This article explores the challenges of multilayer tablet formulation and the approaches developers can take to overcome those challenges.

While the use of biologics has grown in recent years and has drawn much attention, oral solid dosage forms (OSDFs) remain the pharmaceutical industry’s staple. OSDF manufacturers are continuously innovating and exploring ways to reformulate solid-dose products to renew patents and improve efficacy and patient compliance.

Manufacturers are creating effective treatments for an increasing number of major diseases and are gaining a better understanding of comorbidities and the possibilities
of combining patient medications. The efficacy of current treatments is often limited by poor patient compliance resulting from the burden of taking multiple medications daily. Combining multiple active pharmaceutical ingredients (APIs) or combining more than one release profile for the same API in a single dose is often a win for both patients and drug product developers.

Multilayer tablets have emerged as an elegant way to deliver multiple therapeutic payloads in a single dose. Multilayer tablets consist of two to four separate formulations compressed into a single tablet in layers (although three- and four-layer products are rare). Each layer can have a different API and/or release profile, allowing developers to create more effective combination products than with standard tablets. The API levels in the different layers can be the same or different. Multilayer tablets are also particularly relevant as the industry moves toward more patient-centric therapies.

Creating such simplicity for patients poses challenges for developers and manufacturers. Formulation considerations include API incompatibility, the compression requirements of different materials, and excipient selection. Multilayer tablets must also have adequate mechanical strength and hardness to endure processing, handling, packaging, and transport. Difficulties include inadequate hardness, imprecise control of layers and tablet weight, elastic mismatch between conterminous layers, and susceptibility to delamination during manufacture.

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Though matrices may be incompatible with one another, multilayer tablets allow formulators to insert an inert barrier layer between incompatible matrices to prevent interactions. In this connection, formulators have leverage to develop combination products.

If the APIs’ chemical stability is still not acceptable, an alternative is to add a buffer layer between the two API-containing layers. The buffer layer blocks activity at the interface between the two APIs. This approach often leads to a final drug product with superior chemical stability.

Flexibility in release profiles

Multilayer tablets allow a single dose to deliver two APIs with unique in vivo release profiles or to release the same API in two or more different release profiles. Essentially, formulators can develop products that offer both immediate and sustained release for an API. A common approach is to use hydrogels (cross-linked polymer networks), which swell in liquid and sustain release in one portion of the tablet, while the API releases immediately in the other portion.

Fixed-dose combinations also offer formulators the opportunity to create products where APIs potentiate each other to increase efficacy at lower doses and/or change therapeutic indications. Vicoprofen (the brand name for the combination of hydrocodone and ibuprofen) is an excellent example of a combination product in which two APIs work synergistically to enhance effect—ibuprofen reduces inflammation in an area, which facilitates access for the hydrocodone and improves analgesic performance.

This combination of several APIs, release profiles, and potentiating effects of APIs in one tablet simplifies the dosing regimen and contributes to better patient adherence.

Regulatory pathways

To extend the patents on their products and accelerate development, manufacturers are increasingly filing new drug applications following the FDA NDA 505(b)2 pathway, which offers relatively shorter clinical development times as well as economic incentives. Products pursuing this pathway most commonly include new indications and improvements to existing products’ bioavailability. Multilayer tableting can play a critical role in formulating such improved products by increasing dosing convenience and, therefore, improving patient adherence and allowing for new fixed-dose combinations and controlled-release products.

Summary of key challenges

Common problems associated with multilayer tableting include delamination at the interface between the layers due to insufficient adhesion, incomplete segregation of tablet portions, relatively low yield compared with conventional single-layer tablets, and difficulty in achieving the desired weight of individual layers.

Delamination most commonly occurs between adjacent layers but can occur internally in an individual layer after compression, at any point during subsequent processing, or even during storage. This may result in patients receiving an inadequate dose.

Compression

Multilayer tablet presses use a standard upper punch, lower punch, and die assembly on a rotating turret. Whether the tablet has two, three, or four layers, initial layers are compressed with relatively light forces, while the final layer is compressed using the main compression force.

A successful multilayer tableting process requires careful selection of the excipients and process parameters as well as careful study of the mechanical properties of the materials being used. Understanding the nature and physicochemical
properties of both the active and inactive ingredients and how those properties determine the strength and integrity of the multilayer tablet is key. Parameters such as brittleness, viscoelasticity, plasticity, and compaction properties significantly affect the amount of compression required for each layer during manufacture.

Selecting the tablet’s first layer is important because the weight and control of the subsequent layers depend on the fill of the first layer. Compression force significantly influences the strength and interfacial adhesion between the layers, which further influences the mechanical integrity of the tablet. Often, the strength of the interface between the layers decreases as the compaction force on the first layer increases, so it is recommended to only lightly compress the first layer. Since the first layer is subjected to compression more than once, manufacturers prefer to use materials that exhibit greater compressibility and offer good compaction under minimal force, which also allows for enough space for the second layer.

If layers require different ingredients, formulating the layers to have similar properties and compactibility is recommended to encourage superior compaction and layer adhesion. Layers that relax differently after compaction or expand differently after exposure to stressed conditions are less likely to adhere successfully.

**Layer ratios**

The ratio between the layers and the sequence of their arrangement also affects multilayer tablet compression. A ratio at or near 1:1 (where each layer is the same size) often creates the most physically robust tablets, but in practice, different APIs and/or profiles require different formulations, which impacts layer size.

To ensure accurate weight control of each layer during manufacturing, the particle size distribution, flow properties, and compressibility must be optimized. Compressibility is also a decisive factor in ensuring acceptable content uniformity of the APIs.

The relative weight and sequencing of layers are as important as compression, as they directly impact inter-layer delamination or intra-layer capping. To obtain satisfactory API content uniformity, it is recommended to prioritize the compression setting of the layer with the smaller API dose or weight.

Weight ratios for bilayer tablets are most commonly 1:1 or 1:2 but can be 1:3 or even 1:4. During development, layer ratios of up to 1:6 have been formulated, but commercializing such a ratio would be incredibly challenging.

To minimize the risk of delamination, it is recommended to keep the weights of the layers similar or if that is not possible, to maintain consistency in terms of the inactive ingredients used in the layers.

**Patient variability**

API absorption and bioavailability can be substantially affected by a dosage form’s transit through the gastrointestinal tract, so variability in the rate of gastric emptying between patients is one of the most critical parameters. For delayed-release products, variability between patients is especially important, as release begins when the dosage form comes into contact with the higher pH environment in the proximal small intestine.

For multilayer tablets, the pharmacokinetic profiles of each layer must be fully understood and considered during formulation, as patient variability can lead to missed therapeutic windows and variability of the dosages received.

**Highly potent APIs**

The development pipeline for highly potent APIs has become one of the strongest revenue-generating segments in the pharmaceutical industry, and the market holds enormous potential. Highly potent APIs are often combined with others in fixed-dose combination products—often as a means of managing side effects or improving a product’s safety profile with multiple release profiles. Highly potent APIs create a further challenge for manufacturers, who must ensure that appropriate containment strategies and technologies are in place to handle such materials and protect employees.

**Conclusion**

As with many new drug products and dosage forms, the formulation and manufacturing challenges presented by multilayer tablets are plentiful. Success requires careful formulation that considers downstream processing and the physical performance of all the materials involved. Following that, understanding the different compression requirements and having the equipment to handle them is a must.

As multilayer tablets and other fixed-dose combinations gain more prominence, the industry is likely to see more innovation as manufacturers push the boundaries to deliver better products to patients.

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