Seeking stronger bi-layer tablets

The advantages of oral tablets are well known, but their formulation and manufacture are often challenging, and developing tablet products relies largely on empiricism. Indeed, the many unresolved issues associated with tablet development have led researchers to adopt a Quality-by-Design (QbD) approach. QbD, of course, is based on the premise that we have a scientific understanding of the materials and processes involved. It also presumes we can suitably implement the engineering, as outlined in the Materials Science Tetrahedron (MST) concept [1].

While tablets may comprise one, two, or more layers, innovative bi-layers continue to attract the interest of pharmaceutical manufacturers. Not only do they expand product portfolios of fixed-dose combination products, but they also preserve the commercial value of drug molecules. They also enable formulators to easily manipulate release profiles and thus maximize therapeutic effects. Examples include Ambien CR and Paxil CR, both are bi-layers that comprise an immediate-release layer to provide fast action and an extended-release layer to maintain the correct plasma-drug level for hours. In addition, the separation of layers enables bi-layers to deliver two chemically incompatible drug molecules in one tablet. That benefits patients because it eases the pill burden and therefore boosts compliance. Bi-layer tablets also supply the cores of osmotic-pump tablets that can provide zero-order drug release.

Strength tests

The mechanical strength of conventional single-layer tablets is understood much better than that of bi-layer tablets. This gap in understanding stems, in part, from a problem unique to multilayer tablets: insufficient interfacial bonding strength (IBS) between layers. Past efforts to understand this particular problem have been uneven. That is, several factors have been shown to influence IBS, but a mechanistic understanding of the problem has remained elusive. In the last 2 years, however, my colleagues and I have applied a systematic approach to identify and clarify the mechanisms that govern the IBS of bi-layer tablets.

First, we conducted a head-to-head comparison of the two common methods of measuring IBS: shear and tensile tests. The results showed a strong correlation between them, meaning that conclusions obtained in a study using the shear-strength test method can be used to guide another study on IBS using the tensile-strength method and vice versa. Second, we observed that IBS is sensitive to both the material used and the compaction pressure applied, especially the pressure used to make the first layer. For example, when first-layer compaction pressure increases, IBS decreases much more sharply when the tablet is made from an excipient in which plastic deformation dominates (e.g., microcrystalline cellulose, or MCC) compared to one in which brittle fracture dominates (e.g., lactose). This suggests that surface smoothness of the first layer likely plays a critical role in the development of IBS during the final compaction of a bi-layer tablet.

We also learned that brittle-fracture excipients don’t all perform the same way. Among several grades of lactose we studied, SuperTab 24AN (DFE Pharma) provided the highest IBS. Furthermore, we observed—to our surprise—that the direction of ejection affected IBS. For otherwise-identical bi-layer tablets, the layer that was in contact with the advancing punch tended to fracture. This suggests that sufficient stress develops during ejection to deteriorate the mechanical strength present when the tablet is in contact with the punch. Lastly, the IBS of a lactose-MCC bi-layer tablet undergoes a complex change as the ratio of MCC to lactose changes. Initially, the IBS increases, but once MCC exceeds 20 percent, it decreases until 80 percent MCC. Then the IBS rises again when the tablet comprises between 80 and 100 percent MCC.

These observations are fascinating, and we’re continuing our studies in order to explain them. That will require in-depth investigation of the structures of both individual layers and their interface. Using the MST as a guide, we hope the efforts in our laboratory will shed light on this challenging problem and help pharmaceutical manufacturers create more robust bi-layer tablets. Stay tuned.

Reference


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