

# **How Multi-Layer Tablets And Combination Products Are Reshaping Drug Development And Patient Care**



Solid dosage forms are a well-established, widely-used delivery method, yet they are also an area of innovation that can slash drug development times and costs while improving patient outcomes. The tablet technology that brought Aspirin, Lipitor and innumerable other drugs to billions of patients is evolving into multi-layer and combination products.

These tablets combine multiple doses of one or more active pharmaceutical ingredients (API) into a single solid dosage form. Doing so can improve the efficacy and ease of use of new and existing drugs alike. Combination products, also known as fixed-dose combinations (FDC), have a long history of helping manufacturers achieve their therapeutic goals, particularly with regard to managing HIV. FDCs combine two or more APIs in one tablet, an approach taken by GlaxoSmithKline's antiretroviral Combivir in the 1990s and still used in Gilead's HIV quad tablet that won approval in 2012.

Multi-layer tablets take a slightly different approach to delivering multiple therapeutic payloads. The tablets are made up of two to four layers, each of which can have a different release profile and API. This makes creative, more-effective combinations possible. A tablet for attention deficit hyperactivity disorder (ADHD), for example, could first deliver a burst of API to help the patient when they wake up and then

release a slow stream of the same drug throughout the rest of the day. If needed, a third layer could deliver a different API to manage a comorbidity, such as depression.

Such combinations are particularly useful in light of two fundamental characteristics of modern healthcare — we have effective treatments for many major diseases, and patients are taking several of these drugs at the same time. In this environment it is hard to develop new drugs that improve on existing products, yet the efficacy of current treatments is limited by poor patient compliance stemming from the tablet burden placed on patients who are prescribed many medications. Combining multiple active pharmaceutical ingredients (APIs) in a single dosage form can therefore be a win for both patients and drug developers.

### **The Benefits Of Multi-Layer And Combination Tablets**

Decades of pharmaceutical innovation have helped life expectancy in the United States rise from below 70 years old in 1960 to almost 80 in 2011. This increase has occurred alongside rising use of prescription drugs. Centers for Disease Control and Prevention (CDC) data shows that from 2007 to 2008



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almost 11% of people in the U.S. were taking at least five prescription drugs a month. In 1999 to 2000 just 6% were using that many medications. Research published in the journal Mayo Clinic Proceedings in 2013 suggests the number of people taking five or more drugs has continued to rise.

This is a problem for patients. A survey of more than 7,000 patients published in Advances in Therapy found 60% of people taking six or more pills strongly agree their treatment regimen is a burden. A similar proportion of patients said they were occasionally unsure whether they had taken their pills. Many are willing to pay to alleviate these concerns, with 70% of patients saying they would accept up to \$14 in extra monthly out-of-pocket payments to halve the number of tablets they take. Healthcare systems would benefit too, with nonadherence estimated to cost the U.S. up to \$289 billion a year.

Multi-layer tablets and combination products are ways manufacturers can help patients — and therefore healthcare systems — reduce tablet burden. The dosage forms are also attractive from a business perspective. Developing a new drug takes at least a decade, and when outlay on failed candidates is included, Forbes estimates companies spend \$5 billion for each product that wins approval. In comparison, repurposing existing drugs is cheap, fast and low risk. After spending \$200 million and three years on development a firm can be ready to begin selling the repurposed product.

The benefits of such a product to patients and payers are at least comparable to the incremental gains offered by new treatments in therapeutic areas for which effective drugs already exist. The developers of these existing treatments can utilize multi-layer and combination tablets to gain a competitive edge over generic competition and therefore extend the life cycle of a product. Equally, new entrants can repurpose the API to differentiate their product from other generics and the innovator drug.

### **The Technical Challenges Of Novel Dosage Forms**

While multi-layer and combination tablets can cut development costs — and in some cases lower manufacturing overhead by reducing total tablet output — they pose significant technical and business challenges. Production equipment for bi- tri- and quad-layer tablets is expensive and requires scientific expertise to get the best results. The same material attributes and process parameters that dictate production of standard tablets apply to multi-layer versions, but the different structure and use of several APIs necessitates particular consideration.

Intermingling of APIs is one issue. Non-compatibility of many drug matrices means they can be only delivered together as a multi-layer tablet. In this model an inert layer is sometimes inserted between the two APIs to keep them from association



and reacting. Working with a research and development team that understands the physico-chemical properties of the drug matrices and potential excipients simplifies this task. Maximum stability is achieved by using an excipient that is compatible with the drug matrix in each layer of the tablet.

Having separated the APIs it is important to prevent cross-contamination, which occurs when dust from one layer is pressed into the other part of the tablet. At best this leads to a high proportion of tablets failing quality control checks. At worst it results in patients taking tablets that fail to provide the expected therapeutic effect. An effective manufacturing operation will cut the likelihood of such problems arising by minimizing the quantity of dust left on the die plate and cleaning the little that still remains. Modern multi-layer tablet presses utilize vacuums, scrapers and seals to achieve these goals.

Additional challenges include formulation of layers which can be compressed readily together without delamination or friability of the layers. Compressed tablets need to be able to stand up to the rigors of automated packaging systems, conveyor belts and lines. Pre- and main-compression settings on modern multi-layer tablet presses may enable to compressibility of various formulation combinations, which in the past was not possible.

### **The Reasons To Outsource R&D And Production**

The availability of contract manufacturing organizations (CMOs) with expertise in multi-layer and combination tablets means companies can outsource the handling of such challenges. In this model a drug developer will often know the therapeutic effect and release profile they want the tablet to have, but lack the expertise and capabilities to design and manufacture such a product. A CMO with a top-tier R&D team and a solid grounding in multi-layer and combination tablets can turn someone else's vision into an effective, practical dosage form.

Using a third-party to develop and manufacture the product makes economic sense. Buying the expensive, specialized production equipment needed to manufacture multi-layer and combination tablets is the first big outlay for anyone setting up in-house capacity. To make best use of this equipment — and avoid the problems we discussed in the technical challenges section — the firm must then hire a team with experience of setting up and running such production lines. These staff members need support from an R&D team that understands the unique demands of formulating the tablets.

Unless a company plans to develop and manufacture many multi-layer and combination tablets over a long period of time, the costs of in-house capacity



are likely to be prohibitively expensive. For a leading pharmaceutical company that is trying to extend the life cycle of a handful of key products, outsourcing is probably the more cost-effective option. Similarly, a start-up that wants to develop an improved version of an old drug is generally best served by running a lean operation with minimal investment in in-house R&D and production capacity.

### Conclusion

Multi-layer tablets and combination products offer intriguing possibilities for leading pharmaceutical companies, generic manufacturers, patients, and healthcare providers, alike. Each faces a problem that these dosage forms are uniquely able to solve. Developers of innovative drugs and “repurposers” of

existing molecules can use multi-layer and combination products to gain an edge in the highly-competitive market for off-patent products. Patients then benefit from products that simplify their treatment regimen, and healthcare providers see fewer dollars wasted on poor compliance with their recommendations.

Development and manufacture of the dosage forms that enable these system-wide benefits pose multiple technical and financial challenges. However, the availability of CMOs with experience working with such dosage forms lessens the burden these issues place on drug developers. All a company needs is an idea for a dosage form that could improve the lives of patients. A CMO can do the rest.



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