43

CONTINUOUS PROCESSING IN SECONDARY PRODUCTION

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43.1 INTRODUCTION

For the entire history of pharmaceutical manufacturing, secondary production processes have been carried out in batches. There are deep-rooted reasons for this [1], some historical (the ancestry of many pharmaceutical processes come from food or confectionary), some founded in the need to track the "history" of the dosage form (in terms of materials and processes, i.e., the "batch record"). However, even though pharmaceutical secondary production shares many unit operations with other industries, the reality is, many of those industries have already realized the commercial and operational benefits of continuous manufacturing and have started running those unit operations continuously, and have abandoned batch production.

It would be easy to simply justify the continued use of batch approaches for these reasons, however the pharmaceutical industry is coming under huge quality, efficiency, financial and business pressures (which has even reached the public's attention, e.g., in the article in Wall Street Journal [2]), but also the regulatory landscape has changed. The initial PAT Framework [3], the twenty-first century Initiative Final Report [4], the ICH Quality Trio (ICH Q8, Q9, and Q10) as well as the new guidance on Process Validation have all put a focus on the application of new technologies with a science-based approach. They also introduce a new term to the pharmaceutical industry; that of quality by design (QbD).

Running continuous processes during development and commercial manufacturing facilitates both the application of QbD approaches but also (as will be shown later in this text) the ability to implement these approaches in a highly efficient way.

43.2 DEFINITIONS

To be clear from the start, when describing Batch production, we are describing an overall production system whereby the entire mass/volume goes through the unit operation at same time, normal in one "container"; as an example, unit operations such as bin blending, where we start with individual components being added to a single processing unit and during the production process the entire batch changes to reach a single end point—the process is only complete when the entire mass of the blend is uniform. Whereas continuous production describes where the input materials continually enter into the unit operation and output materials continually exit, under a "first in/first out principle," taking the blending example, a continuous blend operation is where the input materials are continually being feed into a continuous mixing process. The outcome of the process is not only continuous but in a steady state, resulting in a uniform output where each unit dose mass is not only the same/having the correct concentration of each component (interdose uniformity) but also that those components are optimally dispersed within the unit dose, thus ensuring correct delivery performance. In the case of continuous blending (and many other continuous processes) the individual dosage is "generated" early on, and in some ways the process consists of a stream of individual unit doses, such that verification of performance of continuous systems has to be considered against this production

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paradigm. It is also very important that continuous production processes are not be confused with flow production in which standard batch operations are simply linked together, for example it is very common for consecutive unit operations in secondary production to be "daisy chained" together, for example a bin blend discharging into high shear granulator, into a fluidized bed dryer, and so on—the bulk material flow maybe linked but the entire batch goes through a transformation at the same time within each unit operation.

43.3 REVIEW OF TYPICAL UNIT OPERATIONS

As previously indicated many pharmaceutical unit operations are shared with other industries, however, we also have to acknowledge that many of the individual unit operations used are themselves continuous operations—as an industry we simple chose to collect the output and form/maintain the batch. So let us first look at traditional solid dosage operations and consider if they are "batch," "continuous," or could be made continuous.

43.3.1 Typical Batch Process Operations

The vast majority of current pharmaceutical products are currently "solid oral doses," commonly known as tablets or capsules. Typically production of solid dosage forms is carried out in three types of process streams. The simplest is well described and commonly called direct compression (Figure 43.1). In a simple direct compression process, the Active Pharmaceutical Ingredient/excipients are dispensed (via a screen to de-lump) into a V-shell or bin blender. Post the blend operation the material is transferred to the feed hopper of the tablet press, postcompression the batch is coated "en-mass" in a pan coater, before packaging.

Small variations on this basic process workflow may occur, for example, replacing the compression/coating steps with an encapsulation step during capsule production, but the general workflow stays the same.

However, if the particle size and/or physical characteristics of the individual API/excipient powders are likely to cause segregation, between or during subsequent processing steps, it is common to introduction some form of granulation step postblending. This is often then followed by an additional (second) blend step when a lubricant excipient is needed to improve flowability within the process and to prevent sticking/chipping during compression.

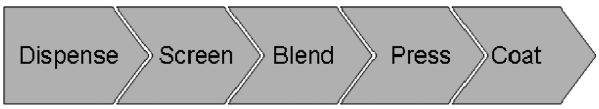


FIGURE 43.1 Schematic of direct compression process.

If the granulation step is "dry" (better known as roller compaction or RC), the premixed materials are forced through two counter-rotating rollers that exert mechanical pressure on the powders during a high-pressure agglomeration or "compact." The compact can be of several forms however in each case the true granulate is formed by milling. Typically, the high-pressure compact formation, and subsequent milling are together described as a single unit operation (Figure 43.2).

In comparison, the alternate is wet granulation (WG), in which shear and compression forces are used along with the wet/massing forces during addition of a binder to firstly generate agglomerated particles using the three phases shown in Figure 43.3.

Leuenberger [5] identified the optimal granulation point as being the initiation of the capillary state. However, granulates in this phase then need to be dried. For this reason wet granulation is typically described as a two part process with the initial wet granulation being followed by drying process (even though the two steps can and often are carried out in the same vessel—commonly described as a "single pot" granulator (see Figure 43.4).

For more detail on the types of secondary production please refer to the specific sections of this publication, they are listed here purely for background before discussing the individual unit operations.

43.4 SOLID DOSAGE UNIT OPERATION

From the process workflows given above it is apparent that several unit operations are common, even repeated. But let us consider each of these "common steps" in turn and consider how they are run now, and what are the opportunities for continuous processing.

43.4.1 Dispensing

Under a traditional batch paradigm the production material is typically weighed in the pharmacy, verified and released, having already been individually bagged ready to be loaded into the production process. However, it is not uncommon for the toxicity (and so containment) of some materials to cause manual handling issues. These are often overcome by automated dispensing systems. In some cases these dispensing systems are connected directly to the production process. Although these systems are typically used to initiate a batch process, they are (in themselves) continuous systems—the first powder into the feeder is the first powder out. In reality pharmaceutical production may use the current range of volumetric and loss-in weight feeders to deliver in an automated way to ensure containment, they were actually designed for, and able to run, as part of continuous systems. Several of the feeder suppliers have even extended their

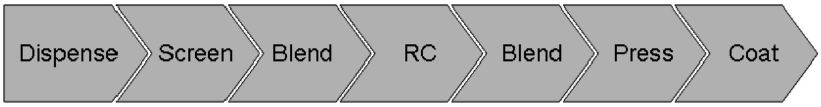


FIGURE 43.2 Schematic of dry granulation process.

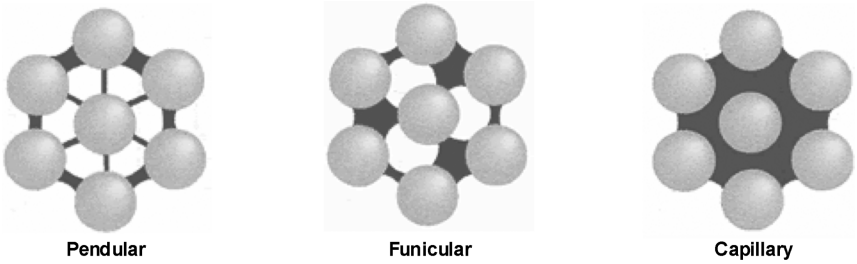


FIGURE 43.3 Three phases of granulate wetting.

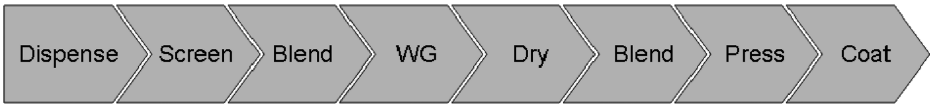


FIGURE 43.4 Schematic of wet granulation process.

product range forward, such that their control system becomes the basis for controlling material flow through the entire continuous system.

Although the basic principle of using existing automated feeders as part of a continuous processing system is sound, what we are trying to achieve is very different. A feeder on a batch dispensing line simply has to deliver, reproducibly, the correct mass of powder. The mass is simply what is needed for an entire batch. So, for example, a automatic feeder dispensing 20% API to a 1000 kg batch process simply has to, reproducibly deliver 200 kg of API. The automatic feeder is able to accelerate during bulk dispensing, slow as it approaches the end point and operate what can only be described as fine step control to end up at the predefined mass. Taking the same 20% API example, on a typical continuous process producing 40,000/500 mg image tablets per hour, the feeder is required to deliver not only exactly 4 kg/h of API but with adequate precision to ensure each of the approx 11 unit doses that will be generated every second, meet requirements around API uniformity. Using this simple example (and in the worst case) the API feeder needs to deliver approx 1.1 g of API every second, reproducibility, across the entire production run (see Figure 43.5). From a mechanical engineering perspective the two are very different challenges (and even worse if the API or excipient concentration is lower (e.g., a typical lubricant addition rate of 1% equates to 55 mg/s addition rate or rather 5 mg/90 ms).

In general the only additional consideration for continuous use is the maintenance of an acceptable level of materials in the feeder charge hopper.

43.4.2 Screening

Even when running under a continuous paradigm it is anticipated that many raw materials will be delivered in as drums/lots/batches. It is a straightforward logistic operation to track the use of the material to final dosage form and in effect allowing traceability of lots to whatever is defined as final batch integrity for compliance purposes. However, in

FIGURE 43.5 K-Tron MT12™ twin-screw microfeeder, capable of both batch and continuous operation.

many cases the performance of the feeder is impacted directly by fluctuations in hopper level, so simply, manually charging the hoppers is not an option. Material handling solutions have been developed for other industries such as food and food ingredients, which are even capable of receiving raw materials on rail or by road, transfer the local storage facilities before charging feed hoppers at local unit operations. These systems can also include flow aids, filtered venting/exhaust systems as well redundancy/parallel storage to ensure supply (see Figure 43.6).

The next step in all typical batch operations is to screen the input materials commonly described as delumping. This is often carried out using a screen mill but is in itself a continuous unit operation (it operates on a first in/first out principle) so although used with a batch paradigm could very easily be used as part of a continuous process. The main considerations when doing so are, does the performance of the screen mill change over time (e.g., does the screen become blocked, or does the mechanical action actually wear or cause the screen to break). These considerations are

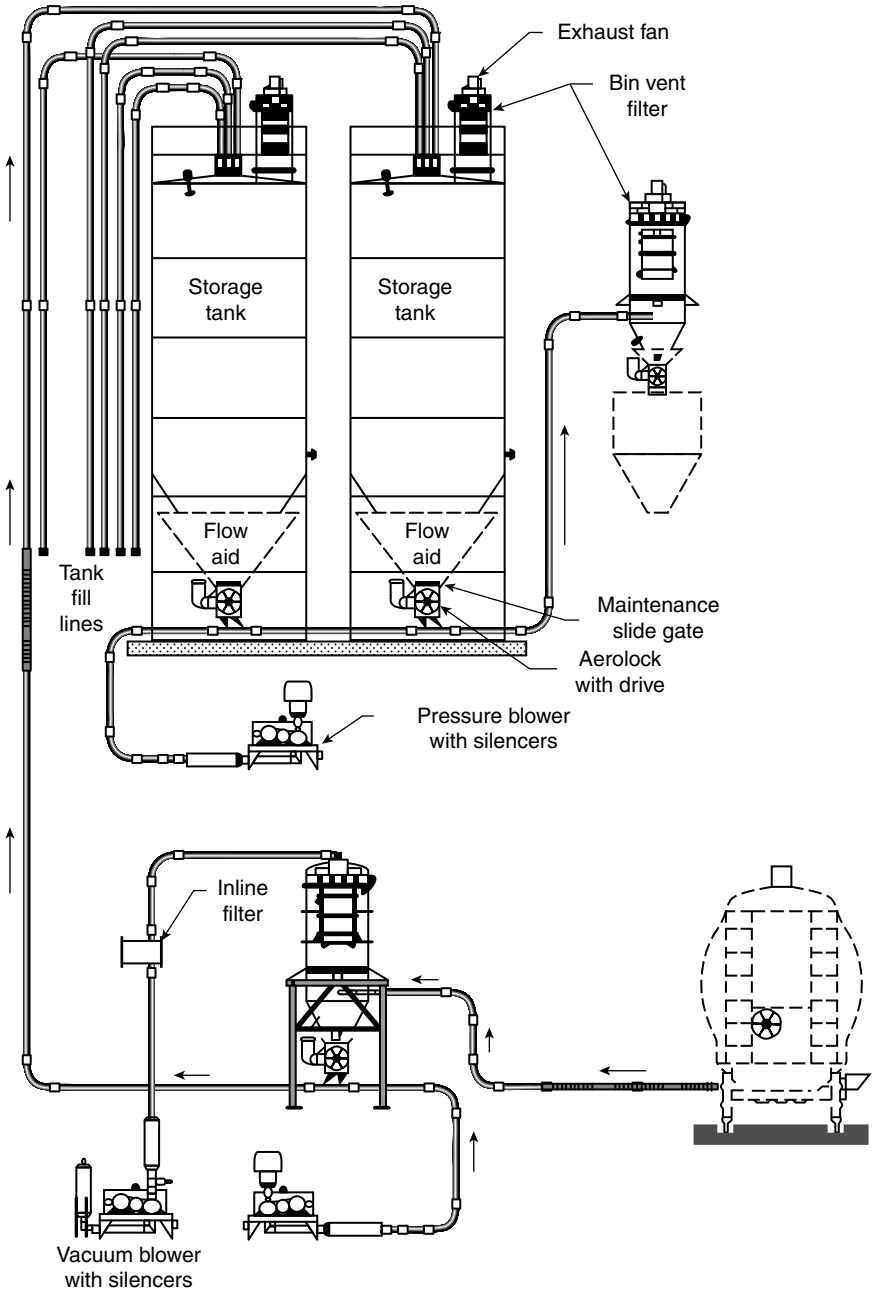


FIGURE 43.6 Example pneumatic conveying system courtesy of K-Tron Premier™.

often not important within a batch paradigm simply because the effects are not seen but critical to a continuous process.

However, a more elegant approach is to combine the screen into the dispensing operation. Many feeders can have mixers, microcentrifugal feeders, or even screens incorporated within their design. Combining the two unit operations in this way simplifies the production process but also has similarities with a dry granulation unit operation where milling is regarded as integral to the granulation process.

43.4.3 Blending

There can be little doubt the blending unit operation is the most common unit operation in pharmaceutical secondary production, it is also the operation with the fewest comparisons to continuous production (because of how the operation is carried out). However, continuous blending is common place in other industries and in the last few years continuous blenders that claim compliance to CFR and cGMP have also become available.

Because of the widespread use of this unit operation, but also because of the lack of experience in applying continuous blending to pharmaceutical processes, this processing step has been subject to the greatest intensity in academic and theoretical research in recent years. Laurent and Bridgwater [6–8] were one of the first to investigate the flow patterns within a continuous blender, using techniques such as tracking radioactive tracer; this allowed them to generate the axial and radial displacements as well as velocity fields with respect to time This was followed by Marikh et al. [9] where the focus is on the characterization and quantification of the stirring action, relating it empirically to the flow rate and the rotational speed of the continuous blender. In doing so it systematically investigates the effects of, operating conditions (such as rotational speed and processing angle) and design parameters (such as blade sign) on the mixing efficiency.

However, the key to the successful use of continuous blending is recognition that the blender actually has to fulfill more than one purpose. Its primary role is to take the variation in the disparate individual feeds (API and excipients) and generate a single uniform blend, such that each and every individual unit dose is of appropriate quality. However, in order to achieve the blender's primary role the continuous blender has to remove any variability remaining from the dosing operation. As such, a continuous blender has previously been described as "variability reduction ratio" (VRR) device. Williams and Rahman [10] proposed a mathematical approach to predict the VRR, utilizing data generated from a residence time distribution test for both and "ideal" and "nonideal" blender. The metric of "ideality" is defined by a mixing efficiency proposed by Beaudry [11]. In another publication, Williams and Rahman [12] investigated this mathematical methodology by using a salt/sand formulation of different compositional ratios. They verified the predicted VRR with experiments and suggested that the results where comparable. They also illustrated that (over at least typical conditions) the mixing speed and VRR were directly correlated. Harwood et al. [13] studied the performance of seven continuous mixers as well as the outflow sample size effect of sand and sugar mixtures. All of these activities was reviewed and then additionally verified by Portillo et al. [14], including experimental investigation of operation and design parameters such as processing angle, impeller rotation rate, and blade design are examined.

In summary all these investigations show that the powder's residence time and number of blade passes it experiences was affected not only by rotation rate but also by the processing angle, and that an upward processing angle and low impeller rotation rate are the optimal processing settings, when combined with optimal blade design. These generate a slight backflow between blade rotation and a turbulent flow within the linear flow of the process.

In Ref. 14 a new type of continuous/in-line blender (manufactured by GEA PharmaSystems) called the Continuous Dry Blender is used—this is the first dedicated, purpose designed for the pharmaceutical industry, continuous blender (see Figure 43.7).

This system is now commercialized and further details are included later in this chapter.

Fundamental research is still ongoing into continuous blending with the primary focus being the addition order of individual components as for the first time the dry blending process can be engineered to allow optimized mixing/interaction of components to effectively "build" the formulation in a structured way. One area where this is critical is around the addition of the lubricant component; or more accurately what type of effect is trying to be achieved by the addition of the lubricant, that is, do we want the lubricant to be in a

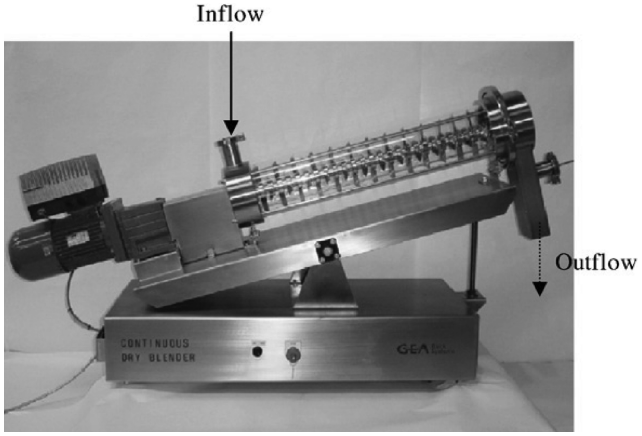


FIGURE 43.7 Early version of the GEA continuous dry blender [14].

distributed within the blend but remain as a discrete powder or do we want the lubricant to be smeared over particles of the other components? In the past, we could change blend time and rotational speed but little else.

Not only continuous dry blenders but also specialized PAT measurement systems, to monitor the blending process, are now commercially available. In the same way that on-line NIR systems are commonly used to monitor the batch blending process [15], ultra fast scanning (diode array) NIR linked to optimized sample presentation systems are available. Using these systems it is relatively easy the get comparative data on the trajectory and end point of both batch and continuous systems and therefore even compare the output from both. If we first look at a simple development scale batch process, an NIR prediction model can be generated trend how each components changes over the blend process over time (Figure 43.8).

In the example above (carried out at in a Paterson Kelly 4qt V-shell blender) we can see the batch process reaches uniformity after around 20 rotations, with one component taking longer to reach uniformity than the other two. If we look at exactly the same composition running from start-up, the plot is slightly different (Figure 43.9).

This data is from a "dry" start-up, that is, from when the feeders themselves are started and with the blender empty. In this case, the continuous blender has a volume of 500 ml and at the powder flow rate used (20 kg/h) so the blender has a residence time of around 90 s—meaning it therefore takes 90 s before powder starts to exit the blender. From this time point it then takes approx 3 min to reach a %RSD equivalent to the batch process.

The significant detail in this case is the start-up process used approx 2 kg of powder to reach this steady state (approx the same weight as used in the 4qt development batch) but there is no scale-up involved moving to commercial scale; the powder flow rate used (20 kg/h) is equivalent to 140,000 kg/year at expected equipment utilization rates (80–85%). We

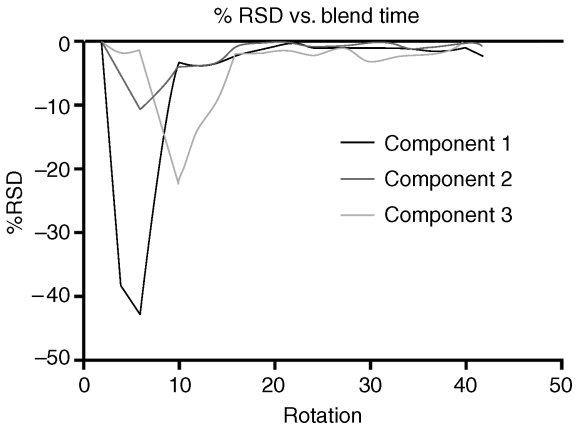


FIGURE 43.8 Typical batch blend plot.

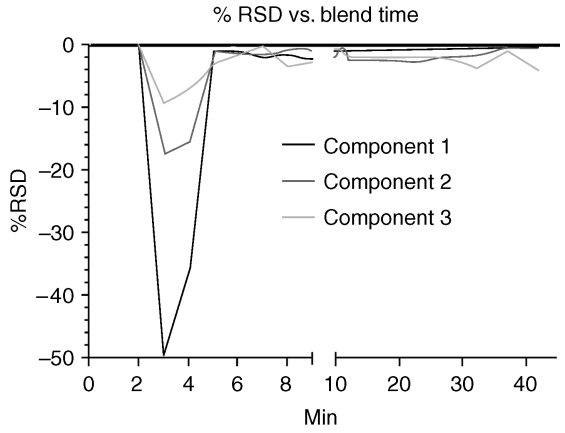


FIGURE 43.9 Typical continuous blend plot.

are able to go from development straight to commercial scale because unlike batch processes with scale in "space" continuous processes scale in "time."

However, we also have to consider the scrutiny of scale when describing measurement systems. In a batch process we can statistically sample (spatially) the output of the blend process; in continuous blending we have a different scrutiny scale, effectively the uniformity of the individual/consecutive unit doses is generated here and simply doing a unit dose scale measurement at a fixed time interval across the batch can miss unit dose to unit dose variability (in much the same way that inadequate or poorly specified sampling will miss variability in a batch process). If we look at the unit dose (in this case the product is 500 mg image) to unit dose variance and calculate %RSD we get a very good demonstration of the high frequency variability in the system (Figure 43.10).

Although direct compression is the simplest form of solid dosage production it has significant restrictions in use.

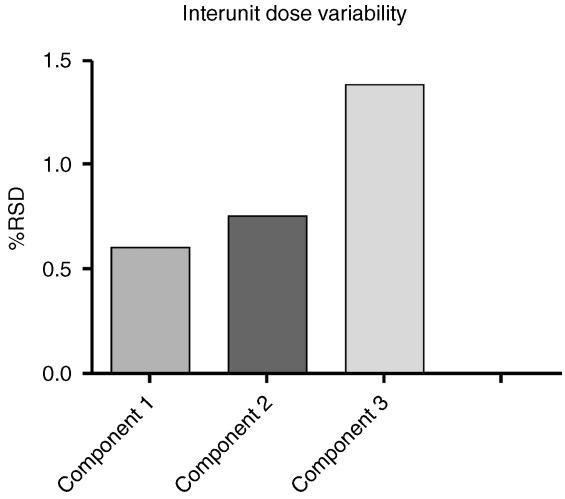


FIGURE 43.10 Typical interunit dose variability plot.

Typically solid dosage formulations do not use API and excipients with comparable physical properties such as particle size, which means there is a tendency to segregate postblending but before the final dosage form is made. Because if this it is very common to follow the first blend step with some form of granulation.

43.4.4 Dry Granulation

As previous described, in dry granulation the blending step is typically followed by another unit operation originally developed for another industry; roller compaction. In typical pharmaceutical processes the roller compaction step is carried out as part of a batch production line, however the activity follows a first in/first out principle and is inherently "continuous." Powder is fed from a feed or charge hopper into the RC unit and between two counter-rotating rolls. The compression force (and utilizing the elastic strength of the individual particles) causes the free flow blend to form solid compacts (sometimes ribbons, sometimes briquettes), see Figure 43.11.

Even though the actual RC activity is "continuous," variations in powder flow into the feed hopper will impact the uniformity of the compacts produced, both in terms of physical (i.e., tensile strength) and chemical (segregation). For this reason most commercial scale and many development scale RC units include a mechanical system (similar in design to an automated feeder) to deliver a constant feed rate at the rollers. Most RC units used in pharmaceutical were themselves developed/optimized with sophisticated feedback controls (for speed, press and even torque) to function with little variability.

Because the mechanism used when reducing variability in the output of the blending step may actually cause variability in the roller compaction step, when using RC as part of a continuous process specific consideration has to be given to changing this paradigm. It is possible that the RC process itself will need to be adjusted in order to cope with varying input and thus ensure a constant output. The fundamental

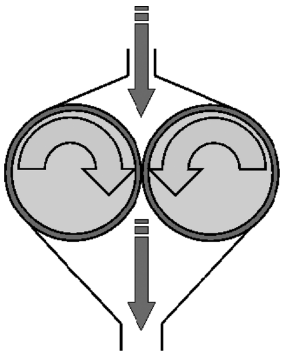


FIGURE 43.11 Roller compaction schematic.

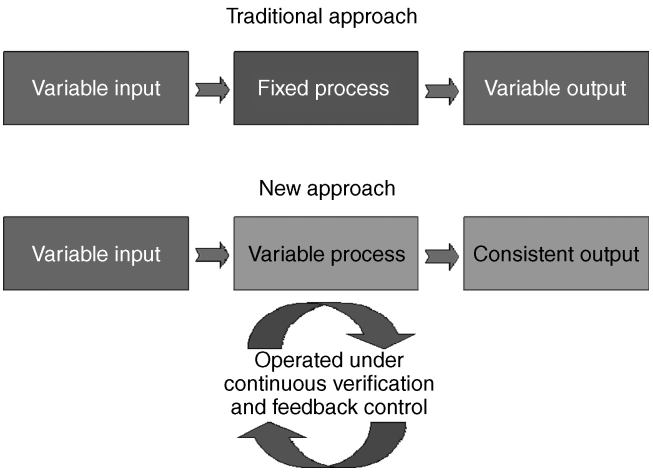


FIGURE 43.12 Continuous quality verification.

change to the way pharmaceutical processes are run is consistent with the current initiatives and is often represented graphically using a form of the diagram below, and is known as continuous quality verification (CQV) and is particularly important to highly constrained traditional processes such as roller compaction (Figure 43.12).

There are PAT measurement systems now available that have the capability to monitor both physical and chemical changes (e.g., density that in turn impacts tensile strength) of roller compaction ribbons. These allow continuous on-line measurement and real-time prediction (Table 43.1). Specific optical measuring heads have been developed that allows the use of NIR directly onto the compacts as the come-off the RC rollers (see Figure 43.13 and Table 43.1).

In this case study, intact ribbons are generated as a result of compaction. This is not always the case and it is essential that the capabilities of the measurement systems are match to the

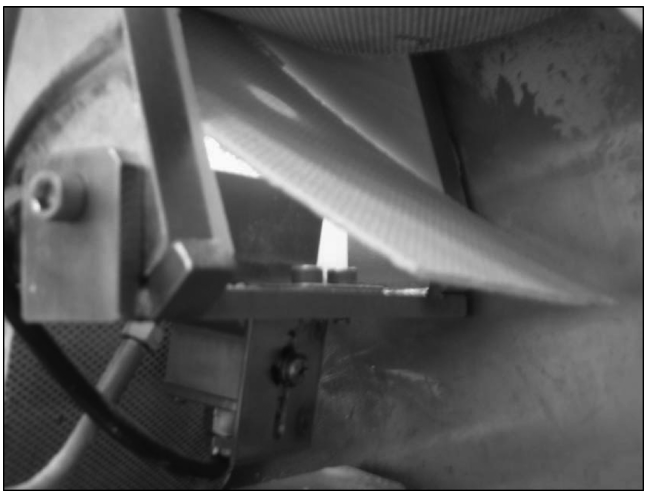
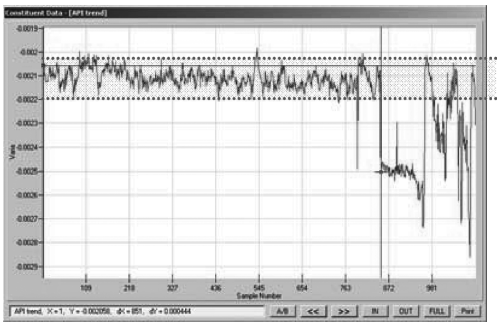
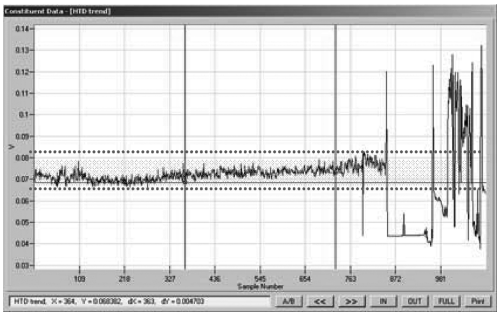


FIGURE 43.13 NIR measurement head installed in Gerteis Macropactor.

TABLE 43.1 Online Measurement of Variability

API trend	
Showing constituent alarm states and the effect seen when a process parameter changes to take the process variance outside expected norms	
Physical variance	
Showing constituent alarm states and the effect seen when a process parameter changes to take the process variance outside expected norms	

application in terms of speed of analysis, rate of analysis, reproducibility, and sample size.

The second component of dry granulation is the milling or granulation step. Here the compacts are typically put through a screen mill, again on a first in/first out basis so inherently continuous. When running this sort of mill under batch conditions (much like the example given for the screening process) the main considerations is around the performance of the screen mill and does it change over time. Particle characterization post the mill can be carried out using focal beam reflectance microscopy (FBRM). FBRM utilizes a spinning laser (of known rotational speed) to measure the chord length across any particle, by simply back calculating the duration of reflection of the laser off the particle (see Figure 43.14).

The laser light is delivered by fiber optic probe so is relatively easy to install in the output stream of the RC granulator, often fitted with optional gas purge to keep the tip clear (see Figures 43.15 and 43.16)

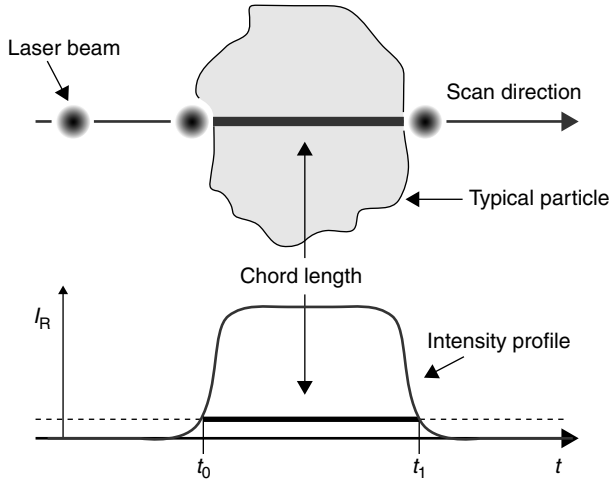


FIGURE 43.14 Theory of FBRM (courtesy of Mettler-Toledo).

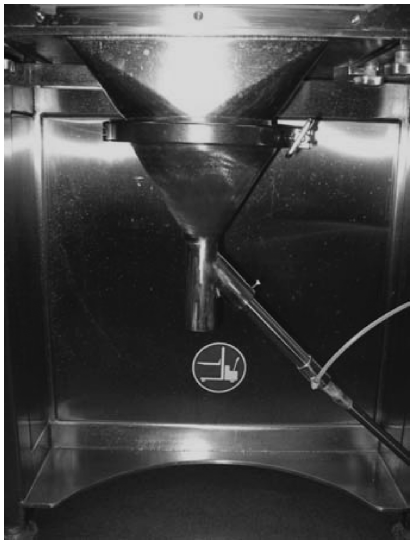


FIGURE 43.15 FBRM with purge tip installed on the Gerteis Macropactor.

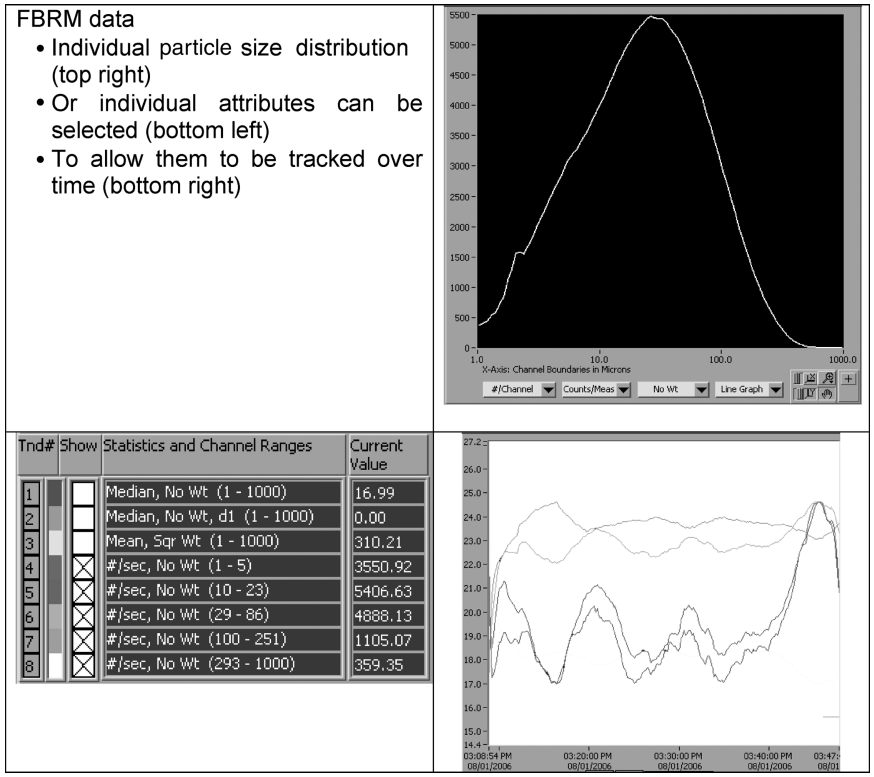


FIGURE 43.16 Monitoring the RC milling process using FBRM.

43.4.5 Wet Granulation

As previously described the need to granulate pharmaceutical powders is common however it is not always possible to dry granulate, possibly because the powders do not have sufficient elasticity (they are two brittle) or because the differences in particle size distribution or physical properties is too great. In these cases it is very common to wet granulate.

Unlike dry granulation the wet granulation is not inherently continuous however there are examples dating back to the mid 1980s, suggesting alternate approaches to traditional wet granulation that could be run continuously or semicontinuously, for example, Koblitz and Ehrhardt [16] published on wet granulation and using continuous variable frequency fluid bed drying.

A breakthrough approach came from Glatt with the launch of their Glatt Multicell (CMC) in the late 1990s. The technology has not seen widespread adoption but is well documented including several publications by Leuenberger [17].

The CMC 30 comprises of a 27 L High Speed Plough–Shear granulator, which equates to a 5–9 kg subbatch (Figure 43.17). The granulator "self-discharges" via a

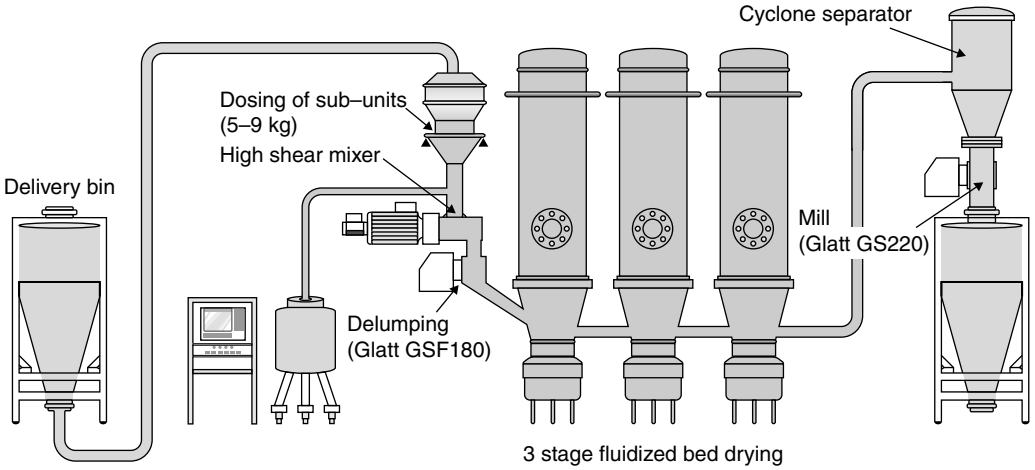


FIGURE 43.17 Glatt Multicell GMC 30.

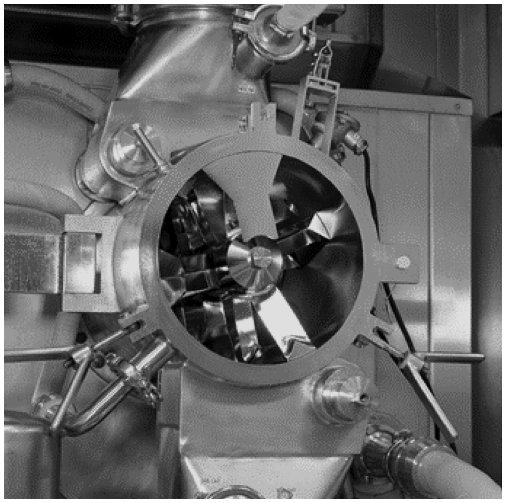


FIGURE 43.18 HSP-S mixer.

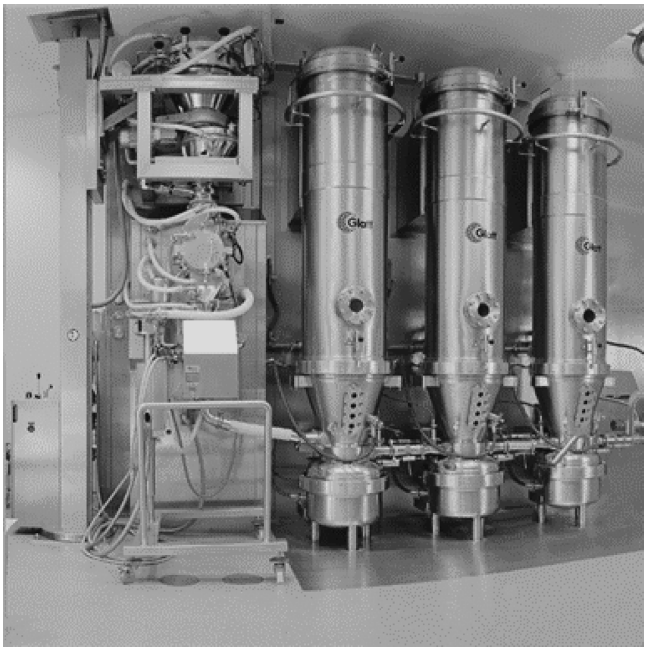


FIGURE 43.19 GMC 30.

delumping system into a multistage fluidized bed dryer. After granulation/wet massing, the material is conveyed sequentially through three stages of drying. In this way, four small batches (one in granulator and three in drying) are processed simultaneously and the cycle repeats for semi-continuous operation (Figures 43.18 and 43.19).

Although this system is best described as a micro-Flow system the technical significance of this system should be recognized, especially as it was one of the earliest examples of continuous verification and feedback control; each of the three fluidized bed towers can be fitted with a noninvasive NIR measurement system, which simply views the drying process through the preexisting inspection windows. A control strategy is then put in place balancing the subbatch throughput (Figure 43.20).

Once dried the subbatches could be discharged directly into a second continuous blender for lubricant addition although all known implementations currently collect the subbatches to form a single batch that moves forward.

In their White Paper for PharmaManufacturing.com, Mollan and Lodaya [18] identified that a continuous fluidized bed granulation system would have five or more functional zones. These are product in-feed zone, product mixing and preheating zone, spraying zone, drying and cooling zone, and discharge zone, with a more detailed explanation being given by Paul et al. [19]. Continuous versions of some of these individual functions are available and have been published. Lindberg [20] used an Iversion mixer (where powders and liquid are metered into a narrow space at the periphery of the grooved disc, which rotates at high speed) to study wet granulation of placebo. Applegren et al. [21] used a similar system to study continuous melt granulation, and a system is commercially available that uses a Planetary Extruder to

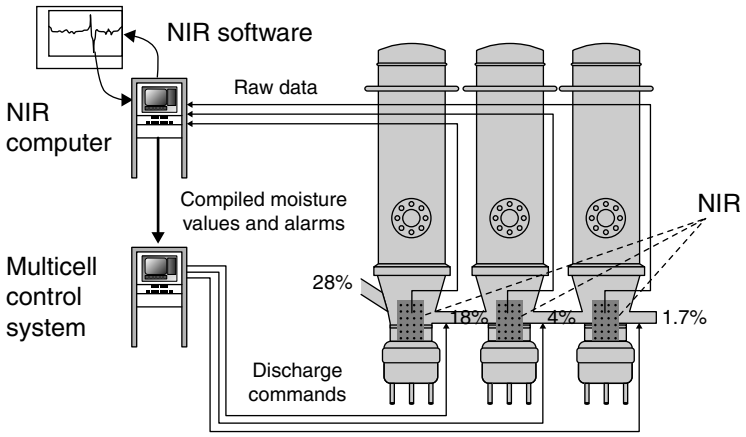


FIGURE 43.20 GMC 30 NIR control strategy.

granulate and Microwave tube to dry continuously. As an alternate to microwave energy there is also a commercial system based on using radiofrequency energy (using wavelengths specific for aqueous drying. Until recently, radiofrequency heating has been used mainly in other industries such as food, paper, and ceramic. Jones and Rowley [22] have reviewed several applications for drying where dielectric heating is used by itself or in combination with other methods.

However, the wet granulation that has the greatest potential for continuous operation is using a twin-screw granulator/mixer. This is a modified twin-screw extruder and relies on twin intermeshing screws that convey, mix, wet granulate, and wet mass the powder blend. These systems offer several advantages over traditional wet granulation processes, and the interchangeability of screw elements ensures flexibility. Twin-screw extruders themselves have been utilized for wet granulation since the 1980s [23, 24], and some aspects of the application are also covered by patent [25]. In addition, Ghebre-Sellassie et al. [26] have published on a continuous wet granulation and drying system that combines twin-screw mixer (for wet granulation and wet massing) with radiofrequency energy (for drying).

Very recently a commercial system has become available from GEA Pharma Systems called the CONSIGMA™. This system is at the center of GEA's philosophy of an integrated tablet line and starts with separate liquid (binder) and powder feed systems (the powder feed either being metered directly or coming from the outlet of one for their continuous dry blender systems). These feeds coming together in a twin-screw granulator, which continuously outputs into either a linear or segmented dryer (Figure 43.21).

FIGURE 43.21 GEA Pharma Systems CONSIGMA™.

Interestingly, currently the CONSIGMA™ does not utilize a second GEA continuous dry blender for addition of the lubricate postdrying. Instead, after drying the product is held in a dedicated discharge hopper/mill and small batch "lubricant" blender/feeder. All of this is under an integrated control system.

43.4.6 Compression/Encapsulation

No matter what the route taken to reach the compression or encapsulation unit operation, and no matter what vendor system is adopted in the step, it will be carried out under a "first in/first out" principle and as such is continuous. As an industry we choose to charge the feed hopper as a batch and collect the output as a single entity. If this step would run truly continuously some consideration needs to be given to dust buildup (even if preceded by a dedusting step), product build up on press tooling (which will cause issues with subsequent defects on tablet cores), and (in the case of encapsulation) the addition of additional raw materials (the empty capsule shells).

The addition of automated tablet testers and capsule checkers for feedback control also allows the compression/encapsulation process to be adjusted in real-time (for weight, thickness, hardness, and Cu)

43.4.7 Coating

When describing the coating process we have to remember there are two input streams. The first is the uncoated cores but we also have to consider the spray solution itself, so even if a continuous coated was feed directly from the press the spray solution preparation also needs to be addressed. That said, continuous coating is performed in food, flavor, and nutraceutical processing and the first commercially available continuous coater with claimed compliance to current CFR for use in pharmaceutical production has recently been launched by O'Hara Technologies. Their design resembles an extension (in depth) of a standard batch rotating drum coater and spray manifold but with the addition of inlet and outlet chutes to create a flow through process. There is still the same level of development needed and adjustments to tablet feed rate, pan RPM and residence amount and/or time all affect the coating uniformity. The unit is quite new to the market but details from the vendor indicate that tablet cooling, elevating and/or waxing can be added at the discharge end of the coater. The unit also includes some improvements to their spray manifold design, improving solution distribution and an update of their air caps, providing better antibearding properties (which are required for continuous operation). The coater is also designed to be run in batch mode during start-up and development. Fundamentally the continuous rotating drum O'Hara unit fills the same gap as

the Glatt Multicell, providing continuous process by adaptation of the current batch approaches.

Another approach would be to investigate alternates to how the sample is presented to the coating spray. Fluidized bed coating is one possibility, and is the basic approach used in the SUPERCELL™ from GEA Pharma Systems. This is a small, modular, batch design where tablets are coated in batches ranging from 30 to 40 g, and even though the system was designed to have a linear scale-up to production it is unique as the tablets are coated, with the coating spray in the same direction as the drying gas (not orthogonal to the drying gas), resulting in a more efficient process. The process time is short, seconds or minutes as opposed to hours, and could be used on a semicontinuous mode. It would be relatively straightforward to make a semicontinuous (and possibly continuous) version.

There is also ongoing fundamental research and development ongoing in academia and industry to creating the radial movement of the tablet cores relative to the coating spray and also to provide an axial movement (to facilitate movement through the coater, so that the tablet cores follow a corkscrew, rather than circular motion, although it is expected that most of this work is/will be subject to IP (intellectual property).

43.4.8 Packaging (Including Printing of Final Dosage Form)

All current Pharmaceutical packaging processes are run as batch processes but are inherently continuous. However, much like encapsulation, consideration has to be given to the multiple input streams (product and packaging materials) and the biggest issue is maintaining a continuous, traceable, supply of package materials.

43.5 CREAMS, LIQUIDS, AND SUSPENSIONS

Continuous processing concepts have also been implemented in the area of sterilization, and solution manufacture. In addition, it is normal for the containers/bottles/ampoules/pouches used to be manufactured along side the actual product, even under the same sterile conditions. It is also common for the product strength or even alternate products to be run concurrently (with the appropriate changeover procedures being run automatically—including appropriate PAT measurement systems to provide verification of the change). This class of products comes as close as any to realizing true continuous processing in pharmaceutical production, as although they typically start and finish with a batch solution/suspension preparation, all over unit operations (including things like "blow fill" container formations, and dosing) run continuously until the product is collected into batches at the end.

43.6 LYOPHILIZATION

Currently lyophilization is carried out in very large batch sizes (based on number of individual samples and there are no indications/research ongoing to suggest this will change in the near future. However, Rey [27] proposed some very interesting concepts on continuous or semicontinuous lyophilization technology based on practices from the food industry where continuous freeze drying is deployed.

43.7 NOVEL UNIT OPERATIONS

43.7.1 Spray Dried Dispersion

These are common in food and other industries and becoming more so in Pharmaceutical, primarily as they provide a way to alter/control the bioavailability of certain API. They also provide a mechanism for holding the API in a something state/form. During the spray dried dispersion (SDD) process, the API and a waxy polymer are dissolved in solvent before the solution is sprayed under controlled conditions to generate a modified API, with defined particle characteristics (which actual make secondary formulation more straightforward—often direct compression). The actual spraying process is continuous (first in/first out) and even current manufacturing approaches could easily be adapted to flow production, but also modified to be truly continuous.

43.7.2 Melt Congeal Extrusion/Spinning Disk Extrusion

Much like SDD production, the melt congeal/spinning disk extrusion process is deployed to modify the availability of the API, however in this case normal to modify the rate of release; they often provide the basis of slow/sustained release formulations. The actual extrusion process is continuous and the batch nature of production comes not even from the initial feeder hopper but from the collection into batch postprocessing.

43.7.3 Webs/Oral Care Strips

Web-based products such as oral care strips bear more resemblance to screen printing than pharmaceutical manufacturing. Their production is continuous but the two input streams are both batch (the support/paper backing and gel like product suspension). Even though the suspension preparation could be made continuous this process is more easily adapted to flow production than continuous.

43.7.4 Transdermal Patches

Much like Web-based products; transdermal patches have more in common with printing than pharmaceuticals. Typical

they are produced by deposition (sometimes spraying, more often roller deposition) into a permeable support medium, over which a protective coat is then applied—forming a sandwich. The support medium and protective coating comes on long rolls (much like the paper used in a cash register and used to provide a till receipt). The solution preparation (typically purely a dilution of the API in a carrier) is batch and normally highly toxic (e.g., nicotine solution used in nicotine patches is classified as an occupational exposure band (OEB) level 4/5 because in solution form it is not only toxic but readily absorbed. It is not likely that production of these types of product will become truly continuous in the near future.

43.8 WHY CONSIDER CONTINUOUS PROCESS FOR DRUG PRODUCT OPERATIONS?

43.8.1 Benefits of Continuous

The biggest advantage in developing continuous processes rather than batch is around scale-up, or rather, as has already been indicated in this chapter the lack of scale-up. Processes are developed at the same process flow rate as they will run in commercial manufacturing; it is purely that the process runs for a longer period of time in commercial production. This is key; the process performance changes with scale, and often development activities are not carried out on the same design of process equipment (e.g., a V-shell blender being used in development but a bin blender used in commercial manufacture). These types of dramatic changes equipment scale result in differences in physical characteristics just as surface area to volume, which lead to significant differences in the way the process to make the product performs.

Typically this goes hand in hand with a reduced equipment footprint, for example, a development scale blenders is around 3 ft tall, while a production size V-blender can be 1–2 stories high, and this is just the blend step—a complete direct compression equipment train with gravity flow between production steps, typically requires a building 3 stories high. The same annual output can be achieved from a self-contained, typically wall mounted, process suite occupying only one room.

Continuous processes also provide the ability to vary batch sizes based on product and demand—we simply run longer. Having a smaller footprint in a cGMP space is a huge cost saving, if the equipment could be "skid mounted" and pulled out of storage only when needed for use. This introduces the idea of the equipment being housed in a cGMP bubble that could (in theory) be dropped into any cGMP facility (e.g., a contract manufacturing organization (CMO)) and run under that facilities compliant processes.

Smaller equipment also typically means cheaper equipment; certainly comparing the cost of the large V-shell to a typical continuous blender has the V-shell costing around 10 times more.

Because these systems are designed to run continuously (with 80–85% availability) they have much higher equipment utilizations rates (a typical batch blender has 25–30% utilization). They are also (typically) highly automated, resulting in lower labor costs and higher operating efficiencies. Another advantage of continuous processing is a reduction in Work In Progress time and therefore inventory that needs to be held, leading to just-in-time manufacturing.

In commercial manufacturing there is also a significant advantage in running processes continually at steady state (rather than those that progress toward an end point); there is a reduction in variance but also it is simple to introduce PAT measurement systems to increase quality and reduce waste through continuous improvement. Especially when we also consider that these systems are typically contained, from start to finish and therefore more applicable to high potency products but also often include automated clean-in-place systems which allow automated changeover between products, which is particularly important when you consider the benefit of efficient start up and shut down.

This last statement is key, if we consider the benefit of continuous purely from a development viewpoint. Part of the twenty-first century quality initiatives is the principle of establishing Process understanding using tools such a design of experiments (DoE). To run a DoE even at development scale with take multiple small-scale batches. Whereas running the DoE (automated) on a continuous system simply means "driving" the continuous process around process space whilst tracking/isolating the product produced (so that the impact on the product performance can be determined). This could be carried out in two ways; the most basic is where the process simply drives to the next set of DoE conditions, waits for steady state, collects product, then moves again; the more complicated and more information rich is there the process trajectory is investigated between the points on the DoE, this allows for a more detailed surface response curve to be generated and the uncertainty within the process space to be lowered.

43.8.2 Cost Analysis

It is possible to quantify possible cost savings by comparing continuous to batch activities based on yield increases (a 2% yield improvement is common simply from start-up and shut savings). As an example a typical direct compression solid dosage formulation requiring 80,000 kg/year, could be achieved by running 100×800 kg batches (about the maximum number of batches possible through a single commercial blender). Start up and shut down of the 100 batches will account for approx 2% or 1600 kg of waste. Whereas the same volume could be delivered by running four separate 52-day production cycles (208 days in total) of a continuous

system running 20 kg/h. The continuous process would waste only 64 kg. This could be further improved if production was carried out in a single production run, however, this would be product being held on inventory (impacting shelf life) for up to 5 months. In addition to the yield improvements, the improved equipment efficiencies would be the equipment that will be available for other use equivalent to an additional 50,000 kg of production.

43.9 IMPLEMENTATION OF CONTINUOUS PROCESSES

43.9.1 Regulatory Implications

One of the main reservations when considering developing and implementing continuous processes is regulatory burden. The first element often to be considered is the traceability provided by running a "batch." According to the CFR, the definition of a batch is

> A specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture [28].

It is clear that the regulatory definitions are already in place to support the concept of a batch being a period of time, whether that time period is very short (possibly even an individual dosage form), per day, or even a longer period if the process output can be adequately controlled using CQV.

"Continuous quality verification is described as an approach to Process Validation where manufacturing process (or supporting utility system) performance is continuously monitored, evaluated and adjusted as necessary."

More specifically "it is a science-based approach to verify that a process is capable and will consistently produce product meeting its predetermined critical quality attributes. With real time quality assurance (that CQV will provide), the desired quality attributes are ensured through continuous assessment during manufacture. Data from production batches can serve to validate the process and reflect the total system design concept, essentially supporting validation with each manufacturing batch" [29].

Under this paradigm the idea of a "batch" is becomes no more than form of tracking and quality assurance. Also of note; currently at the time of writting there is another ASTM activity (WK9192) as part of E55. This is a new Standard Guide for the Application of Continuous Processing Technology to the Manufacture of Pharmaceutical Products and is expected to clarify and give guidance around regulatory implications

43.9.2 Validation

One of the latest documents being drafted as part of the twenty-first century quality initiatives is a new Process Validation Guidance. At the time of writing this is only available in draft form but due to be issued in the very near future. This guidance divides Process Validation into three component parts. New Validation now includes establishing process understanding during development, followed by a performance qualification (PQ) of the process (this step replaces the old three batch validation activity) that is in turn followed by continued verification. Developing a continuous process under a QbD paradigm actually leads to a process with significantly higher level of process understanding (because we would have been able to investigate the impact on the product of many more process conditions (as we drive between points on the DoE). There is even a possibility that our confidence in how the process will run "in commercial manufacturing" (because there is no scale-up) will be so high that we could only carry out the PQ immediately before launch, reducing the financial burden of holding registration/validation material on inventor.

There is also an expectation that continuous processes will be adaptive and under continuous quality verification/feedback control that is aligned with the principle of Continued Verification. It also supports the principle of real-time release (RTR) where the process is under feedback control ensuring the output quality.

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