Layer by Layer: The Fundamentals of Multi-Layer Tableting

The basics of multi-layer tablet formulations and their drug delivery possibilities.

Gernot Warnke, PhD
Head of R&D
JRS Pharma

Tony Carpanzano, BS, R. Ph
Director of R&D
JRS Pharma, LP

OVERVIEW

Multi-layer tableting offers a straightforward solution for a variety of challenging formulations. From multi-phasic release systems—to combinations of incompatibles (APIs)—to gastro-retentive tablets, this underutilized method provides efficiency and cost-savings as compared with more popular complex processes.

This article compares multi-layer formulation options to traditional methods, providing a step-by-step guide to the multi-layer tableting process, and offering crucial tips to formulating and manufacturing robust multi-layer tablets. It demonstrates how tooling considerations, excipient selection, layer design, and tamping force adjustment can affect overall tablet robustness as well as layer-to-layer adhesion.

FUNDAMENTALS OF MULTI-LAYER TABLETING

Patient treatments often combine two drugs that have synergistic therapeutic activity, spurring drug developers to be innovative with fixed-dose combinations. Not all compounds are physically and chemically compatible, thus making multi-layer tablets—with APIs in separate layers—extremely useful. A combination of two or more delivery mechanisms is another reason to use a multi-layer tablet. Ingredients in multi-layered tablets can be delivered at different rates or by different mechanisms, one layer could have a loading dose while the other might provide a sustaining dose of the same medication, or each layer could contain a different sustained-release compound. There are a variety of approaches to formulating these multi-layer tablets.

FORMULATION TARGETS FOR MULTI-LAYER TABLETS

How do multi-layer tablets fit into the landscape of advanced solid dosage forms?

Figure 1: Multi-layer tablet formulation options.

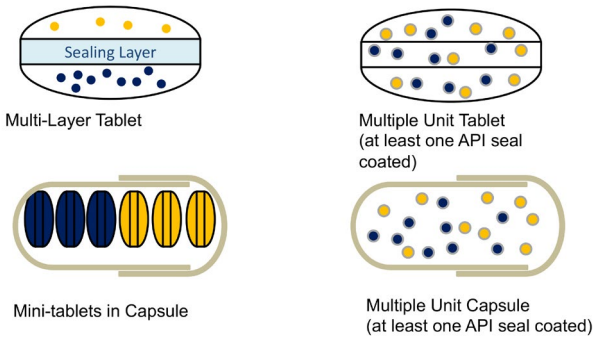


Table 1: Comparing various multi-layer tablet technologies.

Technology	Positives	Negatives
Multi-layer tablets	• Effective and relatively easy way to create separation • Relatively high drug load possible	• Special equipment necessary
Mini-tablets	• Effective separation, high drug loads, easy analytics	• Special capsule-filling equipment necessary
Coated spheres	• No specific equipment required	• Limited value, if both APIs are high dose

Figure 2: Bi-phasic release formulation options.

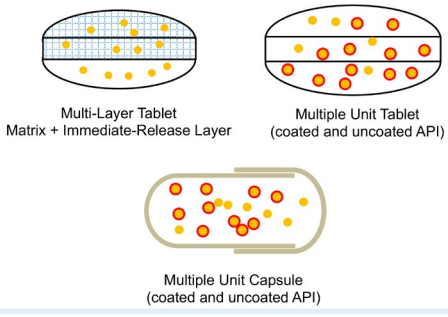


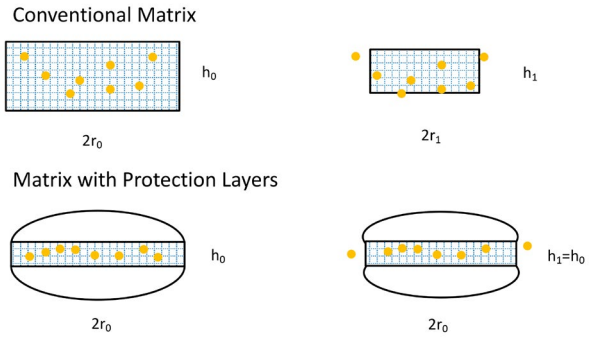
Table 2: Comparing bi-phasic release technologies.

Technology	Positives	Negatives
Multi-layer tablets	• Ease of formulation and manufacturing	• Limited effectiveness for high solubility APIs • Unpredictable GRT • Special tableting equipment
Coated spheres/granules in immediate-release matrix (tablet or capsule)	• Good release control, suitable for wide range of solubilities	• More costly than matrix systems • Bead coating adds cost and complexity • Risk of damage to bead coating during tableting

Multiple APIs. The simplest example for why it is advantageous to produce a multi-layer dosage form is for immediate-release formulations involving two incompatible APIs. A simple bilayer tablet can be enough to make a stable formulation from two incompatible compounds. In cases where there must not be any contact between the two APIs, a third sealing layer can be added in between layers. Some examples of different types of multi-layer tablets can be seen in FIGURE 1. Other more complex approaches to keeping API separate include mini-tablets in a capsule and multiple unit tablets or capsules containing multi-particulates, coated spheres, or coated granules. These technologies provide an effective and relatively easy means of separating incompatible compounds. Coated spheres, however, have limited value if both APIs are high dose. TABLE 1 shows the advantages and disadvantages of various multi-layer tablet technologies.

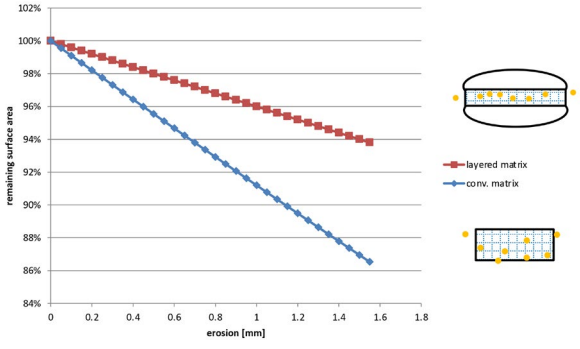
Bi-phasic release. For bi-phasic release, where there is a need for a fast, initial release followed by sustained release, several options are available. The simplest method is a multi-layer tablet, where one layer contains the API in an immediate-release formulation and the second layer contains the API in a matrix formulation. The immediate-release layer disintegrates upon reaching the gastrointestinal fluids, while the matrix formulation layer releases API over time. This also can be achieved with a tablet or capsule containing coated multi-particulates, where the coated particulates provide sustained release, and the uncoated particulates provide immediate release (FIGURE 2). Coated spheres, granules, and multi-particulates—while providing good release control for a wide range of solubility—tend to be more expensive than a matrix system. Bead coating also adds the risk of damage to the bead coating during tableting. TABLE 2 contrasts several biphasic release models.

Figure 3: Multi-layer technique for erodible matrices.



The multilayer matrix technology (e.g., the Geomatrix®) is protected by various patents!

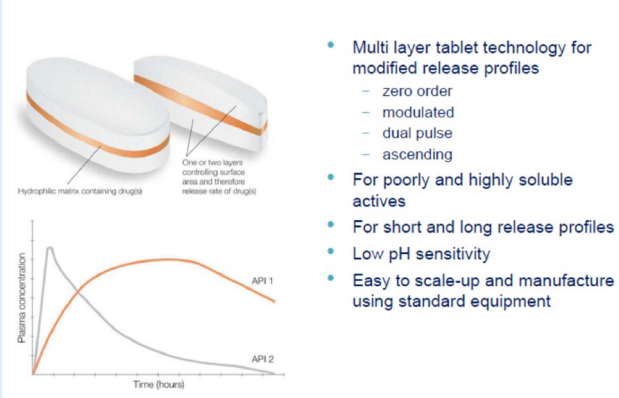
Figure 4: Protective layer matrix reduces the change in release rate over time.



Decrease of the API-releasing surface area of a conventional and a protected matrix tablet (initial dimensions r=5mm, h=3mm)

Sustained release. Multi-layer tablets can be used to provide a variety of sustained release profiles. For example, zero order release, in which a drug is released at a constant rate, is usually the ultimate goal in prolonged release dosage forms. Coated, reservoir-type systems come very close to the ideal, linear release profiles. Nonetheless, they are costly to produce and limited in terms of the maximum drug load per tablet. Erodible, hydrophilic matrices are cheaper to produce and can carry more API-load. These formulations, though, are often susceptible to mechanical stress due to their erodible nature. Furthermore, a conventional matrix erodes from all surfaces and becomes smaller as it erodes, resulting in a change in release rate over time.

Figure 5: Skypharma's Geomatrix™ customizable drug delivery platform.



To address these challenges, several innovative protective layer matrix systems have been developed, where there is a protective layer on the upper and lower faces of the tablet that limits tablet erosion to the sides of the tablet (FIGURE 3). The protective layer matrix reduces the change in release rate over time to bring it closer to a zero-order release than would occur without the protective layers (FIGURE 4). Examples of protective layer matrix system include those using the Skyepharma's Geomatrix™ multi-layer tablet technology, which can provide a variety of modified release profiles and controlled release of both poorly and highly soluble drugs (FIGURE 5), and which is used in GlaxoSmithKline's Requip® Modutab (ropinirole) prolonged-release tablets for the treatment of Parkinson's disease. The extended release of the protective layer matrix system avoids the peaks and troughs that occur with repeated immediate-release dosing. Thus, it provides better therapy over time and results in better patient compliance.

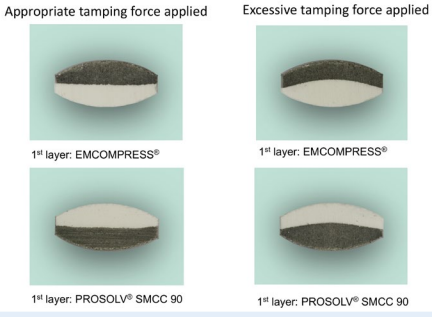
In summary, there are numerous advantages to multi-layer tablets. From a formulation standpoint, they provide separation of incompatible APIs and enable a combination of different release profiles. From the patient's standpoint, they provide convenience, since the patient can take one tablet instead of several tablets, and receive better therapy.

Table 3: Examples of multi-layer API combinations.

API	Reason
Diclofenac and Cyclobenzaprine	Synergistic effect in pain
Losartan	Biphasic release profile
Amlodipine and Atenolol	Improve the stability of the drugs in combination
Glipizide and Metformin HCl	To avoid interactions
Metformin HCl, Atorvastatin Calcium	Development of a polytherapy for the treatment of NIDDM and hyperlipidemia

An overview on bi layered tablet technology, C. Gopinath, V. Hima Bindu, M. Nischala, *Journal of global trends in pharmaceutical science*, Volume 4, issue 2, pp 1077 – 1085, 2013

Figure 6: Biconvex tablets from tamping force study.



From a marketing standpoint, they are elegant products and provide brand recognition. Examples of approved multi-layer products with API combinations are shown in TABLE 3.

MULTI-LAYER TABLETING CONSIDERATIONS

During filling of the first layer of a multi-layer tablet, the powder flow is supported not only by the feeder, but also by the suction created by the downward moving punch. On a high-speed press, those stations are moving rapidly under the feed frame and, in properly engineered tablet presses, the downward moving punch does not begin to pull down until it is underneath the feed frame. With the rapid downward movement of the lower punch, a suction is created. In the case of a multi-layer tablet, this effect only helps filling of the first layer; thus, the flow characteristics of the second or any subsequent layers are an important factor in weight maintenance.

After weight adjustment, the first layer is tamped using moderate forces (typically well below 1 kN). As the position of the first layer is at the lower end of the die, special upper punch tooling with longer tips may be necessary. For subsequent layers, the maximum remaining fill depth is defined by the lower punch position and first layer thickness. In order to minimize excessive movement in the subsequent steps, the lower punch should be positioned in such a way as to avoid excessive over-filling of the second layer.

After tamping the first layer and filling the second layer, the lower punch lifts the tablet to adjust for the right filling volume for the second layer. The first layer must be hard enough to tolerate that adjustment, while at the same time maintaining sufficient surface roughness and porosity to ensure good adhesion between the layers.

After filling and dosing of all layers, the final compression step takes place. While the overall formulation and applied compression force are responsible for the tablet's crushing strength, it is the tamping force and surface structure of the layers, which defines the layer adhesion. This aspect is further studied in the following section.

TAMPING FORCE STUDY

A two-part study on the tamping effect shows that tamping plays a significant role in layer adhesion. The objective of the study was to assess the effect of tamping force on multi-layer tablet robustness by measuring the layer separation force, using 1) bilayer flat-faced tablets and 2) bilayer bi-convex tablets produced by direct compression.

Two layers were used in each tablet. One layer contained 94% PROSOLV® SMCC 90 with a median particle size of 125 µm as a plastically deforming filler/binder and 5% black iron oxide for identification. The other layer contained

99% EMCOMPRESS® (calcium hydrogen phosphate, dihydrate) with a median particle size of 190 µm as a moderately compressible filler/binder exhibiting brittle fragmentation. In both layer formulations, 1% of PRUV® sodium stearyl fumarate was used as a lubricant.

Compression involved alternating the use of the two excipients as the first or second layer with three distinct tamping forces for the first layer and 5 kN for the main compression. Layer separation force was measured using a texture analyzer fitted with appropriate fixtures. The total tablet weight was 1.05 g. The PROSOLV® SMCC layer was 450 mg and the EMCOMPRESS® DCP layer was 600 mg. Both layers were about the same thickness once compacted. The tablet press used was a Fette 1200i with 13-mm flat-face punches for the flat-face tablets.

At first, the lowest possible tamping force was applied. The force was adjusted in a way to achieve approximately 5N hardness of the first layer. Next, tamping forces of 2 kN and 4 kN, respectively, were applied. The main compression force was kept at 5 kN in all three cases.

TABLE 4 shows the results for first layer hardness, overall crushing force and layer-adhesion force.

In summary, the studies yielded the following observations:

- Tablets made using the lowest possible tamping force had the strongest layer bonding. These tablets did not separate between the layers, but they broke within the DCP layer.
- Tablets made using 2 kN and 4 kN tamping force could be separated between the layers
- Separation force was the lowest for tablets produced with 4 kN tamping force; tablets with PROSOLV SMCC 90 as first layer were the most unstable, when applying high tamping force.
- The overall tablet hardness were unaffected by the order in which the layers were compressed.

Table 4: Tamping force study data

First layer excipient	Tamping force (kN)	First layer hardness (kN)	Total tablet hardness (kN)	Separation force (kN)
PROSOLV® SMCC 90	0.15	7	160	39.2
EMCOMPRESS® Premium	0.71	5	180	35.2
PROSOLV® SMCC 90	2.03	78	172	29.6
EMCOMPRESS® Premium	2.03	8	177	26.5
PROSOLV® SMCC 90	3.96	123	169	17.8
EMCOMPRESS® Premium	4.11	11	180	20.3

In the second part of the study, a Korsch EK0 single-punch tablet press was used to prepare bi-convex tablets. The aim of this study was, to visualize the effect of appropriate and excessive tamping forces. (FIGURE 6, left column) When appropriate (i.e. lowest possible) tamping forces were applied, the cross-section of the tablets showed an almost straight line at the interface of the two tablet layers (FIGURE 6, left column). By contrast, excessive tamping forces lead to the formation of a curved line according to the cup radius of the upper punch (FIGURE 6, right column). Apparently, the use of too high tamping forces causes the first layer to be mechanically too strong to re-shape under the pressure of the main compaction step. On the other hand, softly tamped powder plugs will yield to the main compaction pressure, thus forming an even interface.

CONCLUSION

In conclusion, multi-layer tableting provides an inexpensive and simple solution to combine incompatible active ingredients as well as to enable bi-phasic and sustained release.