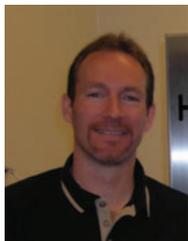


multi-layer tableting Q&A

PRESS MANUFACTURERS WEIGH IN ON MULTI-LAYER TABLETING'S ADVANTAGES, MISCONCEPTIONS, AND FUTURE



RYAN KEEFER
THE ELIZABETH
COMPANIES



JIM CALVIN
THE ELIZABETH
COMPANIES



DOUG KIRSCH
NATOLI
ENGINEERING



GARY BUBB
SMI



LOYD BOWMAN
VANGUARD
PHARMACEUTICAL
MACHINERY

(NO PHOTO
PROVIDED.)

STAN MATTHEWS
IMA NORTH
AMERICA



Multi-layer tableting is getting increasing attention from a variety of industries. While general tablet manufacturing principles remain the same, there is much more to consider because making multi-layer tablets involves multiple—often incompatible—products, additional equipment, and many formulation and operation challenges. For some perspective on this process, Tablets & Capsules spoke with experts from several tablet press manufacturers, including Ryan Keefer, sales and administrative manager, and Jim Calvin, technical service manager, The Elizabeth Companies, North Huntingdon, PA; Stan Matthews, director of sales, IMA North America, Bristol, PA; Doug Kirsch, technical service manager, Natoli Engineering, St. Charles, MO; Gary Bubb, vice president and director of engineering, SMI, Lebanon, NJ; and Loyd Bowman, director of sales and technical support, Vanguard Pharmaceutical Machinery, Spring, TX.

Q What are the main uses for multi-layer tableting?

A Bowman: Back in the late '60s, '70s and early '80s, a lot of companies wanted something different on the market and used multi-layer tableting because it was enhancing, elegant, and unique. Not too many people had it. At that time it wasn't even functional.

Bubb: Even today, consumer perception is important from a marketing standpoint. Multiple layers make it easy to say, "This is the controlled-release portion of the tablet and this is the immediate-release portion." Even though you may not need to make a bi-layer, there's the perception that this one does this, and this one does that. Multi-layers also let you separate two incompatible actives or excipients. Usually they'll survive long enough at the boundary line as long as they're both compressed. Another advantage that's rarely spoken about is that you

could actually use the multi-layer machine as a single-layer tablet press to make a higher-weight tablet. I'm not aware of anyone actually doing it, but at our company we've talked about the possibility. Keeping the same formulation, nobody would know you're making a bi-layer tablet, but you could achieve a higher tablet weight using a bi-layer machine.

Keefer: Another use is that, for products coming off patent, companies are able to extend the patent by just adding a layer or adding an ingredient. There is controlled release and timed release, with a layer or a buffer between ingredients. One might be active immediately when the person takes the pill, and then the other ingredient may kick in 2 hours later.

Q What are the biggest challenges of multi-layer tableting?

A Bowman: One challenge is your sellable product. You might have a scrap rate of 10 or 15 percent of your batch. That's a big hit, especially if you're used to having a 97 percent sellable batch yield for single-layers. And the biggest challenge is knowledge. You could be a Ph.D, but if you don't have the mechanical knowledge, you'll never produce a tablet correctly. Pharmacology school is not going to teach you everything. This is basically solid dosage form engineering. It's very different.

Bubb: There's a lot more involved when it comes to operator training. It's a requirement for the manufacturers to offer a sufficient operator training program so that the client can successfully run the product. Another factor is the production rates are considerably lower. Bi-layer tablet presses typically run much slower, and a single-layer press of an equivalent size would probably be a double-sided machine. Therefore the production rate may be as low as 20 percent of what it would be on a single-layer double-sided machine.

Matthews: But the problems with speeding the machine up are that you lose your weight control, you start to get cross-contamination, and you start to lose more product. To run the machines faster, you must control those three items.

Kirsch: Cross-contamination from one layer to the next is another big challenge. For example, if the first layer is red and the second is white, any granulation bypassing the first feeder will contaminate the second layer, turning it pink. Not only does the final tablet not look as it should, but it could affect the results of the medication. Therefore, it's best to fill light-colored layers first. Clear lines of demarcation between the layers are also problematic. A clear straight line is visually appealing and may be essential to the proper administration of the medication. Dust extraction is also a major concern.

Q Are multi-layers only for "Big Pharma?"

A Keefer: No. We've seen a lot of small-scale OTC drugs produced by smaller companies, vitamin companies, candy companies. Big Pharma might have a little more interest because they have to deal with product patents and who has rights to what. But there's a lot of interest from smaller companies as well. (See the article on page 28, "Bi-layer nutraceutical tablets: Rewards and challenges.")

Kirsch: The confectionery industry had a very successful bi-layer candy-stamp tablet that incorporated an embossed dyed image on the first layer and a small handle on the second. A child would lick the first layer and stamp a temporary tattoo on themselves or on their younger sibling's forehead. The military used a multi-layered tablet in a defensive weapons system. Other uses include denture cleansers and dishwasher detergents.



Candy-stamp tablets are comprised of two layers, one with an embossed dyed image and another with a small handle.

Bowman: Basically it comes down to what size capital investment you want to put into the machine and into the development time. Big Pharma might be able to handle marketing better, but small pharma can still do it and still be profitable too.

Q How has multi-layer tableting evolved since you first encountered it?

A Bowman: The precision of the machinery today is much better than it was 30 years ago. The tableting machines on the market are much friendlier for these multi-layer processes.

Matthews: The biggest improvement has been in the controls, the weight control of the first layer and second layer, and the sampling of the first layer. The improvements have given pharmaceutical companies more control over each layer and the ability to sample each layer and reject tablets if they're out of spec.

Kirsch: The first so-called multi-layer presses that I know of were modified Stokes BB2s. We're going back to the '50s here, so there may be some blank faces, but those were the most mass-produced presses in history. Today they would be marginal at best. Press manufacturers have vastly improved the multi-layer process and have overcome many of the inherent problems. Improvements include zero-clearance feeders, closer tolerances, product recirculation control, and better dust extraction.

Calvin: The process is still exactly the same as it was 50, 60 years ago or longer. The evolution has been in the electronics and the data collection. Before you would've had virtually no idea what the press was running at. You would've grabbed some tablets for weight, walked down

to the QC, dropped them into the tester, and weighed them to see if your adjustment made a difference or not. If it didn't, you'd go back and tweak the machine a little bit more, take samples again, walk down the hallway, and conduct more testing. It would take hours to optimize the running of the press. Now, with all the data that can be collected, you can get a true look at the press parameters at the beginning, middle, and end.

Q Do press components wear more quickly in multi-layer presses?

A Calvin: It all depends upon how the company is maintaining the press, how they're operating the press, the type of granulations they're using, the speed that they're running. So there are a lot of variables. But logically, a multi-layer press will wear tools and upper and lower cams quicker than a single-layer press. The punches are raised up higher and pushed down lower to create that lower tablet—the punch penetration is much greater. The transition of that raising and lowering in the upper cam area is much more abrupt than on a regular press, and so you end up wearing the lifting cams and the head angles of the upper punches more than you would on a standard single-layer press.

Kirsch: Tooling, feeders, and presses aren't greatly affected by the production of multi-layer tablets. There may be a slight effect because of the increased up-and-down movement of punches or sampling of tablets, but this would be extremely minimal.

Bowman: A tablet's a tablet; a tablet press is a tablet press. It doesn't matter; you're going to get the typical wear.

Bubb: In fact, the components may last longer due to the lower speeds.

Q Do granulations need to meet tighter specs?

A Matthews: No, they don't. But I'm sure there are some scientists out there that would argue with me. From an OEM perspective, the products from pharmaceutical companies are all very high quality, and when they go into a bi-layer, they're formulated a little differently, but the quality is not dramatically different from that of single-layer tablets.

Bubb: Granulations do need to meet tighter specs. You must have consistent granulation properties; compactibility changes from batch to batch would require constant adjustment of the machine to get

rid of fuzzy boundary lines or to ensure the two tablet layers adhere to each other. The materials have to flow much better than normal. Multi-layer operation in general is more complex and not as forgiving, so therefore the granulations need to be good and consistent.

Q How might multi-layer tableting complicate PAT and validation?

A Calvin: It really doesn't complicate it. It lengthens it. Instead of validating just one machine, you're validating three. Instead of having one set of feeder controls, you have three sets; instead of having one set of supply hopper controls, you have three sets. Everything's tripled.

Matthews: Bi-layer tableting does definitely increase the amount of tests that have to be conducted during a validation IQ/OQ procedure on a machine. It adds probably 20 percent more work to complete the validation package. For PAT and NIR, it adds extra components because PAT and NIR are typically looking at the product going into the machine and the product leaving the machine. In this case you're going to be looking at two different products, not just at one product in the hopper.

Kirsch: Cross-contamination between layers would be an issue. A uniform dosage of the medication would be another.

Q What are some misconceptions related to multi-layer tableting?

Kirsch: The most common misconception seems to be that multi-layers are very easy or very difficult to produce. In fact, it's somewhere in between.

A Matthews: There are a few misconceptions that I can think of. One of them is that it's not possible to sample the first layer at a very high speed. It's actually very important to sample the first layer at a high speed so you don't waste a lot of material. There is also a misconception that every time you take a first-layer sample you're going to lose a lot of good product. The advancements in the machines have corrected that; first-layer sampling is very quick now. You still lose product but only a minimal amount. Another misconception is that the machines don't have the ability to monitor first-layer and second-layer weight very closely and reject out-of-spec tablets. They can.



A Hata three-layer press from The Elizabeth Companies.

BI-LAYER NUTRACEUTICAL TABLETS: REWARDS AND CHALLENGES

CHIRAG VARAIYA

JARROW INDUSTRIES

Most nutraceutical manufacturers prefer capsules because they require fewer excipients. Capsules also require fewer unit operations, such as granulation and coating, and they mask taste and color better. Nonetheless, bi-layer tablets enable nutraceutical manufacturers to provide more sophisticated delivery of active ingredients and to differentiate their products from competitors.

There are several reasons for making a bi-layer nutraceutical tablet.

Stabilizing incompatible ingredients. The most obvious rationale for making a bi-layer tablet is to deliver two active ingredients in one tablet, especially when the actives are incompatible. DualTabs, made by Idea-sphere, American Fork, UT, are an example of pairing incompatible actives.

The company describes its product as containing a "sustained-release bi-layer mega vitamin and mineral formula." One layer contains fat-soluble vitamins and sustained-release water-soluble vitamins. The other layer contains rapid-release minerals and digestive aids. "This prevents the interaction of incompatible vitamins and minerals for maximum stability and quality," the company claims. By putting vitamins in one layer and mineral salts, betaine, and glutamic acid in the other, the company prevents vitamin degradation.

Another example is Menocal from Nature's Own of Australia. The company describes its product as "a unique bi-layer tablet combining a high-strength calcium supplement for

improved bone density, together with soy isoflavones to alleviate hot flashes associated with menopause." One layer contains calcium and vitamin D3, and the second layer contains calcium, boron, and soybean extract.

Controlled release. Single-layer tablets work very well when the release profile is either immediate or sustained. But when the active ingredient needs to be delivered in an initial burst followed by sustained release, a single-layer tablet poses a formulation challenge. The challenge is even greater when there are multiple active ingredients, and some need to fit an immediate-release profile and some a controlled-release profile. Bi-layer tablets can make the job easier.

Value-added marketing. Nutritional products do not have the same protections on intellectual property that pharmaceuticals do. But one way to differentiate your product from a competitor's is to formulate it into a bi-layer tablet.

Challenges

Conceptually, bi-layer tablets can be seen as two single-layer tablets compressed into one. In practice, there are some manufacturing challenges.

Delamination. When the two halves of the tablet do not bond completely, the tablet falls apart. See photo, below left. You have to make sure the two granulations will adhere when compressed.

Cross-contamination. This occurs when the granulation of the first layer intermingles with the granulation of

the second layer or vice versa. See photo, below center. Cross-contamination between the two layers may defeat the very purpose of the bi-layer tablet. Proper dust collection goes a long way toward preventing cross-contamination. Another photo, below right, shows samples of bi-layer tablets taken from a successful batch.

Production yields. Bi-layer tablets have lower yields than single-layer tablets because of losses to the dust collection required to prevent cross-contamination.

Cost. Bi-layer tableting is more expensive than single-layer tableting for several reasons. First, the tablet press costs more. Second, the press generally runs more slowly in bi-layer mode. Third, you must develop two compatible granulations, which means more time spent on formulation development, analysis, and validation.

Our experience

Our company, Jarrow Industries, installed a bi-layer tablet press in 2004, and today we manufacture several bi-layer tablets, two of which are described below.

Bi-layer N-acetyl cysteine. N-acetyl-L-cysteine (NAC), is a powerful anti-oxidant amino acid and a precursor to the critical anti-oxidant glutathione. It is rapidly absorbed in the blood and has a 1.5-hour biological half-life in the bloodstream. For that reason, we formulated a bi-layer NAC. One layer comprises immediate-release NAC, and the second layer comprises a sustained-release formula-



Delamination



Cross-contamination



Good tablets

FIGURE 1

Example of a release profile of a bi-layer tablet comprising two active ingredients. One layer releases the active immediately. The other releases its active over an extended period.

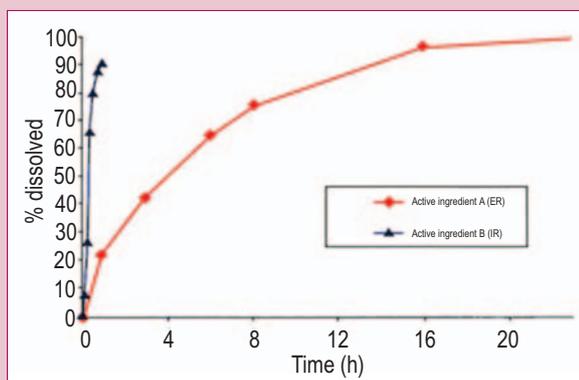
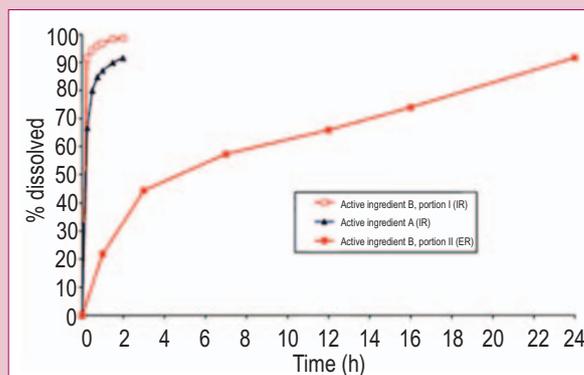


FIGURE 2

Example of a release profile of a bi-layer tablet comprising two active ingredients. Active A releases immediately, as does Portion I of Active B. Portion II of Active B releases over an extended period.



tion of NAC. As a result, the active ingredient enters the bloodstream immediately and maintains its presence over a longer period of time than would be possible in a single-layer tablet. Figure 1 is an example of what the release profile of a similar formulation would look like.

Bi-layer alpha lipoic acid. Alpha lipoic acid (ALA) is a unique lipid- and water-soluble anti-oxidant that is a co-factor in energy production, since it helps regulate glucose metabolism. ALA also promotes the synthesis of glutathione. We formulated a bi-layer tablet that comprises immediate-release ALA in one layer and a sustained-release ALA in the second

layer. This bi-layer's immediate-release/sustained-release format maximizes the presence of the active ingredient in the blood while minimizing gastric irritation and blood sugar fluctuations. Figure 2 is an example of what the release profile of a similar formulation would look like.

Conclusion

In the nutraceutical industry, bi-layer tablets are not common. But they offer an excellent opportunity for manufacturers to separate themselves from their competitors, improve their products' efficacy, and protect against copycat products.

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Chirag Varaiya is responsible for formulation and quality control at Jarrow Industries, 12246 Hawkins St., Sante Fe Springs, CA 90670. Tel. 562 906 1919, fax 562 906 1979. Website: www.jiimfg.com. Varaiya has Bachelor of Science and Master of Science in chemical engineering and 5 years of experience in manufacturing vitamins and other dietary supplements. Jarrow develops, manufactures, and packages vitamin, nutritional, and herbal supplements for nutritional marketing companies and private-label customers.

Bubb: One of the questions that we typically get is, "Can I make a single-layer tablet on my bi-layer tablet press?" And the answer is, "Absolutely. But why would you want to do that?" There's a lot more complexity in the operation and there are two layers of operations to clean instead of one. Even though it's feasible, please don't do it.

Q Does the end user need to think differently about the formulation when he's aiming at making a multi-layer?

A **Kirsch:** Yes. Fines should be kept to a minimum. Uniform moisture content and layer adhesion are important because this will affect friability. Shelf-life and shipping may affect layer separation.

Bubb: You have to think about which layer is going to be your first layer and which will be your second layer. Assuming the bulk densities are similar, the heavier layer should be the first layer. If they're similar in weight, then the next thing to consider is pre-compression. We actually had one formulation where layer one was heavier than layer two, but because layer one was plastically deforming, it benefitted by pre-compression. So we made layer two the first layer.

Q What are some things end users need to consider when integrating multi-layer tableting into their process?

A **Bowman:** When you're doing multi-layer tableting, your tablet speed will go down. Say the machine is rated for 250,000 tablets an hour; you're going to go to half the speed on the double. You'll go down to about 30 percent of the speed on a triple.

Matthews: The feeding of the material is also important. On a traditional single-layer press, you only have one product you're feeding in. Here you need to have two quantities of material above the tablet press to feed each side and two sets of corresponding controls. With a bi-layer tablet you require a little more CFM for your vacuum to keep the machine clean and to keep side A and side B separate. You also should consider a secondary weight control system, which is an offline weight, thickness, and hardness unit to do automatic sampling and checkweighing.

Calvin: Some other important things are the pressures you plan on running at, the dyes you plan on running, the anticipated speeds. Ask yourself which granulation you plan to run at the first layer and which granulation you plan to run at the second layer. But other than in the confectionery industry, making a layered product is the last resort. No one's ever actually told me that in the 20 years I've been involved in multi-layer tableting, but it's the last thing you want to do because it complicates everything.

Kirsch: Operator skills and tablet press condition are major concerns. Considering all the negative aspects, ask yourself, "Is a multi-layer tablet really necessary?"

Bubb: The extremely important thing is that you need to obtain the proper fill cam for the first layer. You can't allow excess material to exit the rear part of the feeder, or it will contaminate the second layer. So it's extremely critical to get the fill as close as possible, as the excess must remain within the feeder volume. Another thing is that upper punch penetration on the layer one dictates the maximum weight for layer two. In other words, the upper punch penetration on the first layer acts like your fill cam and makes a void in the die for layer two. Also, understand as much as you possibly can about the characteristics of each layer on a single-layer machine before you try to go into the complexities of making a two-layer tablet. And I don't know anybody that does that—everybody just seems to jump in with both feet into bi-layer tableting. Spend a few days characterizing each layer. It'll take you a few extra days up front, but it'll save you weeks in the back end.

Q Where is multi-layer tableting headed?

A **Matthews:** The complex extended-release products that are coming onto the market are going to require containment applications, meaning that companies are going to need CIP or WIP tablet presses and auxiliary components to make their product. Other advancements will include better weight control and the implementation of NIR or PAT in 100 percent of the applications, allowing the machines to run faster and at higher quality.

Keefe: The future is bright for multi-layer. By creating multi-layer tablets that have two or three different actives, or two actives with a barrier in between, it reduces the number of tablets that a patient would have to take. That's especially important because of our aging population.

Bowman: I've had a few customers in the last few weeks who are looking at multi-layer for nutritional supplements. Candies and functional gums use it too for things like bittersweet taste. Dishwashing detergents and ammunition can be made by multi-layer. It could be used in the chlorination of your pool. There are many, many applications. Multi-layer technology, if used properly, can help everybody ease their problems.

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