Benefits of Using High-Functionality Excipients in a Continuous Manufacturing Process

Evaluating the performance of an excipient composite versus individual components

Overview

As pharmaceutical companies move increasingly toward changing production methods from batch to continuous processing, there is a need to re-evaluate the types and formulations of the excipients used. Within a continuous process, conventional monofunctional excipients must be added through individual feeders, potentially creating multiple sources of variability. In contrast, a single high-functionality co-processed excipient requires only one feeder, thus enhancing product performance while minimizing variability. This article discusses some benefits of continuous manufacturing and reports on the evaluation of a co-processed excipient composite comprising binder-filler, lubricant, superdisintegrant and glidant, used in tablet production.

Definitions and Benefits of Continuous Manufacturing

While batch production is still the most widely used method of producing pharmaceuticals, the need to streamline processes and improve efficiency is driving change within the industry toward continuous manufacturing. Furthermore, today's regulatory environment is supportive of such moves. Many publications are available from different regulatory bodies and the FDA's Emerging Technology Program promotes the adoption of innovative approaches in pharmaceutical product design and manufacturing.

Continuous manufacturing itself breaks down into essentially three different types (1):

- *Continuous,* where material is simultaneously charged and discharged from the process.
- *Quasi continuous,* where materials are pre-measured in batches and processed through a continuous equipment train (i.e., there are clearly defined batches even though processing is continuous).
- *Semi-continuous,* like continuous manufacturing but for a defined time period (i.e., batches are defined by time).

While continuous manufacturing has been a fact of life in other industries for many years, it is a relatively new concept in pharmaceutical

production, so discussion is ongoing as knowledge grows on how best to implement and manage different processes. The benefits, however, are compelling.

Importantly, continuous processing allows monitoring of product quality in real time using in- or on-line process analytical technology (PAT) tools, rather than the post-production testing, typical in batch manufacture. This significantly improves process understanding and supports on-line product release in real time. In contrast with batch manufacturing, this can mean no quarantine, no costly warehousing and minimal, if any, delay before product can be shipped.

There are physical advantages, too. A typical batch process is likely to include blending, milling or granulating operations, each requiring large pieces of equipment. Continuous processing equipment is generally much less bulky, has a smaller footprint and requires less spacious production facilities. Also, since continuous processing scale-up simply means running the same equipment for longer periods, there is no need for separate equipment in R&D and production.

Some challenges when moving to continuous processes include how to handle start-up, shut-down, out-of-specification material, and how long to run lines before cleaning. Where and how to interface PAT tools into continuous lines, what type of process control strategies to use, and how to define a batch are also considerations. All of these challenges are topics for continuing discussion and development. There is also widespread recognition that some current excipients and API grades are not optimal for continuous production, especially not for continuous feeding. The studies reported here further explore the question of excipient suitability.

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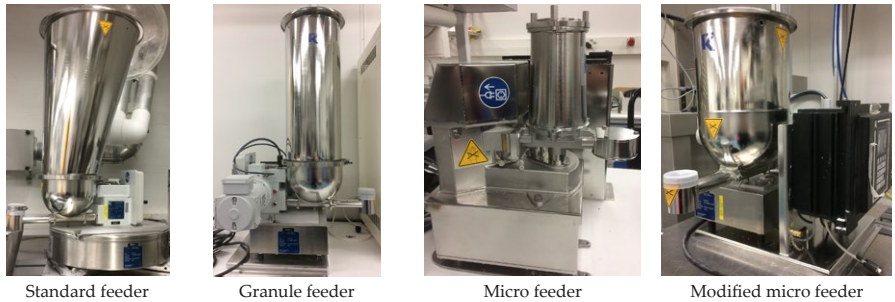
Evaluation of a High-Functionality Excipient Composite

Work described here was conducted by Dr. Ossi Korhonen, associate professor in the School of Pharmacy at the University of Eastern Finland. The aim was to evaluate an all-in-one, homogenous lubricant-coated high-functionality excipient composite (PROSOLV® EASYtab SP, JRS PHARMA) in continuous manufacturing. Of particular interest was its performance in feeding, blending and tableting operations. The excipient composite comprises four individual components: binder-filler (microcrystalline cellulose/Vivapur); glidant (colloidal silicon dioxide); superdisintegrant (sodium starch glycolate/Explotab); and lubricant (sodium stearyl fumarate/PRUV). It was assessed in three separate experimental set-ups for:

- Feeding performance versus individual components
- Effect of feed rate and mixing speed on particle size distribution (PSD)
- Continuous direct compression with API.

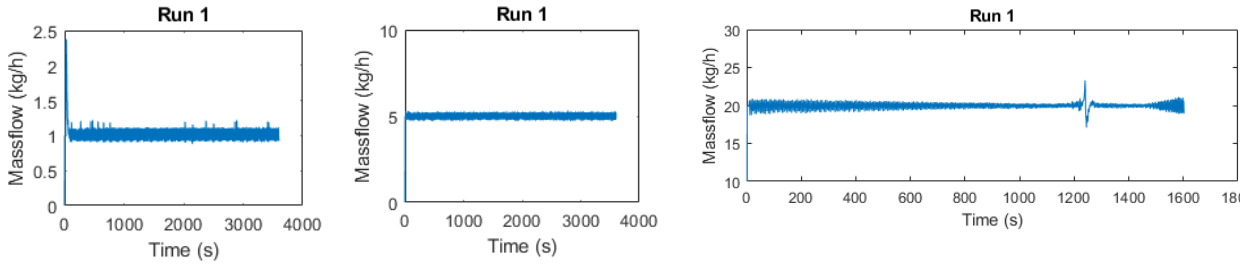
Case Study 1: Feeding Performance. In the first study, the four separate ingredients of the excipient composite were fed into a continuous production process and compared with feeding in only the excipient composite. Several different feeders were used, but all fell into the types illustrated in **Figure 1,** which all operate via loss-in-weight mechanism. Standard feeders are quite large with a 20-kg capacity hopper, while the granule feeder has around a 10-kg hopper. The hopper of the micro feeder has a capacity of 200 to 300 g, while that of the modified micro feeder is approximately 2 kg. Both a standard feeder (twin concave coarse screws) and a granule feeder with a different screw configuration (twin auger coarse screws) were used to feed the

Figure 1: Feeders Used in This Study.



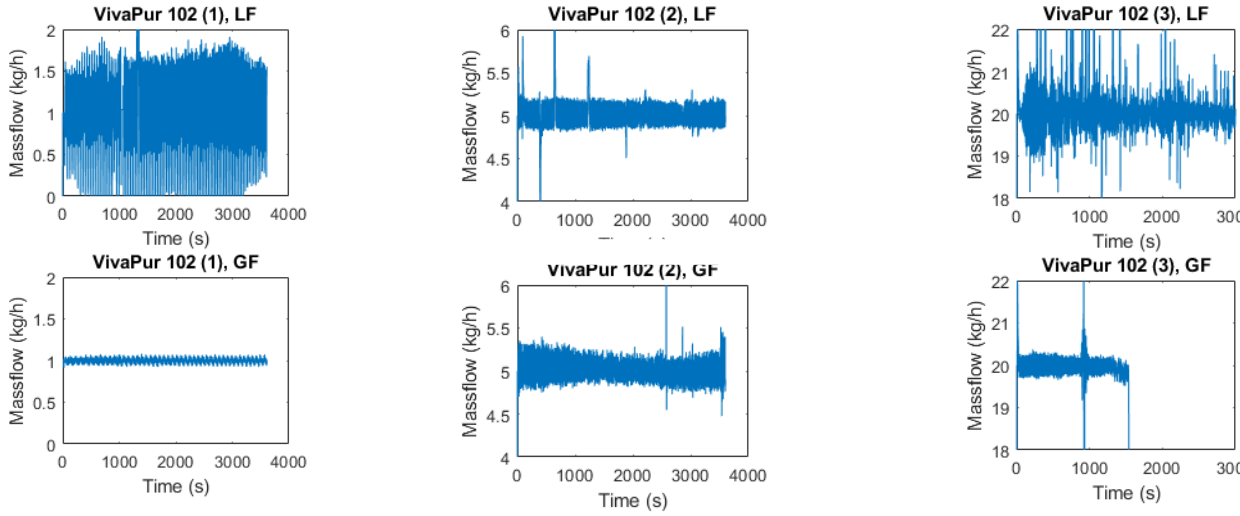
Standard feeder | Granule feeder | Micro feeder | Modified micro feeder

Figure 2: Feeding of PROSOLV® EASYtab at Three Rates Using the Granule Feeder.



- 1 and 5kg/h mass flow were stable
- 20kg/h stable until disturbance appeared at 20min 20 sec (hopper size ~10kg)
- Most propable at this time point, fill level reached the point of impeller of feeder

Figure 3: Feeding of VIVAPUR® 102 Using Standard Feeders and Granule Feeder.



major components: excipient composite and the microcrystalline cellulose (MCC). A micro feeder (twin concave coarse, short pitch screws) and a modified micro feeder (twin concave fine screws) were used for the minor components: sodium starch glycolate, sodium stearyl fumarate and colloidal silicon dioxide.

Three feed trials of the major components (excipient composite and MCC) were conducted for one hour in each case at three different feed rates: 1 kg/h, 5 kg/h, and 20 kg/h. The number of runs was three (n = 3). The minor components were tested at two feed rates, 0.050 kg/h and 0.125 kg/h, each for an hour and then repeated (n = 3).

Test runs for the excipient composite using three different standard feeders at rates of 1 kg/h, 5 kg/h, and 20 kg/h demonstrated stable mass flow throughout. At 20 kg/h, however, less variability was seen at the end of the run, possibly suggestive of some type of shear effect when there is a large mass of material in the hopper. When the granule feeder was used instead of the standard feeder for the same experiment, the 1 kg/h and 5 kg/h mass flows were quite stable, but feed at 20 kg/h suffered a disturbance (see **Figure 2**). Inspection of the unit showed that the level of material had fallen below that of the agitator responsible for delivering a steady flow to the screws. This resulted from the feeder compensating for the low level, causing greater variability.

Figure 3 presents the results obtained when feeding MCC alone. Using the standard feeder, the mass flow plot is very noisy and indicates that material does not flow well at either 1 kg/h or 20 kg/h, but improves at 5 kg/h. In contrast, when the granule feeder was used at 1 kg/h, the feed was very stable. At 5 kg/h, it became a little noisier, but at 20 kg/h material again fell below the impeller and the run was stopped. One reason for the poor feeding of MCC is that, even though the feeders were grounded, the strong electrostatic charge in the MCC causes it to build up on the feeder outlet. This is less likely to happen with the

excipient composite because the colloidal silicon dioxide present tends to discharge static.

Moving to the minor ingredients, which were fed using the micro feeder and the modified micro feeder, the disintegrant (sodium starch glycolate) fed quite well through the micro feeder at 50 g/h, but was much noisier at 125 g/h. With the modified micro feeder, feeding was efficient at both flow rates. Feeding of the lubricant (sodium stearyl fumarate) was better with the modified micro feeder than with the unmodified feeder, but the material did not feed uniformly in either scenario. The colloidal silicon dioxide could not feed at all, due to its high cohesivity and very low bulk density. As a result of this finding, colloidal silicon dioxide was blended in with MCC for subsequent studies.

Case Study 2: Effect of Feed Rate and Mixing Speed on PSD. The Modulomix continuous modular mixer (Hosokawa Micron BV) used throughout these studies features an impeller that runs at high speed. It, therefore, introduces high shear, thus raising concerns that it might cause granule breakage for both the composite and co-processed materials, affecting PSD and possibly the integrity of the final product.

To test this, the excipient composite was blended at various feed rates (1–20 kg/h) and mixer speeds (450–500 rpm). PSDs of the blended materials and of an unprocessed control sample were determined using laser diffraction particle size analysis. The results in **Figure 4** show PSD at D10, D50, and D90. In each case, the blue plot on the left is the unprocessed material and, moving across the graphs, it can be seen that there is essentially no change to the PSD of the excipient composite regardless of the feed rate or mixer speed.

Case Study 3: Continuous Direct Compression. The final study compared two formulations in continuous direct compression tableting. The continuous process set-up comprised Coperion K-Tron loss-in-weight feeders, a Modulomix continuous mixer, and a PTK-PR1000 tablet press. **Figure 5** lists the production settings used. Formulation 1 was made up simply of the coprocessed high-functionality excipient composite plus API, which only requires two feeders. Formulation 2 was the individual excipient components including pre-blended MCC, colloidal silicon dioxide, Sodium Starch Glycolate (EXPLOTAB®, JRS PHARMA), Sodium Stearyl Fumarate (PRUV®, JRS PHARMA), and the API. Here, the individual ingredients were fed separately using four separate feeders, an operation that requires the application of a considerable number of controls to ensure feeding at consistently proportional rates.

For both Formulation 1 and Formulation 2 in this set-up, the weights and API content of the resulting tablets were close to target, with low standard deviations. However, when the tablets were examined more closely, the crushing strength was somewhat lower for those produced using Formulation 2 than for Formulation 1 (see **Figure 6**).

Overall findings. The work conducted in Case Study 1 demonstrates the excellent feeding performance of the

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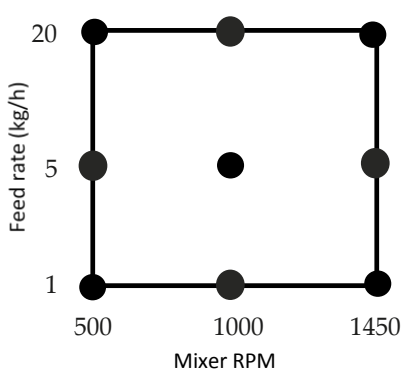
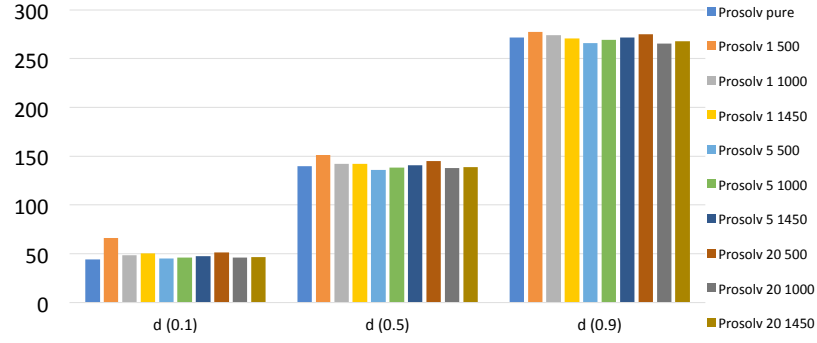
Figure 4: PSD Using Laser Diffraction of PROSOLV® EASYtab SP at Various Feed Rates and Mixer Speeds.





- PSD was measured with laser diffraction after the blending
- No impact on PSD

Figure 5: Production Setting Used for Case Study 3.

Production settings, Formulation 1

Total feed rate	**11.520** kg/h
PROSOLV feed rate	**10.944** kg/h (standard feeder)
API	**0.576** kg/h (standard feeder)
Mixer rpm	**900** rpm
Tablet press rpm	**60** rpm
Pre-compression force	**1-2** kN
Main-compression force	**10** kN

Production settings, Formulation 2

Total feed rate	**11.520 kg/h**
Pre-blend (MCC+CSD)	**X kg/h** (standard feeder)
EXPLOTAB	**X kg/h** (micro feeder)
PRUV	**X kg/h** (modified micro feeder)
API	**0.576 kg/h** (standard feeder)
Mixer rpm	**900** rpm
Tablet press rpm	**60** rpm
Pre-compression force	**1-2** kN
Main-compression force	**10** kN

Figure 6: Weight Variation and Tablet Hardness of 20 Tablets, Formulations 1 & 2.

Samples @20min	Formulation 1		Formulation 2	
Tablet	Mass	Strength (N)	Mass	Strength (N)
1	201,27	133,4	202,66	121
2	202,93	140,3	199,34	117,4
3	200,4	134,8	202,33	128,3
4	200,83	131,8	204,77	130,1
5	198,78	132,2	200,32	118,1
6	198,95	135,4	202,59	135,9
7	203,39	144,5	200,77	119,1
8	201,76	140,1	202,26	129,2
9	199,54	132,5	199,84	115,2
10	199,88	141,5	200,45	115,9
11	201,91	144,9	202,05	133,7
12	202,39	141,4	202,3	133,6
13	200,88	127,8	199,84	124,5
14	201,21	137	200,44	125,6
15	198,69	130,3	201,57	133,8
16	202,08	140,6	200,98	122,8
17	199,32	140,1	201,57	120,6
18	199,76	134	201,53	132,1
19	201,79	146,8	201,7	128,6
20	199,46	141,3	202,29	130,3
avg	**200,76**	**137,54**	**201,48**	**125,79**

excipient composite compared with feeding individual pure components. The latter presented considerable challenges, with colloidal silicon dioxide proving impossible to feed at all, thus not allowing for a true continuous process.

The second case study showed that the excipient composite withstands high shear forces during blending, suffering no effects on PSD. Therefore, it is a rugged composite that does not break up even when subjected to the vigorous conditions.

Finally, the third case study shows that in continuous direct compression, binary mixtures of the excipient composite and API produced tablets of equal or higher quality than those from the powder blend containing individual components.

Conclusion

Continuous manufacturing with the binary mixture of excipient composite and API was easier to set up, run, monitor, and clean than using the individual ingredients. With fewer feeders required, it also occupied less space. The coprocessed high-functionality excipient composite (PROSOLV® EASYtab SP, JRS PHARMA) proved highly suitable for direct compression tableting. In practice, using such a composite rather than the individual excipients makes it likely that far fewer in-process feedback and feed forward controls will be needed, along with a reduction in PAT. Since the end-product may also be more amenable to real-time release, this both simplifies and accelerates production.

Reference

1. P. Kleinebudde, J. Khinast, J. Rantanen, Eds.*Continuous Manufacturing of Pharmaceuticals* (Wiley, 2017).