Making the Grade

Conventional multiple unit pellet systems can often present drug manufacturers with formulation difficulties. However, an innovative tablet production line has been developed that eliminates segregation and significantly increases process yield

By Jan Vogeleer at Courtoy

Keywords

Multiple unit pellet system
Process yield
Particle segregation
Uniform blending
Out of specification concentration

Many pharmaceutical manufacturers have reported that producing multiple unit pellet system MUPS) tablets, using conventional bin blending to feed a tablet press, poses significant challenges regarding process yield, productivity and batch content uniformity. This is because MUPS blends are susceptible to particle segregation. However, a new production method has been developed that eliminates these inefficiencies and product quality risks.

MUPS is a pharmaceutical solid-dosage form produced by compressing a mixture of drug-containing pellets and powder excipients (see Figure 1). The pellets have a spherical core that contains or is coated with the active ingredient, and have one or more protective layers to control drug release. The powder phase typically comprises a pre-mix, which contains components such as fillers, binders, lubricants and a disintegrant. On the whole, the pellets in a MUPS formulation have a mass percentage of 20-70% and range in size from 300µm to 2,000µm, whereas the excipients are usually smaller than 200µm. As a result, MUPS formulations can behave very differently in terms of flowability, compressibility and the risk of segregation, depending on the concentration and size of the pellets.

Blend Uniformity

The particle size of the powder phase excipients is typically between 50µm and 200µm, whereas the bulk density of the pellet phase is generally greater than 0.7g/cm^3, and the density of the excipient mixture is 0.4-0.6g/cm^3. These significant differences in average particle size and density make a MUPS mixture extremely sensitive to segregation. Therefore, it is vital to maintain blend uniformity during storage, transport and feeding of the MUPS formulation into the tablet press, right up until when the blend is fed into the dies for compression.

If segregation occurs during transfer, tablets could be produced with an out-of-specification (OOS) pellet concentration and, therefore, an OOS active pharmaceutical ingredient (API) content. The uniformity of the produced batch would subsequently fail quality assurance checks, and the batch would have to be rejected.

Production Method

MUPS formulations are typically prepared by dry blending the pellets and excipients in a bin blender and discharging the mixture into a drum

Figure 1: MUPS tablet

Figure 2:
MUPS segregation

or intermediate bulk container (IBC). The IBC is then transported to a storage area or compression room, where the outlet chute is connected to the inlet of the tablet press. During these procedures, percolation and heap segregation might occur inside the container as a result of vibration and gravity. This means that blend uniformity inside the container cannot, in many cases, be guaranteed (see Figure 2).

When the container discharge valve is opened, the MUPS formulation drops into the tablet press feed chute and paddle feeder. Elutriation segregation will occur during the descent. If the IBC is not properly vented, this type of segregation will also occur inside, owing to air movement through the blend bed. These multiple occurrences of segregation often result in severe blend composition variations within the batch, and the pellet content of the resulting tablets may vary significantly. As a result, during the compression process, large quantities of OOS tablets are produced – mainly, but not limited to, the beginning and end of the batch.

Unfortunately, at this stage, it is not possible to detect whether the pellet content of a tablet is within specification or not, and so OOS tablets cannot be identified and rejected by the tablet press. Generally, these limitations are dealt with by one, or both, of the following:

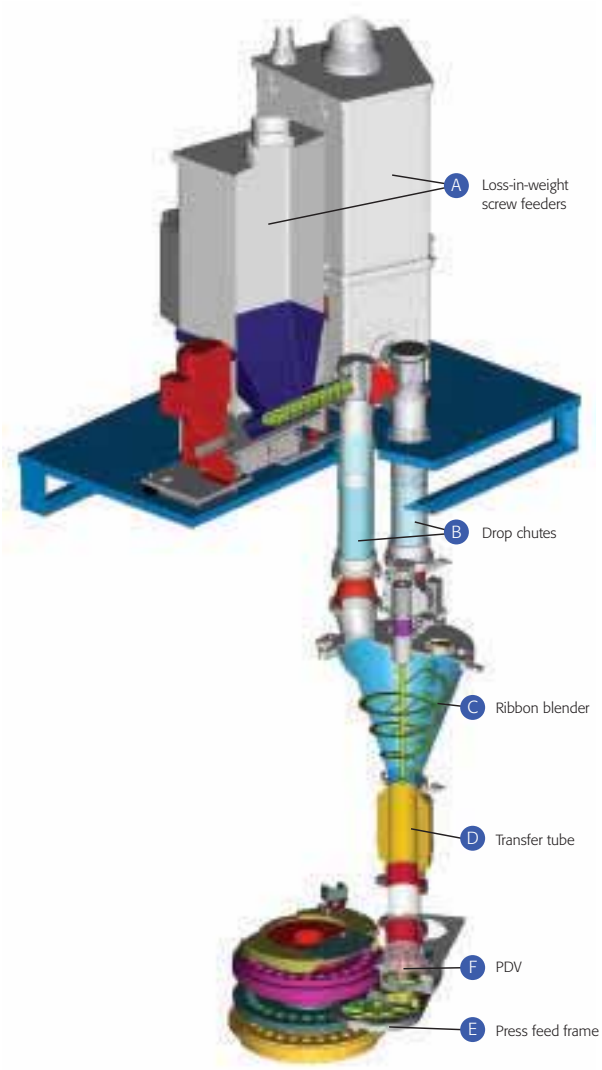
- Rejecting a fixed amount of tablets at the beginning and end of the batch – up to 15% in some cases
- More frequent tablet sampling and API analysis to assess batch uniformity. If too many tablets fail the analysis, the entire batch is rejected

Clearly, this is a wasteful production method that results in poor productivity and yields. There is also a significant quality risk linked to releasing OOS batches.

Continuous System

To increase process yield and guarantee tablet quality, an innovative new MUPS production method – a continuous dosing, blending and compression system – has been developed (patent pending). This system eliminates the production inefficiencies and quality risks by minimising segregation and monitoring the process online to detect OOS tablets (see Figure 3).

Figure 3: 3D representation of MUPS feeding system



Two loss-in-weight screw feeders, either gravity or vacuum fed, are installed above the tablet press – one feeds the pellets and the other feeds the premixed excipients. The type and configuration of the feeders can be adapted to the characteristics of the pellet or powder phase and fine-tuned for particular applications. Both the pellets and excipients are continuously fed via drop chutes into a conical ribbon blender above the tablet press, which mixes the two product streams into one uniform MUPS formulation stream that feeds the tablet press. The fill level of the blender is accurately controlled as it determines the residence time in the blender and hence the blending time.

The conical blender is installed directly above the tablet press inlet to minimise the transfer distance between blending and compression and reduce the risk of segregation to an absolute minimum. The transfer tube from the blender to the tablet press feed frame measures approximately 60cm and could induce segregation if it was directly connected to the paddle feeder. To avoid this, a special valve was developed to ensure 'plug flow' via a vertical powder feed tube: the powder dosing valve (PDV). The PDV is mounted just above the paddle feeder inlet and driven by a separate electromotor. Finally, the design of the feeder base plate and paddle wheel have been modified to avoid segregation, as well as pellet damage, in the feed frame.

Enhanced Process Yield

This continuous dosing-blending-compression system has been developed, built and extensively tested (see Figure 4). The results were significant:

- Stable content uniformity is ensured throughout the entire batch, decreasing the risk of batch rejection
- Start-up losses were reduced by a factor of three (from 15% down to 5%), and further reduction possibilities have been identified
- Process stop and restart occurs without any product losses
- End-of-batch is accurately controlled with minimal product loss
- Tablets with an increased risk of OOS pellet content are detected and rejected

The system can be further enhanced with an integrated dual control system that measures two quality parameters for each tablet (thickness variations under constant pre-compression force and peak force at main compression) as opposed to a single parameter (peak force at main compression) in conventional presses. By measuring and combining these two signals, tablets with a deviating pellet concentration can be detected.

Figure 4: MUPS trial machine

It cannot predict the pellet concentration, but can detect tablets with an increased risk of OOS pellet content. Such tablets can then be rejected, which significantly reduces the risk of producing a batch that does not meet content uniformity criteria.

Jan Vogeleer is Managing Director of Courtoy Compression, part of GEA Pharma Systems and manufacturers of tablet presses in Belgium. He has a wealth of experience as an innovator of novel compression technology and has pioneered the design of new solid dosage equipment, increasing production speeds, reducing cleaning times and minimising downtime.
Email: courtoy@gea.com