. Here we focus on final dosage formation, including in this analysis the overlap between it and chemical synthesis, reaction engineering, and work-up. While we cannot with certainty predict which technologies and technology strategies pharmaceutical manufacturers will adopt in the future, we do believe that the future can be very different than the current approach, and herein we outline the vision of continuous manufacturing for final dosage formation, the barriers to achieving that vision, and how the industry should work to overcome those barriers.

While the technologies, and therefore development and manufacturing expertise, needed for the final dosage formulation aspects of continuous processing are different than those needed for chemical synthesis, reaction engineering, and work-up, there are many areas of overlap. These include crystallization, powder handling, solvents processing, process safety, and process monitoring and

control technologies. In fact, as continuous manufacturing becomes more and more prevalent and new technologies come about, we expect that the various development and manufacturing specialties will tend towards convergence. There will still be various areas of expertise, but specialists will need to interact with other specialists much more than they do presently, in order to coordinate process development, and the differentiation among process development teams will become smaller and smaller. For example, the solvents for chemistry development will need to be chosen to take into account work-up, in addition to, at least for the last chemical step, processing aspects of final dosage formation, such as drying and mechanical properties. Furthermore, while we expect a transition period during which batch technologies are converted to similar flow technologies in which there will still be substantial in-process powder handling such that actives and excipients are processed heterogeneously, in the long run we expect that the advantages of homogeneous processing will be such that most, if not all, continuous processes will involve homogenous processing technologies, in which actives and excipients are processed together. Homogeneous processing will necessitate new approaches to final dosage formation and corresponding new technologies, all of which will need to be integrated tightly with the other aspects of the process.

For these reasons, we term the subject of this white paper "final dosage formation," keeping in mind that in the world of continuous manufacturing terms like "upstream," "downstream," "drug substance" and "drug product" could be considered transitional terms, and may very well disappear. The focus here is on formation of tablets for oral dosage, but the reader will readily see how the approaches below can be used to produce alternative dosage forms, including films, depots, inserts and implants.

2. How the Vision of Continuous Pharmaceutical Manufacturing will Change Final Dosage Form Operations

Given that continuous manufacturing encompasses integration, a systems approach, flow, and model-based control, future continuous facilities will be set up quite differently than existing facilities. Below, we discuss the trade-offs involved in dedicated final dosage form process trains versus multi-use process trains. We do envision, minimizing if not eliminating, powders handling. In addition, even if processes do not achieve full continuous manufacturing as we have defined it, steps in that direction should prove to be of significant benefit across the industry, from brand pharma companies to generics, from small-scale production to large–scale production, and from simple to complex formulations. Integration within a systems approach itself leads to a reduction of process steps, as the number of "correction" steps can be reduced or eliminated. In batch processes, actives are almost always formed upstream into powders that typically do not have the properties needed for downstream. Thus, initial downstream steps typically include milling and blending. These can be streamlined in a continuous process. Furthermore, batch downstream steps often include granulation so that the mixture will have the properties needed for further processing, which is needed because the mixture does not inherently possess the desired properties. Given that continuous manufacturing naturally encompasses more up front understanding, a continuous process would be designed and controlled such that the mixture has the desired properties engineered when it is made. Many of the batch upstream steps are not needed in continuous processing, particularly those at the interface of upstream and downstream. For example crystallization and drying of the active might not be needed at all. Additionally, filling of the bulk active and transportation might not be needed, not to mention removal and dosing of the active in downstream batch processing.

The continuous manufacturing plant could be capable of running constantly 24/7 for 50+ weeks/year, with no significant downtime for major cleaning (except in product or process changeover), as is the case in other industries ranging from foods to petrochemicals. For pharmaceuticals, such a process easily affords an annual production of 1 billion tablets, which

translates to only 120,000 tablets per hour, a throughput that is typical of a single pilot scale line using conventional technologies.

Because continuous processes are run under a constant state of control, there are inherently no dynamics (other than the transients associated with start-up and shutdown), and the process is much easier to maintain accurately. Furthermore, they are controlled using detailed process models, which themselves are used in advanced algorithms, leading to a much lower risk of going out of specification than batch processes. Because of in-line process analytical technology (PAT) tied to the control system, the dream of real time release (RTR) becomes a reality in a natural way, as part of the process approach. And in the rare case of process perturbations, real-time rejection of small quantities of non-conforming product can be performed without sacrificing the defined batch. The processes themselves are more robust, leading to lower risk of stock-outs.

Furthermore, a manufacturing train for production of Phase III clinical materials could be developed so that it is the commercial process, run for a short time for clinical supplies and year-round for commercial production. Thus, a scale-up step is skipped, allowing reduction of critical path timeline and reduced risk of development and manufacturing delays.

2.1. Heterogeneous versus Homogeneous Processing

We that expect that many, if not most, continuous processes that are developed in the near future will be "heterogeneous processes." These are processes in which the components tend to segregate, a problem must be controlled throughout. These processes will be designed by leveraging existing powder handling technology (i.e, incorporating common drug product formulation unit operations) as many current drug product unit operations inherently have continuous flow or semi-continuous flow (e.g. roller compaction, tablet compression). The focus of this initial approach will be in the integration of these unit operations into a single line. Product quality is assured during processing by using in-process monitoring by PAT and/or parametric control. Such an approach will benefit from no open manual handling of actives, increased safety, smaller equipment footprint and shorter processing times. However, these processes are far from achieving the full benefits of continuous manufacturing and have the tendency to become Rube Goldberg processes, i.e. overly complex. Due to the familiarity of the technologies involved, however, they are easier to develop from a technical standpoint and from the standpoint of obtaining managerial and regulatory approval. For example, an existing batch process, consisting of steps such as blending, granulation, milling, blending, tableting and coating could be replaced with a corresponding continuous process incorporating the same steps. This flow process would still have many of the advantages discussed above, but would likely be far from reaping the full benefits of continuous processing. There would still be significant powder transport challenges, unnecessary process steps that need to be eliminated, and higher risk of process issues. Thus, we consider these heterogeneous processes as the initial step in the transition from batch to homogenous continuous processing.

True continuous manufacturing involves "homogeneous processes," in which the components processed exhibit no significant segregation on whatever the key length scale is, typically between Ångstroms and microns. Thus, they need not be homogeneous on the molecular-level, as continuous process steps can lead either to a solution, a melt, or a dispersion. The distinguishing feature is that the active-excipient combination is engineered to have the key properties needed in order to make directly the final dosage form. For example, the synthesis and work-up can deliver the active in a purified solution in which the excipients can be added and dissolved. Then the solution can be dried and made into the final dosage form. Alternatively, the active and excipients can be melted or the active can be nucleated on excipients. Another approach is that the active can be crystallized separately and incorporated with the excipients in crystalline form, followed by direct formation of the final dosage form. Examples of such homogeneous processes include extrusion, spray drying, thin film formation, electrospraying and electrospinning, and injection molding and calendaring, as discussed below. Homogeneous processing offers the true potential of continuous manufacturing.

Because homogeneous processing utilizes different technologies and it naturally involves integration, it will necessitate different organizational approaches for both development and manufacturing.

3. Challenges and Barriers

Given the tremendous benefits of continuous manufacturing, why is it that it has not become the industry standard? The main reason is a "business as usual" approach embraced by a highly conservative industry. Specifically, it has been seen that new manufacturing approaches must be proven both technologically and financially superior, and tied to a product before widespread adoption will take place. This leads to the "chicken and egg" conundrum that technologies must be already adopted for the industry to adopt them. This is coupled with the fact that process development and manufacturing have not had a high profile in the pharmaceutical industry. Typically, pharmaceutical companies perform low level investments in new technologies to assess viability, and intensify those efforts only when tied to a specific product. For equipment manufacturers, since these companies' main customers are in the pharmaceutical industry, which tends to be more averse to adopting new manufacturing technologies, and therefore innovation in manufacturing equipment tends to be incremental.

Part of the "business as usual" approach is rooted in the fact that the industry is highly regulated. Regulators in the US have been saying for years that the industry should adopt continuous manufacturing, and a few companies have filed for select processes to be continuous. But companies, rightly or wrongly, are wary of regulatory filings that consist of anything unconventional. These perceptions create a vicious circle, in which lack of attention to, or investment in, manufacturing innovation leads to lack of demonstrated value, which leads to lack of investment, etc. An additional concern is that the pharmaceutical companies seek approval for their products worldwide; while FDA and select other agencies maybe forward-looking in this regard, continuous processing may not be approvable by many other global regulators.

The good news is that this is starting to change. Some regulatory agencies are driving the industry towards continuous manufacturing and are working to break down both real and perceived regulatory obstacles. As the benefits of continuous manufacturing are understood more and more by management, investments are being made to overcome the view of continuous manufacturing as a complex and progressive approach to process development and manufacturing continue to become more and more prevalent. The question then becomes not whether or not the industry should adopt continuous manufacturing, but how and when it will do so.

3.1. Business and Organizational Challenges

A perceived hurdle for industry in moving toward a continuous manufacturing paradigm is the established batch asset-base; whereby significant capital was invested in batch manufacturing during the rapid pharma expansion during the 80's and 90's. However, capital investment in a new continuous manufacturing plant could be offset by substantial savings, including savings in API development costs, in addition to reducing or eliminating scale-up risk. Furthermore, continuous manufacturing could substantially reduce the costs of API during development. Overall, such an approach allows for rapid product development while naturally realizing the full vision of Quality-by-Design, due to built-in process understanding.

In a commercial manufacturing plant, continuous manufacturing has the potential to realize a true "lean manufacturing" paradigm and many benefits in areas of quality, operational, environmental, and financial. These benefits arise through continuous process monitoring and control, lower energy consumption, higher production yield, and shorter cycle times. Continuous manufacturing also

requires a smaller, highly skilled workforce and smaller plant footprint making it ideal for implementation in the United States, which allows manufacturing to be in close proximity to R&D centers. This can stimulate further innovation and ensure a more seamless transition from development to commercial manufacturing. Given all of these benefits, it is envisioned that the likely first step of most pharma firms will be to convert, or integrate, many existing batch operations into a continuous manufacturing plant (heterogeneous processing) prior to investing in a true (homogenous) continuous manufacturing operation.

Secondary markets, aka emerging markets, bring a unique set of opportunities that can often be best addressed via a continuous manufacturing strategy. For example, local manufacturing is often required by governments in order to speed access to markets or gain access in the first place. When this is the case, a small, flexible facility, which can meet the local or regional demand for a multitude of products, is often desired. Continuous manufacturing, with a small facility footprint and high turnover capabilities, can often meet these needs. Admittedly, the desired personnel capabilities may not currently exist in secondary markets, but the robustness of steady state operation, coupled with automated systems, training, and online, remotely accessible PAT can counteract the lack of local talent with the desired skillset. Although it can be difficult to maintain facilities located within secondary markets, portable manufacturing systems (aka factory on a truck) could ease maintenance by allowing entire facilities to be relocated to centralized locations when needed. Furthermore, in the desirable case where additional capacity is needed quickly, additional portable manufacturing systems can be rapidly deployed to meet market needs. Thus, continuous manufacturing can be beneficial for accessing the opportunities as well as addressing the challenges presented by secondary markets.

3.2. Challenges Facing Manufacturing & Development

There are many manufacturing and development-based challenges faced by the continuous manufacturing paradigm, from the mindset of the engineers and scientists who develop the formulation and process, to the quality units within a company, to the government regulators overseeing the industry. When a technology is immediately enabling, and allows for new medicines to reach the market that would otherwise fail in development, few will question whether extra work should be done to enable success. This has been the case for the development of amorphous solid dispersions, which are a recent example of a new technology rapidly finding adoption within the pharmaceutical industry. Specifically, amorphous solid dispersions have enabled formulations to be more efficacious at a lower dose by increasing the solubility of otherwise poorly soluble APIs. In contrast to that example, for continuous manufacturing, the payoffs are not immediate and the benefits are spread out through research, commercialization, and supply. Thus, extra time and effort must be spent in research and development, all for a payoff that may or may not be achieved years later when a product hits the manufacturing floor and the market.

From a regulatory perspective, continuous manufacturing may present extra up-front work for the regulator. In order for quality to be assured, a regulator must learn the new manufacturing process and the potential failure points. Often, quality practices that were developed for batch processes are blindly applied to continuous processes. Furthermore, the larger number of measurements seen in continuous processing is often a hindrance, as more data increases the likelihood of chance observations of out of spec production. To combat this, engineers, scientists, and regulators will have to upskill in statistics, so that the new data presented by continuous processes can be properly analyzed and understood. Ultimately, a new continuous process must be shown to be superior to the alternate batch process, a challenge at which the continuous process is expected to succeed. While many of these obstacles can be overcome through exposure and education, ultimately it is the higher quality achieved through steady state operation and online analytics that will drive acceptance of continuous manufacturing by both internal and government regulators.

Early in development, limited resources demand that project teams design a formulation and process that is “fit for purpose”. In other words, resource expenditure must be limited before a potential

product is shown to be worthy in the clinic. After proof of concept is achieved for a particular molecule, development typically moves towards a focus on the target product profile (TPP), which addresses the requirements of patients and caregivers for a given product. Having achieved the TPP, late stage development groups begin to focus on the manufacturing requirements such as long term operational robustness, production scale and product cost. At this stage, a product will generally have spent significant time in the clinic, and any formulation or process changes will be perceived as a risk to both the timeline and product performance. Thus, programs that start at small scale with batch operations often result in products at large scale being produced using batch operations.

Product development using continuous manufacturing requires a certain amount of bravery, and a new mindset towards research and development. In order for the most benefit to be realized, continuous processes must be embraced at the earliest possible stage. For any researcher, the benefit of a continuous process towards conducting a sequence of experiments is rapidly realized. With some simple automation, and perhaps scaled-down apparatuses, screening of both formulation and process parameters can be rapidly achieved. This rapid execution, however, comes at the cost of high material consumption rates. Ideally, equipment dimensions would be scaled down such that the benefit of continuous processing can be achieved alongside low consumption rates, but pharmaceutical equipment manufacturers are only now beginning to observe this opportunity. If continuous processing is achievable early in the development cycle, testing of more formulations and process conditions per kg of API would be expected to result in better formulations and more robust processes. Because continuous processes are inherently more "data rich", new information technology systems must be developed to collect, process, and analyze the rich data streams that are generated with every experiment. These data streams should ultimately result in higher quality products, as online analysis systems "sample" a higher fraction of every batch, sometimes by a factor of 100x or greater. Product filings also become easier in some regards, as more of the process space is sampled and more is known about each condition tested. Electronic batch records become easier to implement as well, as does prospective process analysis and continuous process verification, as each relies on an automated stream of high quality data for optimal implementation. And once products developed with a continuous manufacturing mindset reach commercial production, the compounding of benefits will begin to be realized. Hence, it is envisioned that product development teams that fight the obstacles and adopt continuous manufacturing strategies early in development will reap benefits for not only themselves but for the patients who need the product and the commercial production sites who supply it.

To achieve widespread adoption of continuous manufacturing technologies, new generations of equipment, sensors and automation will need to be developed, together with approaches to performing in-line tests such as friability, disintegration, and dissolution. This will most easily be achieved through collaboration among equipment manufacturers, academics, and pharmaceutical companies. In addition to smaller scale equipment, equipment manufacturers will need to work together to standardize the connections between unit operations. New sensors will also need to be developed, to address needs ranging from online particle size measurement to mass flow rates in particulate systems. In a continuous manufacturing environment, system integration becomes of high importance, as unit operations have to communicate in order to maintain control. Companies that can serve as a "one stop shop" will gain prominence, as the need for one manufacturer who can provide equipment, sensors and control systems becomes a key desire. Finally, the challenge and potential of "big data" will become central, and systems that integrate sensing, automation, analysis and control will become highly sought after.

3.3. Overview of Technical Challenges

There are several inherent technical challenges to continuous manufacturing that may be more or less relevant depending on the specifics of the product. One is powder characterization and handling, particularly for low dose production, including process modeling. Another is how to do start-up and shut down as rapidly as possible with minimal waste. In general, it is a challenge to develop accurate process operations models of various steps in a continuous process. Other challenges include

materials issues, such as build-up over long run times, loss in weight feeding especially for cohesive materials, maintaining mass balance with the lack of mass flow powder meters , material tracking through system via residence time distribution, balance of need for system capacitance and short residence time, and need for online PAT. Ways to address these are included throughout this white paper and involve a combination of equipment technologies and control systems. Details of technical challenges for specific technologies are discussed below.

Together with the fact that continuous manufacturing is the ultimate in lean manufacturing, flexibility is a key aspect, either in meeting a need to produce in the same line product with different content of API or different products or different volumes during the year. This is an important evaluation element for the design of a continuous line, in terms of size (capacity) and modularity (different products) with the possibility to adopt different paths for the product through various modules according to the formulation chosen. Consequently if it is needed to change production on a line, the cleanibility and the setup time become extremely important, cleanup including waste at the beginning and end of production. The need for flexibility is likely to influence the level of continuity of the system, in terms of integration between upstream and downstream.

Even homogeneous processing necessitates powders handling for precursor materials in chemical reactions and blending excipients or even active materials. As discussed above, an annual production of a billion tablets means 120,000 per hour of continuous production. If each tablet is 400 mg, addition of a solid material at 1% of total weight means addition at about 480 g/hr. This is certainly feasible, but at a factor of 10 lower production, achieving accurate doses of powders and assuring smooth flow can be a challenge.

A related challenge is the development of small-scale equipment for early studies. Small-scale synthesis may be routine but small scale spray drying or melt extrusion is potentially more difficult, especially blending and coating. Spray drying, in particular, and related methods, which use pure streams of actives or active/excipient solutions, could have many advantages in that the effects of the solid state chemistry of the drug could be minimized, and amorphous dispersions or pure crystals could be made directly, depending on the desired formulation and the properties of the API molecule. Solvent recovery could pose a challenge with spray drying, but in general it can be incorporated seamlessly into a continuous process.

Clearly, the availability of small-scale continuous manufacturing lines capable of making clinical supplies (even phase I), which could then be scaled up for larger scale manufacturing, would be a major advantage. This capability would significantly accelerate drug development, especially if the small-scale equipment was predictive of larger scale processes. For example, a mini melt extruder, only slightly larger than a ballpoint pen, is available as are mini spray dryers. Little is known about the ability of these units to scale to larger manufacturing processes and they are too small to meet demand even if run continuously. Additionally, little is known about the ability to incorporate these units into a mini-continuous line.

One concern during continuous manufacturing is the modeling of variances, and how they might propagate through a continuous process. Specifically, if a disturbance enters the first unit operation in a series, the question arises as to whether that disturbance will spread out, and if so, by how much. To answer this question, an in depth understanding of the residence time distribution of each unit operation is required, as this serves as the transfer function which translates how input variability is related to variability in the output of each step. In addition to understanding each unit operation's transfer function, care must be taken to understand the system capacitance and delay times associated with material transport operations between steps. Because complex interconnected systems with time delays are inherently non-linear, care must be taken during design and testing of the individual and overall system controls to ensure that the system dynamics do not become unstable and lead to control system runaway or other chaotic phenomena. The careful design of mixing steps and buffer tanks in a continuous process can be used to help smooth process dynamics, by dampening and delaying process variability. Ultimately, it is expected that model-based control

using knowledge of the residence time distributions would be a key element in aiding this process, and flowsheet modeling will enable testing of system dynamics outside of the plant environment.

Start-up and shut down is a key challenge particularly for the vision in which the pilot process will become the commercial process, and scale-up occurs in time as opposed to volume. For an anticipated billion tablet a year product, one might need somewhere between 10,000 – 5,000,000 tablets for phase III, meaning, in many cases, fewer than a single day's output. To make these cost effective, start-up and shut down would need to be minimal. This can be achieved by minimizing system volume to the extent possible, as the average system residence time for a given throughput will increase proportional to the holdup volume, and typically 3-5 residence times must pass before a first-order process achieves steady state. In addition, smart sequencing of unit operations during start up and shut down can further decrease losses. For example, a continuous blender could be filled completely, and mixed in a batch mode (with no discharge) for a few moments prior to allowing material to pass to the next process step. Although the material processed would not be considered steady state, it could still be processed so as to meet the product's blend uniformity specifications, and thus would be considered good material.

3.4. Key Choices and Design Constraints

In determining a plan of action for moving to continuous processing, companies will need to make design choices that may lead to constraints. These include:

- Multiple small-scale operations versus fewer (or one) large-scale operations
- Custom lines for each drug versus platform lines
- Use of existing technologies versus incorporation of new technologies
- Determination of how much front end loading of research to invest in, particularly given attrition rates
- How integrated the approach should be for commercial production and during product development including scale-up

What companies will decide will depend on a number of factors including a product's timeline, process lifetime, specific nature of their business in various countries, size and nature of their pipeline, and their willingness to take on higher risk for higher rewards. Ultimately, maximum benefits will be achieved by realizing the full vision of continuous, but during the transitional period, companies need to pursue strategies that make sense for them, while continuing to pursue the ultimate vision.

4. Technologies for Continuous Final Dosage Formation

4.1. Overview

The true benefits of continuous manufacturing can be harvested when new technologies are implemented. That means designing a continuous process with the mindset of continuous processing. That mindset is difficult to acquire given the inertia of batch processing between both process designers and among managers. Thus, in many companies there is likely to be a transitional period in which batch approaches are converted to continuous. This results in lower perceived risk and lower up-front investment (although does not result in maximal benefits). The key to doing this, however, is to avoid the Rube Goldberg problem, in which process elements are added to correct problems of other process elements, the opposite of what continuous manufacturing is supposed to be.

4.2. Upstream-Downstream Interface

As discussed above, maximum benefits of continuous processing can be achieved by process integration, when the upstream and downstream parts of the process are combined seamlessly. When this occurs, there are two major routes by which the active can be transferred from the upstream to the downstream part of the process. One of those is as a solid, either dried or in a slurry, and the other is dissolved in a solution.

If the active is transferred as a solid, the process as a whole should be designed so that the particle size is at the final specification and the residual solvent can either be incorporated into the final dosage form process (for example as an granulation agent) or can be removed by drying. In general, the process should be designed as a whole, so that what occurs downstream does not involve corrections of what should have been done upstream.

4.3. Powder Handling

4.3.1. Transitional Technologies and the Challenges of Powder Handling

Today tablets represent the majority of pharmaceutical solid dosage forms available on the market. Of this group the vast majority are produced through batch processing of one of three general pathways: wet granulation, dry granulation or direct compaction.
Wet granulation (the original solids manufacturing approach) involves first spraying a liquid onto a bed of powder while it is mixed by pneumatic or mechanical means and then removing the liquid from the material with a second process step. The water sprayed into the bed serves as a means to bind individual particles together into a larger agglomerated particle. The purpose of creating the agglomerated materials is to create a powder, which will flow better and not be prone to the segregation problems often found in blends composed of the smaller sized primary particles. It is a common practice to mill the material after drying to break down any larger sized agglomerates.

The most popular alternative to wet granulation is dry granulation, in which pre-blended material is continuously compressed between two cylinders (referred to as rollers) in a device known as a roller compactor to produce a compacted strip of material known as a ribbon. After the ribbon has been formed it is converted back into a granulation by milling the ribbon into smaller agglomerates. As with wet granulation, the goal is to produce a granulation that has superior flow properties and a lesser propensity to segregate based on constituent size. The main strength of the dry granulation approach is it does not require a complex/costly drying step.

The final, least used, and newest approach to tablet manufacturing is direct compaction. In direct compaction, material is blended and feed directly to a tablet press for compression. The advantage of the direct compaction approach is its simplicity. Its main drawback in batch operation is that the powder needs to have good flow properties and not be prone to segregation.

In the pharmaceutical industry, all of the three pathways described above for the production of tablets have been done in discrete batch wise based operations. However, there is no fundamental reason that these process steps have not, or could not, be done continuously. In fact, all of the batch wise unit operations used in the pharmaceutical industry have continuous analog(s) in other fields of manufacturing such as foods, petro-chemical and agriculture. In the past 10 years, the industry has begun to investigate the potential of continuous manufacturing for solids dosage form. To date, three companies offer some form of continuous manufacturing platforms for solid dosage production (GEA, Glatt, Lodige).

The three table production routes described above us a combination of five basic unit operations: weighing/dispensing, blending, granulation, size reduction, compression, and coating. Continuous equipment capable of fulfilling each of these roles is described below.

4.3.1.1. Weighing/Dispensing – Continuous Feeding

The objective of the weighing/dispensing operation is to measure out the correct ratio of ingredients specified to compose the final product. In a continuous operation, this requires feeding each material at a specified *rate* such that the final product will have the proper composition. This is accomplished through the use of Loss-in-weight (LIW) feeders. LIW feeders are comprised of a hopper mounted on top of a positive displacement screw feeding system all of which is constantly being monitored by scale/load cell. When the screws are in motion, powder is feed from the material hopper into the process and the total weight of the screw feeding system and the hopper is decreasing at a rate equivalent to the rate at which material is being feed into the system. The scale on which the feeder is mounted continuously monitors this loss in weight and can adjust the screw speed so that the rate at which material enters the system remains on target.

However, the granular nature of the material being fed leads to a limit on how accurately this LIW loop can control the addition of the material. This is due to the fact that powder streams do not act like either a solid or a fluid. When energy is applied, they can be made to flow and in special circumstances act very much like a liquid (e.g.. fluid bed). When energy is removed, they can hold shape and act like a solid (e.g. angle of repose measurement). This complex behavior leads to variations in the interaction between a feeding screw and the material both within the screw and at the exit of the feeder. This leads to variations in the feeding rate even under strict loss in weight control. At high feeding capacities the discrete nature of the powder stream becomes less significant and feeding accuracy is greatly improved. The main challenge is in feeding materials accurately at slow speeds where the variations can become large compared to the rate at which the material is being fed. Therefore, minor components (lubricants and disintegrants) are often the most susceptible to feeding limitations.

4.3.1.2. Blending

The most common type of continuous blender is known to as a tubular blender. Tubular blenders are comprised of a horizontal (or nearly horizontal) tube with a bladed impeller running down its central axis. Material is typically feed into one end at a steady state and the blades of the shaft move it along the length of the shaft. At the far end of the tube there is an exit where the material is passed to the next process by gravity.

The mixing objective in continuous blending can be categorized into two separate modes: radial and axial. Radial mixing can be explained by considering two powders, A and B, being feed into a blender each on opposite sides of the blender's axial center line at a constant speed. A snapshot of a radial cross section of the blender tube near the entrance at steady state would show two unblended powders (See Figure 1). If the blender is properly designed and operated, a snapshot of the radial cross section near the exit of the blender would show two powders blended together. The key aspect of radial mixing is that it is a steady state process, and can largely be considered time-invariant.

However, radial mixing alone does not give a complete picture. As described above, some variation in the rate at which granulator materials are fed will exist for all feeders and can be significant for minor components, which require lesser feed rates. If a continuous feeder simply radially blended the incoming materials, then any noise from feeding would pass right through the blender and end up as variation in the final solid dosage form. As a consequence, a continuous blender should be designed to encourage incoming powder, which comprises the process stream to spend a variable amount of time within the blender. The larger the variation in the amount of time the constituent particles of the blend stay in the mixer the more the mixer is averaging out the noise of the upstream

process. This is referred to as axial mixing and it can be visualized as mixing along the length of the cylinder.

In a continuous process, it is critical to understand that the feeding and blending systems must be designed to work in concert. The accuracy with which the available equipment can dispense each component must be fully understood. A suitable blending system must be designed to ensure that the level of variation present for each component in the process will be averaged back to within the product specifications for concentration.

4.3.1.3. Granulation

Wet Granulation

The present standard approach to wet granulation is the fluid bed granulator. In a fluid bed granulator, the powder material is fluidized by air and the granulation takes place by spraying the bed with a binder solution. After the spraying phase is completed, the bed can be kept fluidized until the air movement dries the bed to the specified level.

While not common in the pharmaceutical industry, fluidized beds are often run continuously. They come in two categories, troughs and rounded beds. In the trough approach, a linear bed is fluidized. At one end, the additional material is fed, which raises the level of the bed and pushes the fluidized bed towards the far end where the material exits to the next process. Spray nozzles can be placed along the length of the bed to spray binder and agglomerate the particles. The last length of the bed can then be used to dry the particles. The rounded bed approach involves continuously feeding material into a conventionally shaped fluidized bed while the bed is being sprayed. When the bed is at its desired volume, material is removed at the same rate it is fed in and the stream of agglomerates are classified by size. Material found to be too small (under-agglomerated) is recirculated back into the bed for further processing and the larger material is allowed to progress to the next unit operation. In this configuration a second fluidized bed would be needed for drying.

Dry Granulation

Roller compactors are fully continuous processes. They continuous feed powder to the rollers, which produces the ribbon. The ribbon is continuously fed to the mill, which then transforms the ribbon back into a granulated material. No changes are needed and the roller compactors can be integrated into a continuous line as they are.

4.3.1.4. Size Reduction

The most commonly used size reduction equipment in the industry is the Conical-mill – commonly referred to as the co-mill. Co-mills push incoming material through a conical screen using an impeller, which forces material near the screens surface through the spaces in the screen. Co-mills are inherently continuous equipment and can be used without alteration. However, the manner in which they are operated will be somewhat different. Currently, the material to be milled is dumped on top of the co-mill the mill speed is set and the mill is run until all of the material has run through the mill. In a continuous process, the materially will be constantly feeding the mill and it will be necessary to match the speed at which the mill is processing material to the speed at which the line is running.

4.3.1.5. Compression

Tablet presses are another example of equipment that currently runs continuous. The only challenge with adapting a tablet press to a continuous line is devising a control strategy to match the production rate of tablet press to the rate at which it is being fed materials. In batch compression tablet press speed is typically not varied and therefore special attention will need to be dedicated to implementing an effective level control system in continuous.

4.3.1.6. Material Handling Challenges in Homogeneous Processing

Even after a paradigm shift towards homogeneous processing, it is highly likely that granular materials will need to be fed into the process. The engineering framework for dealing with these additions will be the same as described above in the feeding/blending system. The feeding system will need to be characterized for how accurately it can dispense the material, and then the system will need to include enough back mixing to adequately time the average of the process stream to keep the product within its pre-determined specifications.

4.4. Emergent Continuous Processes for Homogeneous Production of Final Dosage Forms

The key final dosage formation technologies include homogeneous technologies, primarily with polymer excipients. If actives and excipients are blended in solution, crystallization must be addressed, either obtaining the desired crystal form or avoiding crystallization for a desired amorphous dispersion or solution. Alternatively, mixtures can be formed with crystalline active particles and even particles of excipients in a solution with other dissolved materials. Either way, the properties of the blend must be tuned so that the final dosage form can be made directly. A key issue is the dosing of the active, whether small or large. Small dosing may be stabilized as a solid amorphous solution, thereby also allowing dispensing via a solution, instead of a powder. In this case, the properties of the mixture or blend are controlled primarily by the excipients and can be tuned in a relatively straight forward manner. For large dosage pharmaceuticals, the properties of the active will have a large effect on the properties of the final blend, making it much more difficult to tune.

We describe the following:

i. Spray drying
ii. Electroprocessing
iii. Casting
iv. Injection molding
v. Printing
vi. Continuous coating
vii. Ultrasound Compaction

Spray drying should be familiar to most in the industry. It is an inherently continuous technology in which a solution is sprayed through a nozzle into a vessel in which a gas such as nitrogen is blown in order to dry the airborne droplets. Typical droplet sizes are on the order of 10-200 μm. In order for these droplets to dry sufficiently, commercial spray drying equipment is often required to be quite large (several stories high) although for process development there are small-scale spray drying apparatuses that can fit in a typical laboratory.

Spray drying is particularly advantageous for amorphous products, which dissolve fairly easily, since on the one hand the particle sizes can be on the large side for pharmaceutical products, and on the other hand, drying might be fast enough such that adequate crystallization might not occur. Annealing can be used to affect crystallization, but that might not be sufficient for active material in a polymer matrix.

Having extolled the virtues of spray drying, it is important to note that, as currently practiced, the preceding and subsequent steps are not inherently continuous, and these would need to be modified to integrate seamlessly into a continuous process. Specifically, to become truly continuous, the challenge of continuous mixing during polymer/drug/solvent solution preparation must be resolved. Although continuous inline solid/liquid mixers are available, the slow dissolution dynamics of polymers can limit performance. Furthermore, after the spraying process is complete and the semi-dry polymer/drug particles exit the primary drying chamber, they are often collected in a bulk vessel,

and held in a wet state until a subsequent secondary drying step. This secondary drying step is needed to reach ICH solvent limits in most circumstances, and is currently practiced as a batch process with long cycle times. Truly continuous spray drying would need to conduct this secondary drying in a more time efficient manner using some of the continuous drying technologies described elsewhere in this paper, starting from the moment of powder collection out of the primary drying chamber.

Electroprocessing is a related approach to spray drying, but there are some key differences. First, in addition to droplets, fibers can be produced. Processes that produce the former are called electrospraying and the latter electrospinning. Because of the electrohydrodynamics of electroprocessing much smaller shapes can be formed, droplets and fibers with submicron diameters. Furthermore, in electroprocessing, droplets and fibers can be formed through nozzles (generally at low rates) or from a liquid surface with an electrode underneath. The latter is generally done on a spinning cylinder electrode and is called free-surface electroprocessing. Electroprocessing can be performed with single-phase fluids or with heterogeneous mixtures, for example solid crystals suspended in a polymer solution. Once electroprocessed material is generated, it will need to be shaped into a final dosage form by a compression and cutting operation or a combination of the two.

Another way to make a final dosage form is liquid casting. The challenge in doing this is to get acceptable drying, particularly if a tablet is cast directly. Another approach is to cast thin films, dry them sufficiently, and then shape them into tablets or whatever the final dosage form is. Casting can be performed with the active in solution or entrained as a powder. Another exciting approach for casting is that the excipients can be cast and dried, followed by nucleation of the active directly on the excipient film surface. These surfaces can be designed either with patterns or with surface functional groups to yield the desired polymorph, crystal size distribution and morphology.

Tablets are relatively simple shapes that can be directly formed when an API is mixed with a flowable excipient such as in polymer dispersions. Injection molding is one technique that can be used as it is a technology that has been used for decades to make inexpensive plastic parts. These parts can be simple in shape or extremely complex with tight specifications of features. More recently, the tablet geometry has been directly formed through a process called calendering, with equipment available through manufacturers such as Dr. Collin GmbH. Whatever the shaping equipment, it is usually paired with the extrusion process and will use typical melt extrusion methodologies as described elsewhere in this manuscript,

Another technology is printing, in which either separate droplets of active and excipient or solutions of actives and excipients are formed into a tablet via an approach such as ink-jet printing. This approach promises tight control over dosing and excipient amounts, but can have significant issues with drying.

Application of ultrasound leads to a transition of polymers into (semi-)liquid state, offering the possibility of embedding drug into polymer matrices. Hence, UltraSoundAssistedCompaction (USAC) might be an alternative to common techniques in solid dispersion preparation. Critical parameters are identified as follows: ultrasound energy, compaction force, amount of powder and the distance between sonotrode and product slug.

In all of these technologies, forming discrete final dosage units will be necessarily semi-continuous, for the very reason that those dosage units are discrete. Developing robust ways to keep these final dosage formation processes running for long periods of time without disruption will also necessitate new technological approaches.

Of course, this is just the beginning and innovative research will no doubt develop a range of new technologies as continuous processing continues to spread.

4.5. Excipients and Formulation

A general challenge with the above approaches is how to choose excipients to create a formulation, which has the right pharmaceutical properties (in vivo release and PK), stability, and processing properties (particularly mechanical properties that will allow shaping into the final dosage form). A key challenge is proper *in vivo* release. In contrast to traditional powder tablets, in which disintegrants can be added and solvent can easily get to them through pores in the tablet, leading to tablet swelling and disintegration, the above dosage forms do not have typically have pores between solid particles.

One solution is to engineer pores into the dosage forms either with bubbles or by drying individual droplets sufficiently before making the final dosage form, such that solvent can access the core of the tablet. Another solution is to choose a formulation that dissolves rapidly in vivo, either directly, or by putting in a network of rapidly dissolving material.

Another key set of properties, in addition to stability, is that the blend has the proper processing properties. Whatever the technology, it needs to be able to flow, be deformed, shaped, and/or compressed with differing target properties depending on the final dosage formation technology used. Current batch formulation approaches that have been worked out for powders are most likely not appropriate for continuous processing. This opens up a whole new realm of formulation approaches and possibly a need for new excipients.

Possibilities for future new excipients are best understood by studying the example of melt formulations, and similar examples can be studied for other process technologies such as spray drying. Melt formulations, using specialty polymer excipients, are anticipated to play a central role in the future continuous manufacturing of homogeneous dosage forms due to the simplicity and wide applicability of the process. Current polymeric excipients used for homogeneous solid dosage manufacture often exhibit limitations such as:

- High processing temperatures
- Narrow processing ranges
- Low dissolution rate of drug into excipient matrix
- Limited physical stability
- High hygroscopicity
- Sub-optimal drug dissolution rate and low solubility (or supersaturation) *in vivo*

To reduce processing temperatures and expand processing ranges, polymers with lower Tg can be used, but this often comes at the cost of reduced physical stability. To regain this physical stability, one option is to design polymers, which are thermodynamically stable when combined with drugs. This stability can be gained through specific interactions between the drug and polymer, be they ionic or hydrogen bonds, or simple hydrophobic interactions. Of course, the designers of drugs also have a role to play in achieving this future state, as higher potency drugs with a lower required dose will inherently be more stable in matrix formulations. Already, trends are beginning to emerge towards more specialty excipients, whether copolymers with different monomer ratios, or substituted polymers with different sidegroups at varying levels and in varying patterns. An example of this can be seen by examining the substituted cellulosic polymers, and the variety and amount of functional groups that are bonded to the cellulose backbone to form new polymer grades. Looking towards the future, it is expected that many more options will become available, utilizing copolymers that are random and block, straight chained and branched, substituted and patterned, and the optimum will be selected via high throughput screening or computer modeling with the drug being formulated. Finally, upon development of an array of purposefully designed excipients, continuous manufacturing of homogeneous dosage forms can begin to take shape.

4.6. Transitional Continuous Technologies

Transitional approaches, in which batch technology are converted to continuous, include granulation, blending and direct compaction. Roller compaction and extrusion are ways of carrying out granulation, and extrusion can be used directly for blending. There currently exists equipment to perform all of these in stand-alone continuous operations, but integration still remains an open challenge.

4.6.1. Continuous Drying

Continuous drying technology development will be a key aspect of continuous process development. The challenge will be to achieve sufficient drying in a reasonable amount of time. We envision multiple types of drying approaches utilized even in a given process, depending on specifications and the degree to which the material holds the solvent. Approaches include, squeeze drying, belt drying, drying through a screw, and fluid bed drying. Other approaches include washing with solvents that extract the hard to dry solvent, and overall process design to streamline drying.

4.6.2. Continuous Coating

Typically, film coating is done in a process by which tablets are sprayed with a pigment containing polymer solution while being tumbled in a dry air stream. The drying air removes moisture, leaving behind an elegant tablet coated by a thin film of colored polymer. Although most film coatings are added for taste masking or elegance purposes, film coating is also sometimes used to add functional coats to tablets, which can delay or control release of the API until the desired time after administration. While film coating of batches from 1kg to 300kg is common, production cycles can run for more than 2 hr between pan loading, spraying, and unloading. Two options are often discussed in the context of continuous manufacturing. Continuous film coating is the name given to the process where tablet cores are loaded at one end of a long rotating perforated cylinder, the tablets pass through a multi-gun spray zone, and coated tablets are simultaneously removed from the opposite end. While this design is truly continuous, it suffers from high dispersion at low mass flow rates, leading to high variance in the amount of coating applied. As an alternative, short cycle duplex batch coaters operate by having one coater loading or unloading while the second coater is spraying. By operating the two coating cycles out of phase, a semi-continuous flow is maintained. Although dispersion is not a problem in this arrangement, the short cycle duplex batch coaters do not enable the same turndown ratio afforded by the continuous coating process, and thus are more difficult to operate when production conditions vary. Both approaches warrant consideration when designing a process train that necessitates a film coating operation.

4.7. Technical Approach to Development of Continuous Equipment

As described above, there is a “Catch-22” to development of continuous equipment, as pharmaceutical manufacturers want equipment that has been tried and tested, and equipment manufacturers will not make significant investments in new equipment designs unless they are assured customers. Thus, the major way out of this conundrum is for pharmaceutical manufacturers to accept the risk, and start investing in new approaches while trusting that the newly developed approaches will provide the financial benefits to justify the initial investment. While pharmaceutical manufacturers must lead the way, equipment manufacturers should also be proactive in making investments in transitional continuous approaches and also at least research investments in equipment for true continuous operation. The equipment manufacturers who do not do this might very well find themselves left out of future markets, as equipment manufacturers who have not previously had a presence in the pharmaceutical industry, but do have equipment suitable for continuous, will start to target this new and substantial market.

4.8. Systems Engineering, Characterization, and Control for Final Dosage Form

The Control white paper, and others, covers the overall approach to process design and control. Here we mention the specific challenges in those areas to continuous final dosage formation. The challenges are two-fold: accurate and robust models are difficult to obtain and inline analytical approaches are difficult. On-line analytical approaches to characterize solid materials are especially challenging, including particle size determination, composition, and crystal form analysis. Nevertheless, approaches exist to perform characterization, even of solids, and we envision that, on the one hand, as more and more investments in continuous are made, better and better models will be developed, and better inline analytical methods will be developed on the other. In fact, the two go side by side, as better analytics will lead to better models and vice-versa. All of these, together with model-based control, will make continuous manufacturing processes streamlined, of high quality, lower waste, and increase value.

5. What the Industry Should do and Timing Including Resource Allocation

Given the projected advantages of continuous manufacturing, the industry should initiate continuous manufacturing efforts immediately. Each company should go through its product (development and in-line) portfolio and choose one or more products for some degree of continuous manufacturing. This could be a life-cycle management product, but the real value is in a new product, chosen as early in the development phase as possible, for example at proof of concept in the clinic. Of course, a new product in development has a much higher risk of attrition, so ideally multiple products would be chosen. In addition, a company would have to be highly confident that the choice of continuous manufacturing would not delay regulatory approvals across global markets. To the extent possible, a platform approach should be chosen for phase III and commercial production, thus, reducing expenses and the risk that all chosen products would not go at least to phase III clinical trials.

As the initial investment required to develop a continuous process is likely to be more than that of a corresponding batch process, and because new equipment would likely need to be purchased (and even resources spent on development of the equipment), management should consider this to be a research investment for which the payoff is likely to be not so much with the given continuous process, but with the ultimate benefits to continuous implemented in the company as a whole. The future of pharmaceutical manufacturing is continuous. The earlier a given company gets there, the sooner it will reap the benefits.

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