Hands-on Lean Plus

PEER REVIEWED

Socio-economic pressure as well as increasingly strong competition has clearly made the entire healthcare industry focus a lot of attention on reducing costs. Not so long ago *Costs per kilogram, OEE, and number of Stock Turns* were 'alien' indicators to the pharmaceutical industry, but now they are considered virtually 'holy' figures.

As usual, this industry takes things quite seriously, and has perhaps sometimes taken too much of an academic approach.

Time to place both feet firmly on the ground.

This article delivers some hands-on examples that will help improve your solid dosage facility, all approached from a *powder handling* point of view.

Common sense….

But First This

The debate on the benefits of 'continuous' versus 'batch' will certainly carry on for a while longer, and much like the classic 'nature or nurture' discussion, the outcome is likely to pitch somewhere in the middle rather than one way or the other. It requires case-by-case evaluation and not a magical *one-size-fits-all* approach.

The point is that a continuous and automated plant, probably designed for a single product, does not cope very well with the frequent changeovers that are required to address increasing numbers of type variations. A surplus of manpower, not needed once the plant is running, is back on the payroll straight away in order to fulfil the frequent and complete line dismantling requirements associated with cleaning to simply be able to realise changeovers to other products. The demand for this kind of flexible manufacturing only seems to grow further and further.

Still today, many equipment and plant designs are not effective at coping with rapid changeovers, and production managers are often forced to slip back to the notorious 'campaigning' or 'white to black' scheduling methods, all leading to increased inventory; the biggest *waste* of all.

It makes perfect sense to further invest in the development of a continuous process line as a potentially effective principle for the production of a single product family only. But in parallel, there is a huge field to be explored of so-called 'low-hanging fruit', ready to be picked. This field concerns *batch-operated (multi-product) solid dosage facilities.*

In a flexible environment, the quickest changeover is achieved when the discrete unit operations can work in parallel and independent from one another when necessary (one step being processing while the next one is cleaning). This typically leads to the use of buffering intermediate bulk containers (IBCs) for the transfer of batches – or lots – from one process to the next.

It All Starts with Powder

Materials handling in an oral solid dosage (OSD) facility starts with raw materials in powder form. If they are free-flowing, they are prone to segregate, and if they are poor-flowing, they get stuck easily, creating serious process transfer problems. And then there is everything in between…

Segregation during transfer can be avoided by using dense phase vacuum transport, but such a method is relatively slow and increases cleaning times. A better solution is to use gravity and IBCs, or inter *process* containers (IPCs) as they are sometimes called.

A must is to then design the 'bin' for *mass flow* because funnel flow will give 'rolling' – segregating – effects. Only when the product is really free-flowing (which is hardly ever the case) is mass flow easy, provided the IBC has steep angles at its conical lower part. However, these angles create height and consequent additional investment for cleanroom dimensions, as well as operational cost for extra room-cleaning time – an unnecessary waste.

Using *cone valve* technology not only reduces this height issue (the lifting cone promotes mass flow in itself, so steep bin angles are not required), it also covers another notorious problem: *bridging & blocking.* Besides creating a potential quality issue, the product getting stuck has to be avoided for two main reasons.

First, when the feed is interrupted, the effectiveness of the process is seriously in jeopardy. This could mean, for example, that a tablet press performs, on average, to only two-thirds of its design capacity!

Secondly, if the transfer is completely stopped due to serious bridging, the IBC has to be opened in order to provide for a manual intervention of some description. Containment is lost and cleaning of the area is the consequence. Cleaning is a waste in itself but also consider that the overall equipment effectiveness (OEE) of the process reduces even further.

In short: modern cone valve technology prevents these issues and increases process OEEs, as well as reducing cleanroom investment costs immediately.

Figure 1: Cut-through photo of a Cone Valve IBC System

Traditionally, inter process transfer layouts had a low priority in terms of building design and process equipment selection.

It is only recently that there has been early recognition of the significant impact which batch transfer methods have on the 'lean success' of a plant. This is why professional plant design engineers nowadays keep the handling aspects in mind from day one of the conceptual stages.

Let's briefly focus on some practicalities around the typical pharmaceutical unit operations.

Dispensary

Traditionally, dispensing is a very manual job (sack-tipping, drum-tilting etc.). Modern manufacturing execution systems (MESs) can provide reasonable security that the formulation of the batch is correct, but only indirectly, and the process is still sensitive to operator error. Although improving the level of quality assurance, automatic dispensing systems are quite hard to financially justify. Only high-running single-product facilities or larger multi-product (generic) companies can afford *automatic* or semi-automatic raw material formulation systems and achieve a proper return on investment (ROI).

For such an investment, typically the raw material consumption should be in the region of at least 3000-5000 tonnes per year or 1-2 batches (or dispensed 'lots') per hour. Figure 2 shows such an IBC-based flexible automated recipe formulation system, as used for example in the infant formula industry. Similar systems for large quantity excipient dispensing have come into play and might get more attention in the near future.

Figure 2: Flexi-Batch® Automatic Formulation/Dispensing System

Granulation

Although quite a wasteful process, batchwise wet granulation is still the most popular way of improving the flow properties of a powder. Normally the starting materials do not possess the best properties from a flowing point of view, and bridging or blocking often occurs.

Sometimes an improvement can be found by using granulated excipients or by the addition of flow improvers that do not add value to the medicine in any other way. However, this is not a very cost-effective solution.

Here the proper choice of IBC can improve matters drastically, using one of the styles described earlier. Compared with a butterfly valve, a cone valve IBC has the additional benefit of a significantly increased discharge speed into the 'waiting' downstream process.

This has a positive effect on the OEE of the granulator and its overall output. To put this in perspective, for high-capacity process lines, up to 80 hours of extra 'free' granulation time per year can be achieved. If the pre-granulation batch does not flow well, this can increase much further!

Another widespread granulation method is 'dry' roller compactor-based granulation, which is still gaining popularity. Clearly the continuous nature of the process (no scale-up issues), as well its relatively low energy consumption, is largely responsible for this.

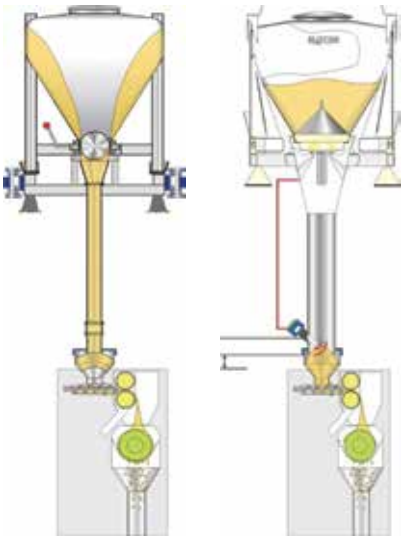
Here *controlled,* rather than fast, transfer is the goal. Often roller compactors are *flood-fed* and for good-flowing powder blends, this works fine, although segregation problems can easily appear. However, there is a contradiction here: why would you granulate a free-flowing, uniform blend in the first place…?

The reality is that the materials that are fed are not so easily flowing after all, with bridging often occurring, especially when batches become bigger.

In addition, product densities at the start of the batch transfer can be higher than at the end, due to differences in powder load from top to bottom. The auto-adjusting roller pressure can cope with feed variations to a certain extent, but certainly more consistent flake thickness results are found when the vertical screw-feed hopper of the machine sees a more or less constant quantity of powder, refilled volumetrically with level probe control. A cross-feeder could also provide for this, however this type of equipment also requires extra cleaning time.

A butterfly valve is not suitable for controlling powder flow, whereas cone valve IBCs are. Such a refill system can basically mimic the validated laboratory conditions of hand-feeding the roller compactor.

Figure 3a: Roller Compactor Feed - Flood-Feeding Principle
Figure 3b: Roller Compactor Feed - Controlled Feeding Principle



Blending

A prime benefit of an IBC blender over a stationary blender, such as V-cone or hexagonal ones, is the intrinsic containment of the batch inside the blender chamber, which is in fact the IBC itself (see Figure 4a). There is no transfer of powder *into or from* such a blender, which ensures the absence of room 'contamination'. The blender does not require cleaning between product or batch changes (nor does the room, for that matter). The IBC needs to be washed eventually, but this operation takes place after final transfer of the blended batch to the next process – *after* it goes ''off-line'' and is no longer influencing effectiveness.

The additional investment costs of a single IBC tumbler compared to a stationary one is to be offset

against its much higher OEE and consequential overall blending throughput. Up to three times as much is not uncommon. In addition, stationary blenders need to be placed in separate (costly) cleanrooms due to the powder transfers taking place, whereas IBC blenders can be part of an open design materials handling floor.

Combining the IBC blender with cone valve technology reduces – if not eliminates – segregation effects that could occur when discharging traditional bins or emptying a stationary blender. Nowadays, bins from 500 to 3000 litres can be placed in one and the same machine.

Figure 4a: IBC Blender
Figure 4b: V-cone Stationary Blender

Tablet Press or Capsule Filler

Here all materials handling issues come together. Bridging or blocking requires operator intervention and is devastating to the machine's effectiveness (for example, Metformin is notorious for bridging). If flow is a bit better but not totally perfect, segregation starts to kick in, which would call for cone valve technology, proper venting and absence of container vibration.

Before fixing building or compression room heights, proper attention must be given to the materials handling aspects of the plant. Enough space should be available above the presses in order to gravity-feed directly from the IBC above. This space should be determined by economic batch or lot sizes and matching powder IBCs, and *not* the other way around. If the 'Lean' exercise calls for big batch IBCs, a 'through-floor' application should be considered. Technology exists to prevent segregation following the drop through a longer chute.

Figure 5: Feeding a tablet press 'through the floor'

Tablet Handling

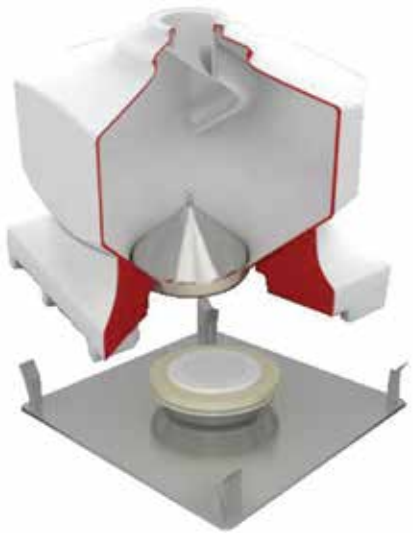
Many OSD factories handle their tablets in small kegs, drums or boxes. A complete, compressed batch can take up to 20 - 50 of these units. It is a very time-consuming and wasteful activity to split up a batch in so many small operations:

- Collect empty drums
- Add liner
- Close the liner
- Place a lid
- Print off a label and attach it to the drum
- Place the drum on a pallet

If you are able to collect the tablets in a gentle non-damaging manner in a tablet IBC (Figure 6) of a size that matches the next process step (e.g. coating), then the operating time is reduced considerably.

This requires a special type of IBC like the one illustrated; it has a special inlet chute to protect the fragile tablets.

Figure 6: High-density Polyethylene Tablet IBC



Around the Coaters

Especially when filling and emptying the faster film coating equipment, a significant capacity increase can be obtained when utilising full-batch IBCs rather than individual drums or kegs. Because the *waiting* of the machine is drastically reduced, the full-batch loading and unloading systems can increase the overall coating output by 20-30%.

Loading the Primary Packing Lines

Like the coating process, loading the line with a full-batch IBC provides for much-reduced handling, labelling and registering of the individual drums. An important addition to this is the significant reduction of open transfers. A full-batch IBC placed on top of a blister or bottle-filling line has only one connection and a much-reduced risk of contamination.

Figure 7: Matcon IBC loading a blister line

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