

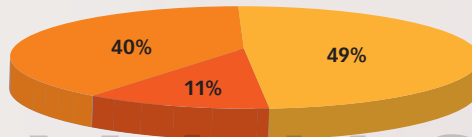
Multilayer tablets: a piece of cake?

Solid dosage forms are the most popular method of drug delivery and no doubt many of you spend your days toiling over troublesome tablets! Although tablets are widely established throughout the pharma industry, this doesn't mean it is an unmoving area. Indeed, many Big Pharma companies are scrutinising their traditional tablets to see if they can be made even better. According to a recent poll on PharmTech.com, manufacturers are seeking to reformulate or reinvent their currently marketed solid-dose products to both renew patents and improve efficacy.

One possible way to achieve both of these is to reformulate tablets into more exotic forms such as multilayer tablets, fixed-dose combinations or other innovative dosages. Of course, changing one thing to another in the pharma industry is never easy!

For this special feature, we bring together experts in solid dosage for a special

What is driving manufacturers to reformulate or reinvent currently marketed solid dose pharmaceutical products?



- Need to renew patents
- Availability of new excipients
- Opportunity to improve efficacy and patient compliance

roundtable on the formulation and manufacture of multilayer tablets. We also speak to researchers about fixed-dose combinations, which have raised much controversy in the industry as experts mull the potential for adverse effects. **PTE**

Expert views

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Multilayer tablets: a piece of cake or just a passing fad? We bring experts together to find out.

Q How has demand for multilayer tablets altered in recent years? What factors have influenced this trend?



Behrens: Fixed dose combination drugs are becoming increasingly popular, particularly as lifecycle management strategies seek to extend intellectual property and minimise generic exposure by creating an innovative dosage

form. The multilayer tablet is a viable way to combine different actives for a synergic therapeutic effect, or different formulations of the same active in order to achieve a specific release profile. Furthermore, multilayer tablets can avoid interactions between different drugs and optimise each formulation in terms of pharmacokinetics and manufacturability.

Calvin: The growth of high-potency and combination drug products over the last decade has made multilayer and tablet in tablet (core tablet) hot topics in the pharma industry. These novel delivery systems have been essential not only in formulating new products, but also in helping pharmaceutical companies to extend patents.

Ethirajan: Among other advantages, triple-combination therapy in a single-dosage form is being used to promote better treatment adherence by providing a convenient single tablet. As well as increasing patient compliance, multilayer tablets can help to reduce the cost of medication.

Q Considering the split drivers of compliance and patent extension, do you think multilayer tablets will continue to be successful in the future?

Behrens: If we think of fixed dose combination drugs as a way to treat two closely related diseases, or to improve compliance and thus efficacy of prescribed medicines, we believe that this trend will continue. However, multilayer tablets could be a less frequent option if, in the future, the drugs are designed to be mixed into a unique powder that can be processed in a standard tablet press.

Today, most combined actives are existing drugs. In the future, a higher number of combinations will be achieved with new formulations that are specifically designed to be combined from the development stage. In this case, the properties of the different compounds



can be optimised to be combined, minimising possible interactions.

Calvin: I believe that the demand for multilayer and tablet in tablet technology will continue for many years to come, particularly as new high-potency drugs, which are often combined with other drugs in a single multilayer tablet generate a demand for layer technology. Many matrices are incompatible with one another, but with multilayer tablets, formulators can insert an inert barrier layer between the incompatible matrices to prevent an interaction. Also, developments in the technology have made multilayer tablets easier to produce. For instance, for core tablets, developments now enable the core to be positioned more precisely within the tablet.

Kirsch: Multilayer tablets have been manufactured for a long time; more than 50 years that I know of. They are not going away—even though many companies including press manufacturers wish they would!

A new possible need for layered tablets is the recent FDA Draft Guidance for Industry Tablet Scoring. Uniform dosage and assurance that a patient is capable of splitting the tablet properly are two of its concerns. Accu-Break Pharmaceuticals developed and patented a unique method using layered tablets to address these issues. The first (bottom) layer is a drug-free placebo. The second (top) layer containing the API(s) is scored deep enough to reach the second layer. The first inactive layer is merely a holder for the active second layer and when broken, result in a uniform dose. A tri-layer tablet with an inactive centre layer for split dose combinations has also been developed. Simple, yet brilliant. Wish I'd thought of it! What other future possibilities are there for layered tablets?

Ethirajan: Multilayer technology will continue to be an option in the future for several reasons:

- Pharma companies will file new patents or extend existing patents on their company name on combination product to win market exclusivities.
- Generic drug makers may use new technology as an option to work around existing patents for markets product.

- Advancements in the technology by equipment manufacturers who recognised the importance of meeting regulatory requirements to market their high speed machines for production.

Most importantly, a single tablet containing multiple medications can be both cheaper and more convenient than separate tablets.

Q When formulating multilayer tablets, are any special considerations required for factors such as levels of fines, bulk densities and granulation properties?

Behrens: For efficient tableting, granule flow is crucial and a certain amount of fines is needed to guarantee proper filling and binding of the tablet. It is also important that the tableting machine is designed so that the filling range can cope with bulk density. In addition, the system should avoid the carry-over of particles or fines.

Calvin: When utilising a tablet press with the proper powder-feed system, there is usually no need for any special considerations or factors such as levels of fines or granulation properties to be determined. The only consideration would be the bulk density of the granulation. Depending upon which layer is the lighter density granulation, it would normally be used on the first layer if the tableting press has a limitation of the upper punch penetration of the layer tamping stations that regulate the depth of fill of the consecutive layers.

Kirsch: The level of fines must always be considered, even for non-layered tablets. Excessive fines will result in poor tablet quality, as well as tool binding and tablet press overheating, which exacerbates sticking and picking issues. Although fines are a necessary evil for proper tablet compressibility, it is critical that these are kept to a minimum when compressing layered tablets otherwise cross contamination from one layer to the next will be increased as fines will pass under feeders and scraper blades. Bulk densities are also a consideration because light or airy granulations require increased depth of fill and pre-

compression. Pre-compression of the first layer is required for clear demarcation lines between the layers. If the press does not have sufficient upper punch penetration to pre-compress/tamp the first layer, then the desired weight may not be achieved and there will be insufficient volume in the die bore for the next layer. Some modern presses are only capable of 4 mm upper punch penetration, whereas many older presses were capable of almost 10 mm penetration, which, in many cases, made them better suited for layered tablets. Granulation properties would be much the same as with non-layered tablets with the exception of reduced fines; good flow and compressibility are always desired.

Ethirajan: It is beneficial if both layers have relatively equal physical properties, such as the amount of fines, bulk density and granulation properties. It is also ideal to maintain granule size less than one half of the layer thickness to achieve a clear scrape-off. Specifically, fines below 200 meshes can smear or coat the turntable surface and it may not be possible to achieve a clean scrape-off, which can lead to layer cross-contamination.

Q How can common formulation issues, such as the combination of incompatible products, be overcome?

Calvin: The incompatibility of multiple drug matrixes is often paramount in the decision of a new product design process. As I mentioned earlier, however, this issue can be overcome by keeping the matrices separated by an inert 'barrier' layer to prevent drug interaction.

Kirsch: Incompatible APIs are the main driver for layered tablets. They enable incompatible ingredients to be administered in the same tablet without degrading the actives. As for excipient choice, this is why we have R&D; use what works.

Ethirajan: Incompatibility between the tablet components can be overcome by having the incompatible ingredients in different layers.

It is critical to understand the physicochemical properties of the drug substance, and preformulation compatibility studies will help identify such incompatibilities so that certain excipients can be avoided or be separated into different layers for better drug product stability. Multilayered technology is used in many instances to overcome incompatibilities between drug substances that need to be administered in a single dosage. Occasionally, in the case of three-layer tablets, a thin placebo layer may be used between the outer active layers to avoid incompatibilities.

Another vital part in developing multilayered tablets is excipient selection. It is preferable to use excipients that are compatible with the drug substances in both the layers to maximise drug product stability. Generally, scrapers present in the multilayered machines are non-metallic in nature; hence, it is imperative that

the use of abrasive excipients that may ruin these scrapers is avoided. Using excessive amounts of lubricants should also be avoided because these may interfere with adhesion between layers. Excipient choices should also be based on the functionality of a particular layer (immediate release versus controlled release).

Q How can the weight of individual layers be monitored and controlled accurately?

Behrens: When producing bilayer tablets, the in-line control of production, combining compression force measurement and statistical weight check are challenging for several reasons. If the compaction force for layer one is extremely low, it could be very difficult to obtain a clear signal from the strain gauges. Low force compression rollers are available to help deal with this. The reduced mass ensures more accurate and reliable

measurements. Another critical point is statistical sampling of the layers for weight checking. For sampling, the first layer has to be compressed at a higher force to achieve enough hardness to make sampling and weighing possible. Some systems can achieve this by using specialised systems. For example, to avoid the production of second-layer-only tablets during layer one sampling, lower punches can remain in the up position while the fill-shoe for layer two is stopped.



Calvin: Usually, two different process control methods are employed to achieve this. The first, standard method is to utilise

force control, which monitors the layer tamping pressure by means of a strain gauge transducer that, in turn, provides feedback to the press controller. This information is used to automatically

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adjust the metering cam to keep the set pressure constant to maintain the correct weight and tamping pressure. The strain gauge should be sized so that it will be sensitive enough to "sense" the lighter tamping pressures required for producing a tablet layer compared to the strain gauge that would be required for final tablet compression.

The secondary method is to select a multilayer tablet press that automatically collects sample tablets from each layer at regular intervals and then sends them to a weight testing unit, which would be included in the press control feedback loop, to provide in-process checks along with weight control.

Kirsch: Tablet press manufacturers will be responsible for this through improved technology and engineering. By utilising quality by design, the science of the formulation is understood and the design space can be exploited to deliver a controllable

process. Controlled processes deliver a product with the required critical quality attributes that define what is to be delivered to the patient.

Q How can layer cross contamination be avoided?

Behrens: Product losses can be very high when making layered tablets. Usually strong vacuum aspiration is used to clean the residual product on the die table after the dosage of each layer, thus preventing cross contamination. Over the years, vendors have developed several technical solutions that minimise the quantity of powder remaining on the die plate that needs to be removed by suction.

Calvin: Layer cross-contamination can be avoided in a few different ways. For example, ensuring the feed frame is correctly adjusted and not leaking powder, properly adjusting the vacuum

being applied to the front of the feedframe to keep the die table clean, and installing dies that are manufactured to the high limit on overall die height. Whenever the granulation characteristics and tablet size deem it necessary, a "Tail Over Die Scraper" (a delrin cover that is held in place against the die table with spring steel to keep any granulation form slinging out of the die through centrifugal force) may be needed if any powder loss is incurred due to centrifugal force.

Kirsch: Proper press set up is essential. Turret die tables have a certain amount of vertical run out. Often overlooked is the simple task of indicating a die table to locate the high point. Feeder clearance must be set at this point to achieve a minimal amount of clearance between the feeder and die table to reduce

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granulation loss. Scraper blades must be in good condition and free floating on the die table to reduce cross contamination. Die tables must also be in excellent condition as any wear or damage will contribute to granulation crossover. Proper dust extraction is also needed as presses suited for layered tablets generally have more and/or specifically designed vacuum nozzles. Again, reduced fines would be important. Another crucial point I need to emphasise is that skilled press set up technicians and operators are a must!

Ethirajan: Scraper and seal conditions of the feed frames are very important. It is also essential that excess granulation passing the scrape-off be vacuum cleaned so that fines from one layer don't cross contaminate the other. Reduced fill cams may be used to reduce the amount of granulation that needs to be scraped off from overflow of the die.

Q Aesthetically, what consideration should be given to colour?



Kirsch: Aesthetics are always important to the consumer. However, as a manufacturer, the first concern would be, what the

cost is and how well does it compress? Colours as well as flavours can affect tablet compression. Some may be more heat sensitive than others, resulting in picking or sticking issues. Others may have excessive fines resulting in punch and die binding, which increases tool and press wear.

A common error is developing a new product in R&D on a slow, partially tooled press and then submitting a New Drug Application before testing it on a production machine. The R&D press may not even have the same type tooling. If the product was developed on a 'D' tooling press and the production press was a 'B', dwell time would be reduced, resulting in poor layer cohesion or soft tablets. Partial sets of tooling will result in more time under pressure, therefore increasing tablet hardness. Again, poor layer cohesion and soft

tablets could be an issue on a high-speed press. Production presses run at higher speeds and temperatures, increasing possible sticking, picking, laminating and capping issues.

The criteria for colour or flavour choice should be what is least costly and runs best on a production press and not just what "looks pretty". There is a middle ground somewhere for marketing and production. Marketing will not have to deal with the production headaches. It may cost thousands or hundreds of thousands to do a trial on a production press, but would be more cost effective than wasting millions fighting it in full-scale production.

Ethirajan: Colours play an important role in multilayered tablets. Firstly, it is a method of visual process control during compression. The extent of cross contamination, if any, can be easily seen when granulations of different colours are mixed during compression. When a colour coating is not present, coloured tablets also give a visual description to the drug product. In the case of over-the-counter products, colour and aesthetics play a major role in consumer choice.

Q The pharma industry is paying increased attention to in-process controls and process analytical technology. What are the challenges of applying these methodologies to multilayer tablets over standard single layer tablets?

Behrens: PAT systems based on transmission or reflection are seldom used on monolayer tablets. The amount of validation is high, and even more complex for bilayer or multilayers. It is also difficult to repeat the measuring results on each layer. The industry has to put more efforts into this issue.

Calvin: The only additional challenge when pressing a multilayer tablet versus a standard tablet relates to process control to ensure that the prior layer is at the correct weight before allowing any automatic weight change to occur. The first layer must

be in the correct weight range before any changes happen to the second layer. In the case of a three-layer tablet, the first and second layers must be in the correct weight range before allowing the third layer to make any weight adjustment.

Kirsch: PAT is best used during development to understand the variables involved in achieving the formulation design for a quality tablet. Transferring the PAT methods to manufacturing is necessary only when the information generated by the measurements is required to achieve the necessary process control to deliver the desired product. However, PAT measurements can provide information for feedback control, which can offer the manufacturer an opportunity to move toward real-time release of a product. If traditional tablet press variables are properly controlled and a quality granulation is delivered to the tablet press, then the due diligence time spent in process development pays off with a robust manufacturing process that does not require process analytical instrumentation.

Ethirajan: All controls that apply to a single layer tablet must be performed for each different layer in a multilayer tablet. For example, in a bilayer tablet, the granulations for each of the layers are manufactured separately. Both layers have a drug, and then both layers must be monitored and controlled for drug uniformity in the blend/granulation. During compression, in-process controls for weight must be used for both layers. Hardness for the first layer and hardness for the final tablet must also be monitored. If controlling the specification for one of the layers is more challenging, it also affects the formulation and scale-up of the entire process.

Q Batch yields for multilayer tablets can often be lower. What future improvements would help increase yields?

Behrens: Vendors have developed many new systems and machines that can help in this area. I believe that one important feature of such systems is user-friendly software.

In addition, simple features that enable shorter set-up times can be beneficial.

Calvin: I disagree; the batch yield is not affected by the reduced tableting speed, but it is reduced by several other factors. Operating a layer press is the same as operating several presses at the same time; for example, in the case of a three-layer press, you have three different powder feeders possibly containing three different granulations that can contribute to reduced yield. The feeders can contribute to the loss if care is not taken during set up, or if they are not properly adjusted to the die table and are allowed to leak powder. The second major contributing factor to batch yield is the vacuum. If the vacuum applied to the die table to eliminate cross contamination is not correctly balanced, then granulation may actually be vacuumed from the feedframe during operation.

In particular, tablet layer sampling can be one of the foremost

contributors to batch yield loss. During tablet sampling, powder loss cannot be avoided because of the compressions that must be removed and discarded due to the "sampled" layer that is missing during the collection process. Batch yields can be increased by simply taking the time to properly adjust the powder feeders to the die table, correctly balancing the vacuum and by collecting the minimum amount of layer samples needed for the in-process inspection requirement.

Kirsch: Bi-layer tableting speeds are reduced by at least 50% as double sided presses function as single sided presses due to the second layer. Layer cohesion issues, tablet hardness, cross contamination, or other compression issues may result in a further slowing of the press. Press manufacturers are always researching ways to improve multilayer press efficiency. Layer sampling typically slows production. Fette has introduced several

methods to reduce sampling delays and a "punches up" option to eliminate second layer only tablets. Older layer presses discarded excess product whereas product recirculation of individual layers is now possible, which greatly increases yields. Improved load cell resolution will more accurately control weight for individual layers allowing for higher speeds. Presses are available with 100 or more stations of tooling which will certainly increase output. It would be advisable to invest in a purpose built press engineered for layered tablets. Retro fitted or converted presses do not function as efficiently.

Ethirajan: Production rate yields are generally lower. This is because a two- or three-sided machine only makes a single tablet with each head revolution. Also, the need for vacuuming off the granulation that passes the scrape off after each fill station causes higher granulation loss relating to low batch yield. **PTE**

Fixed-dose combinations

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A single dosage form that combines two or more active ingredients is known as a combination drug or fixed-dose combination (FDC). One of the most obvious benefits of an FDC is that it reduces the number of pills that must be taken, which can lead to improved patient compliance. However, FDCs have also been a topic of concern, mainly because of the perceived potential for increased adverse events. PTE speaks with researchers to explore the benefits and concerns of FDCs, and some of the challenges involved in their formulation.

Q Why have FDCs been criticised in the past?

Gupta: The use of FDC was previously discouraged because of cost considerations, lack of flexibility in dose titration and doubts over the bioavailability of the individual components (compared with the bioavailability of the constituent components, when given separately). Another concern was that the use of FDCs would be associated with the increased risk of adverse events. Over the last few years, however, the findings of several clinical trials and observational studies have refuted most of these concerns (1–4).

Findings from recently conducted clinical trials have virtually removed

any doubts over the comparative efficacy and safety of an FDC versus its corresponding free-drug combination. Moreover, in several situations, the use of FDC was associated with significantly improved efficacy. For example, in the ACCOMPLISH Trial, blood pressure control rates (within first six months) improved significantly among previously treated hypertensive patients, from 37% to 73%, with the use of a single pill FDC of two antihypertensive agents. Another trial using a low-dose FDC, STITCH Trial (Simplified Treatment Intervention to Control Hypertension), found that those allocated to treatment with an FDC compared with the usual care

were more likely to have a better blood pressure control, with no adverse effect on tolerability.

Other studies have also shown that the total costs (direct and indirect) related to the use of any FDC is likely to be lower than the use of its corresponding free-drug combination, particularly because of a reduction of indirect costs related to disease complications. Indeed, a quick look at the costs of available FDCs in the UK shows that the direct cost of several FDCs is similar or cheaper than the cost of the two constituent components given separately. Additionally, the cost to patients at the point of delivery is cheaper with an FDC compared with the prescription