Important considerations include selecting which granulation to use in which layer, monitoring layer weights, and preventing cross-contamination.

The pharmaceutical industry’s interest in bi-layer tablets has grown because they promote patient convenience and compliance. They do so by combining multiple active pharmaceutical ingredients (APIs) in a single dosage form while avoiding chemical incompatibilities between APIs by physically separating them.

Bi-layers also enable pharmaceutical manufacturers to create controlled-release drug profiles and apply osmotic push-layer technology. Other benefits include patent extensions, marketing advantages, and brand recognition. But making bi-layers presents some challenges. This article discusses some tools and techniques to help you overcome them.

Bi-layer tabletting follows a principle similar to that of single-layer compression, except that the bi-layer operation compresses two granulations, one on top of another in layers. This process requires two systems of feeders, dosing stations, and compression rollers.

Selecting APIs for layers

To develop a bi-layer tablet, you first must determine which granulation will be which layer. The bottom layer, or layer one, allows a greater weight and typically, tablet presses permit up to 19 millimeters of fill depth. The layer-one dosing process is identical to that of single-layer operations, and selecting the fill cam size is critical because excessive overfill can lead to material waste and unacceptable product yields [1].

The punch penetration allowed by the upper compression roller limits the weight of layer two, the top layer of the tablet. Eight millimeters is a typical maximum value for the industry’s multi-layer tablet presses, but you can increase that value by increasing the overall length of the upper punch. It is possible to increase that value by another 2 to 4 millimeters if the tablet press allows it.

To determine if it does, inspect the upper punch’s clearance as you manually rotate it 360 degrees on the tablet press, with all parts installed, including the feeders. The additional length requires adjustments in the human-machine interface software to increase the values of the upper punch’s penetration above what the Tableting Specification Manual lists as the standard operating limit for the upper punch, which is 133.35 millimeters. In the Eurostandard the limit is of 133.60 millimeters.

Compaction characteristics

Another factor to consider in layer selection is the granulation’s compaction characteristics. Layer one experiences two compression events, whereas layer two experiences only the final compression stage. Undergoing two compression events—one of which is essentially the pre-compression stage—means that a granulation that compacts poorly or that is strain-rate sensitive may be better as layer one. That may also pay off if you scale up to a high-speed bi-layer tablet press because any challenges you face on a small-scale R&D machine will worsen on a larger-scale machine due to its higher loading rates and shorter dwell times and because the two compression events will increase total compression time [2].
Figure 1 shows the profiles of two formulations, one with poor compaction characteristics and one with acceptable compaction characteristics. The direct-compression blend (DB), shows an increase in tablet strength up to 100 megapascals of compaction pressure, after which it loses strength due to capping. The wet-granulated blend (WG) shows a continuous increase in tablet strength as compaction pressure increases.

If those two blends are to be used in a bi-layer tablet, the DB blend is clearly the better candidate for layer one. In bi-layer tabletting, layer-one compaction involves a tamping force only—consolidating the material and reducing its volume in the die—which leaves room for the second-layer material. The light amount of force also reduces air entrapment and creates more particle-to-particle contact sites that are favorable for bonding when the final compression event occurs.

The profile in Figure 2 is for a material that is strain-rate sensitive, which means it’s affected by turret speed, dwell time, or both. As turret speed increases, the robustness of tablets made from the DB blend suffers, whereas tablets made from the WG blend are insensitive to speed. In this case, too, the DB blend would be better as layer one.

**Weight measurement**

Another challenge associated with bi-layer tabletting is controlling and measuring each layer’s weight, which pharmaceutical manufacturers typically achieve by sampling or separating the layers and measuring them independently. A high-quality force-instrumentation system designed for bi-layer tabletting can provide real-time measurement of each layer’s weight. Using that data, you can establish a force-weight profile for each layer’s material and set force limits based on acceptable weight tolerances.

Look for a force-instrumentation system that accommodates custom sensors with a high-sensitivity output at the required measured force. A typical 100-kilonewton button load cell for layer one does not fit that criterion because the required tamping force for bi-layer tabletting is typically less than 1 kilonewton, which is less than 1 percent of the button load cell’s full-scale loading. With that range, it cannot provide the accuracy and high-sensitivity output required. A 10-kilonewton full-scale, roll-pin sensor is a better fit for the application. It can be used to measure the force at each punch station for each layer, identify weight issues for individual layers, and alleviate the need for frequent sampling.

**Cross-contamination**

Bi-layer tabletting also poses the challenge of preventing cross-contamination between layers, necessitating proper press setup and an efficient vacuum system. A high-quality tablet press with tight tolerances is also very important. Worn die pockets and excessive turret runouts are common causes of cross-contamination. Even with a high-quality tablet press, cross-contamination can occur from the chamfer where the punch enters the die. Powder can accumulate in the chamfer and contaminate the other layer. To prevent that, use dies with a radius edge at the die bore instead of a chamfer. This is called a multi-layer lead-in and will eliminate powder accumulation.

Establish a force-weight profile for each layer’s material and set force limits based on acceptable weight tolerances.

**References**

