In batch manufacture of a tablet formulation, you process predetermined quantities of API and excipients together in a single unit operation, which you complete in its entirety before passing to the next unit operation. You have a predetermined batch size and theoretical yield. Some of your unit operations may be inherently continuous, such as sieving, milling, and tablet compression, but you typically carry out blending and wet-granulation on the entire batch at once. In continuous manufacturing at a quasi-steady state, all unit operations are occurring simultaneously. As you continuously feed the API and excipients into the equipment train, you produce tablets and remove them from it.

Each type of processing has advantages and disadvantages. For example, if some catastrophic failure occurs in batch processing, you may lose the whole product batch, while in continuous manufacturing, a catastrophic failure may cause you to lose only part of the batch [1]. In truly continuous operations, operator intervention isn’t possible if you need to accommodate variations in component properties, such as end-point detection in wet granulation or dry blending. If the process requires an intervention, you must consider some form of hybrid approach, in which you run a particular unit operation in batch mode and then convert the process train back to continuous mode again. An even better option would be to engineer the variability out of the formulation and/or process.

Another advantage of continuous manufacturing is that it allows for real-time release testing (RTRT), when combined with an appropriate set of PAT sensors and controls, which saves on costly post-process testing.

Constraints on adoption of continuous manufacturing

Again, in truly continuous manufacturing operations, the opportunity for operator intervention and/or processing to an end point is nonexistent unless you implement such controls using a hybrid approach, which isn’t optimal. Continuous manufacturing requires you to resolve other issues as well, including:

- Determining how to meter low-dose and very-fine materials, including highly potent APIs (HPAPIs) and excipients present at low levels in the formulation, such as lubricants, glidants, and possibly disintegrants.
• Understanding the variability of the critical material attributes (CMAs) of the excipients and/or APIs and determining how this variability impacts the drug product’s critical quality attributes (CQAs). The CMAs may include some properties in the pharmacopeial monograph specification but will likely also include additional physical or chemical characteristics.

As with any drug product development process, whether batch or continuous, you must also address other factors, such as bioavailability, manufacturability, and the chemical and physical stability of both the API and the dosage form, among others. Routinely manufacturing an acceptable finished drug product requires:

• Creating segregation resistance in the final blend, even for continuous direct-compression processes. This involves adequately dispersing the API throughout the blend to achieve both content uniformity and bioavailability—particularly for some poorly water-soluble APIs—and maintaining that dispersion until manufacture of the final unit dose (by forming an ordered mixture, for example, in which the blend components adhere to each other to form ordered units);

• Ensuring the flowability of the final powder blend into the tablet die or through the capsule dosing mechanism to achieve acceptable weight and content uniformity; and

• Ensuring the compactibility of the final blend for tableting or consolidation during encapsulation.

Excipients and continuous manufacturing

Excipients will play an important role in the transition to continuous pharma manufacturing, and the industry can facilitate that transition by encouraging progress in the following areas:

• Improved understanding of the excipients currently in use;

• Creation of new grades of existing excipients;

• Development of new co-processed excipients; and

• Development of new chemical excipients.

Improved understanding of current excipients. Formulators should consider using excipient-characterization methods beyond the methods in the pharmacopeia monograph and the traditional functional-assessment methods, such as compaction of powder blends to assess lubricant performance. This may involve using analytical methods not traditionally associated with excipient characterization.

For example, Delaney et al. used solid-state $^{13}$C-nuclear magnetic resonance (SS $^{13}$C-nmr) and other characterization methods to investigate magnesium stearate from different commercial sources and were able to show that at least three, and possibly four, types of magnesium stearate were commercially available [2]. The data also suggested that a batch-to-batch variability can exist in magnesium stearate from the same supplier.

Pharmaceutical manufacturers have long recognized that magnesium stearate is a problematic excipient. Can the variability found by Delaney et al. explain at least some of the performance variability seen with magnesium stearate? Applying other spectroscopic methods, such as near infra-red (NIR) and Raman spectroscopy, to excipients on a regular basis may further enhance our knowledge of their characteristics and variability.

Creation of new grades of existing excipients. As discussed previously, continuous manufacturing puts additional constraints on excipients. It might not be possible to overcome these constraints using existing excipients and grades. Excipient suppliers may be able to develop new excipient grades to meet the needs of continuous or other advanced manufacturing methods, but only so much leeway exists within an excipient’s monograph definition and specification. Potential users may be reluctant to use excipients that exceed those bounds, since revising a pharmacopeia monograph takes time. Many companies prefer to use materials that comply with the monograph because the regulatory filing is more straightforward.

Co-processed excipients can provide functionalities and performance that non-co-processed excipients most likely won’t be able to achieve.

Development of new co-processed excipients. Co-processing has great potential to solve many problems related to continuous pharmaceutical manufacturing and/or other advanced manufacturing technologies. Co-processed excipients can provide functionalities and performance that non-co-processed excipients most likely won’t be able to achieve. Co-processing may also be a means to incorporate excipients at low levels without requiring an extra feeder and/or avoiding the problems associated with metering poorly flowing materials.

For example, using the co-processed excipient silicified microcrystalline cellulose (SMCC) is a convenient way to add colloidal silicon dioxide to the continuous manufacturing train while simultaneously enhancing direct-compression carrying capacity or post-wet-granulation compactibility compared to adding the individual components separately. This concept of ease of addition of low-concentration excipients could possibly be extended to other materials, such as lubricants, surfactants, and disintegrants, and even to APIs.

Other co-processed excipients are available that may find application in continuous manufacturing. Functionalities and/or performance characteristics for which co-processing may provide the solution could include improved blend-segregation resistance, improved compaction for both direct-compression and wet-granulation applications, and improved hot-melt processing.
A disadvantage of new co-processed excipients is that they don't have pharmacopeia monographs and require a safety/toxicology assessment. However, if you can demonstrate that no new covalent compound forms, you can bridge this assessment back to the individual components. This is less desirable than being able to simply declare that the excipient is a compendial material, but it's a lot more straightforward than introducing an entirely new chemical excipient (see the following section). The disadvantage of not having a pharmacopeia monograph may be more than offset by the enhanced functionality and performance compared to a new grade of an existing excipient.

**Development of new chemical excipients.** Finding entirely new chemical excipients is the least appealing option for developing excipients for continuous manufacturing. The uncertainty regarding a new chemical excipient's ultimate regulatory acceptance makes pharmaceutical manufacturers very reluctant to risk a new potential blockbuster drug product on the new chemical excipient. Only five new chemical excipients that have entered the market in the last 30 years or so are currently being used in commercial pharmaceutical products.

This trend is likely to continue for the foreseeable future. In the absence of an independent assessment by regulatory authorities, acceptance of a new chemical excipient requires an overwhelming technical need that can't be met by existing excipients. Presently, this doesn't seem likely for continuous manufacturing.

**Conclusions**

Formulators need to be aware that differences likely exist in the constraints on excipients between batch and continuous processing in the manufacture of finished drug products. It seems likely that conventional, single-component excipients and grades won't be able to provide all the answers. Of the alternatives discussed, new co-processed excipients seem to have the most promise to solve some of the challenges of continuous manufacturing, such as metering low-dose components and improved blend-segregation resistance.

**References**


*Chris Moreton is partner and vice president of pharmaceutical sciences at FinnBrit Consulting, Waltham, MA (www.finnbrit.com).*