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Mini review

Critical factors in manufacturing multi-layer tablets—Assessing material attributes, in-process controls, manufacturing process and product performance☆

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ABSTRACT

Advancement in the fields of material science, analytical methodologies, instrumentation, automation, continuous monitoring, feed forward/feed back control and comprehensive data collection have led to continual improvement of pharmaceutical tablet manufacturing technology, notably the multi-layer tablets. This review highlights the material attributes, formulation design, process parameters that impact the performance, and manufacturability of the multi-layer tablets. It also highlights on critical-to-quality elements that needs to be addressed in the regulatory submission.

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1. Introduction

Multi-layer tablet dosage forms are designed for variety of reasons:

- To control the delivery rate of either single (Bogan, 2008) or two different active pharmaceutical ingredient(s) (API) (Kulkarni and Bhatia, 2009; Nirmal et al., 2008).
- To separate incompatible APIs from each other, to control the release of API from one layer by utilizing the functional property of the other layer (such as, osmotic property).
- To modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release (Efentakis and Peponaki, 2008; Phaechamud, 2008).
- To administer fixed dose combinations of different APIs (LaForce et al., 2008), prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device (Maggi et al., 2005), buccal/mucoadhesive delivery systems (Park and Munday, 2002), and floating tablets for gastro-retentive drug delivery (Sungthongjeen et al., 2008).

This design feature provides, unique product performance objectives otherwise not achievable by conventional tablets, but also brings a new set of challenges for formulation design, manufacturing process, controls and product life performance requirements. In addition to manufacturing science challenges, they also add challenges in establishing relevant regulatory controls to meet the product performance requirements over the life of the drug product. To meet these requirements a higher level of understanding in the ingredients and manufacturing variables is critical to manage the risks associated with product acceptability over the life cycle to avoid batch failures and batch recall. Thus the development and production of quality bi-layer tablets require a comprehensive understanding of the product and process in order to address challenges in manufacturing such as accuracy in weight control of each individual layer, de-lamination/layer-separation during manufacturing and storage, insufficient tablet breaking force and cross-contamination between the layers (especially for incompatible APIs). This review focuses on critical-to-quality elements in the pharmaceutical drug development and focuses on regulatory perspective of design and development of bi-layer tablets. In addition, it addresses utility of a risk-based approach in design and development of bi-layer products as an integral part of the manufacturing process, rather than relying on post-production testing.

2. Bi-layer technology platform

One of the forerunners in utilizing bi-layer technology is osmotically controlled tablets, in which, the drug and osmotic layer are

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compressed together and coated with a semi-permeable membrane to control the release rate. This design has its own benefits and challenges and there are a number of products on the market using this technology. However, over the course of time, bi-layer technology was transformed to accommodate other drug delivery applications, such as, delivering incompatible APIs, controlling the releases multiple APIs at different rates and releasing actives at different sites, just to name a few.

Because bi-layer tablets are susceptible to de-laminate along the interface of the two layers during compaction, it is critical to understand the weight control of each layer, control of total weight of the tablet, compaction behavior within each layer of the formulation and the adhesion mechanism between layers and their relationship to compaction parameters.

3. Compaction principles governing weight control

Unlike conventional tablets, bi-layer tablets require three weight controls, namely, individual layers and the final tablet weight control. The complexity in the weight control significantly increases the level of sophistication needed in the rotary press designed for multi-layer tablets. Typically, in closed-loop control systems, two different types of control mechanisms for weight are involved. In the first case, typically called a force control system, a fixed force is applied during compression and the actual exerted force is measured. The measured force on the individual layer is utilized to calculate the acceptable range around the mean during the process set up. The acceptable range of the measured force from the set point is sent as a feedback for weight control during beginning of compression cycle.

Alternatively, the layer or tablet thickness is indirectly used as a feedback for weight control. In this case, the peak force encountered during compression for fixed tablet thickness is measured and the acceptable range for the established peak force for given run weight is sent as feedback for the weight control (Ebey, 1996). For example, the upper punch is programmed to travel a fixed distance in the die cavity. The range for the resulting force is established for the target weight of first layer during set up. The compressed first layer is rejected if the measured force during first compression does not fall within the range. The same cycle is repeated for the second layer compression and both the layers are rejected if the resulting force during second compression does not fall within the range established for total tablet. Though both the approaches are very similar in manufacturing the tablets, the feed back mechanism differs. Ultimately, the compressed tablet is required to retain the adhesiveness between the two layers during the shelf life of the product. The primary process parameter that may impact adhesion as a quality attribute of the drug product is compression force.

4. Compression force

Since the material in the die cavity is compressed twice to produce a bi-layer tablet, compressed first with layer—one followed by both the layers, the compression force affects the interfacial interaction and adhesion between the two layers. A certain amount of surface roughness of the initial layer is required for particle interlocking and adhesion with the second layer. As the surface roughness of the first layer is reduced, the contact area for the second layer is significantly reduced at the interface and makes the adhesion weaker. Immediately after final compaction, the compressed second layer may release the stored elastic energy unevenly and may produce crack on the first layer which could act as a stress concentrator and eventually making the tablet interface weaker. This may result in capping or de-lamination of the tablet along the interface either during manufacturing or immediately after (Inman et al., 2007). The level of compression force used in the first layer compaction determines the degree of surface roughness of the first layer. The higher the first layer compression force, the lesser the surface roughness resulting in reduced adhesion with the second layer. Therefore, for a given final compression force the strength of interfacial adhesion decreases with the increasing first layer compression force. It implies that the extent of plastic/elastic deformation of the first layer has profound effect on the strength of the interface (Inman et al., 2006). Thus, understanding the interaction and adhesion behavior between different layers composed of various ingredients with differing physico-chemical properties during compaction is critical to understand the failure mechanisms of bi-layer tablets. Understanding of material attributes of the excipients and API that undergo compression and compaction is decisive in predicting the interaction.

5. Material attributes: elastic and plastic deformation

Compressibility and the tablet breaking force are dependent on the nature of the API, excipients and compaction parameters. Material properties such as brittleness (di-calcium phosphate), ductility (microcrystalline cellulose) and elasticity play central roles. In addition, porosity, shape of the granules and morphology significantly influence the compression process. Significance of material attributes depends on ratio of API to the excipients in the drug product. If the drug product consists predominantly of API, then the material attributes of API need to be evaluated and likewise for a potent or low dose formulation, the attributes of the excipients become increasingly significant.

Brittle and plastic deformations of the excipients have significant impact on the compaction process. Compaction of predominantly ductile material is a result of plastic deformation as long as the stress developed by the elastic recovery does not exceed the bond strength (Danielson et al., 1983). The additive effect of individual material attributes and the material attributes of a blend, may not be the same as in the binary mixtures and to address this issue, several models are proposed to predict the compressibility behavior of the binary mixtures with the input of individual material attributes of the excipients. For example, Busignies et al. (2006) have calculated the mean yield pressure[1] during under pressure (in-die) and after the elastic recovery (out-of-die) of the tablet. However, a proportional relationship was not valid for the mean yield pressures calculated based on the individual yield pressure. A predictive approach was proposed by these authors to indirectly obtain the mean yield pressure of a binary mixture from the data of the individual materials. The predictive approach used the linear mixing rule observed with the porosity. The validity of the model was verified and compared with the experimental values. The interesting fact is that the authors have used predominantly a ductile material such as microcrystalline cellulose and brittle material such as calcium phosphate and lactose for preparing their binary mixtures.

During compression, brittle materials such as di-calcium phosphate, acetaminophen and lactose tend to fracture and fill the voids. On the contrary, the ductile materials, such as microcrystalline cellulose and corn starch tend to undergo deformation. These material attributes impact the surface characteristics of the tablets. Narayan and Hancock (2003) observed that the brittle materials generally produced smooth (surface) and brittle compacts, where as the

[1] Mean yield pressure is derived from the Heckel equation (Heckel, 1961a,b): $\ln(1/(1-D)) = KP + A$. Where, P is the compaction pressure, D is the relative density, K is the slope of the linear portion of the Heckel plot, and A is the intercept. The reciprocal of K, mean yield pressure, often provides a measure of the plasticity of the material. Materials that readily undergo plastic deformation tend to have relatively higher slope, giving low yield pressure, than those that undergo brittle fracture (He et al., 2007).

ductile materials produced rough (surface) contacts and ductile compacts. Therefore, if the first layer is predominantly composed of ductile material and the second layer predominantly of brittle material, their interfacial interaction and the tablet breaking force needs additional scrutiny. Thus, for robust manufacturing operation for multi-layer tablets the material attributes such as mechanical and compaction properties individual layers should be similar. Or, alternatively the individual layers may include a well-balanced proportion of both brittle and ductile material (Yang et al., 1997). Because there is more than one layer, the precision needed for controlling the individual weight of the layers demands predictable and consistent behavior of the final blend such as flow property and particle size distribution. Thus, for directly compressible material, material attributes including the flow property and particle size distribution of the ingredients undergoing compaction will play a major role. However, that situation changes when granulation process, such as wet granulation and roller compaction or slugging are utilized to improve the flow properties, blend uniformity or compressibility.

6. Manufacturing process

In addition to physico-chemical attributes of the excipients, manufacturing processes such as wet granulation/roller compaction and addition of binders increases the level of complexity in understanding the critical factors governing compression and tablet breaking force. Thus, the tablet breaking force and the tablet's propensity for de-lamination/capping either during manufacturing or during storage need to be carefully observed. Apart from the critical material attributes of individual components and final blend, the tablet press has large influence on the manufacture of multi-layer tablets. The level of pre-compression force, punch velocity, consolidation time (time when punches are changing their vertical position in reference to the rolls as the distance between the punch tips are decreased), dwell time (time when punches are not changing their vertical position in reference to the rolls), relaxation time (time when both punches are changing their vertical position in reference to the rolls as the distance between the punch tips increases before losing contact with the rolls), and the applied force can have significant effect on the critical quality attributes of the tablet (Muzzio et al., 2008). For instance, the extent of compact densification and resistance to compressibility within the die cavity was impacted by compaction pressure and the punch velocity. It was demonstrated that increase in the punch velocity between of 50 and 500 mm/s decreased the porosity reduction on individual layers (Yang et al., 1997).

6.1. Skipping first layer compression

As described earlier, the number of compressions in manufacturing of multi-layer tablets is equal to the number of layers in the multi-layer tablet. If the first layer is not compressed before addition of second layer, there is a possibility of uncontrolled mixing of granules of first layer into second layer at the interface. In addition, if the first layer is not compressed before addition of second layer, due to the centrifugal force during the rotation of the turret, the granules of first layer may shift toward the outer periphery of the die cavity resulting in an angled (skewed) interface. A clear demarcation between the two layers is desirable since it is not only appealing and but also visually assures that there is no cross-contamination.

6.2. Tablet breaking force

According to the current USP, tablet breaking force is the force required to cause the tablets to break in a specific plane. The tablets are generally placed between two platens, one of which moves to apply sufficient force to the tablet to cause fracture. For conventional, round (circular cross-section) tablets, loading occurs across their diameter (sometimes referred to as diametrical loading), and fracture occurs in that plane. Tensile strength provides a more fundamental measure of the mechanical strength of the tablet and it considers geometry of the tablet. Tensile strength is calculated by the following equation (*USP* < 1217 > *Tablet Breaking Force*; Fell and Newton, 1970):

$$\text{Tensile strength} = \frac{2F}{\pi Dh}.$$

F is the load required to break the tablet diametrically (as opposed to de-laminating or capping), "D" and "h" are tablet diameter and thickness, respectively. Thus, tensile strength estimates force per unit area of the tablet at breakage. This equation is applicable only for the tablets that have flat surface. For tablets that do not have flat surface, curvature needs to be considered while calculating the surface area.

It is well documented that the mechanical strength of a tablet can be generally characterized by measuring the tensile strength using the compression test introduced by Fell and Newton (1970). In case of a matrix tablet the impact of components properties, such as particle size and shape, effective contact surface area and tablet porosity on the tensile strength is well documented (Nikolakakis and Pilpel, 1988; Sebhatu and Alderborn, 1999; Chan et al., 1983).

To simplify the process, alternate approaches of determining adhesion strength as a measure of binary tablet performance have been developed and reported in the literature. An apparatus to measure the shear forces needed to separate the layers in the radial direction and relate these forces as a measure of adhesion strength was reported by Dietrich et al. (2000).

Although measurement of tensile strength is appropriate for assessing the tablet strength, pharmaceutical firms tend to measure the tablet breaking force, which is essentially the load to break the tablet. Another measure for mechanical strength is the crushing strength-friability ratio (CSFR). Regardless of how the tablet is evaluated for its strength, a measure to assess this critical attribute must be fully evaluated and the choice of the test method must be supported by the formulation and the manufacturing process. The integrity of the tablet needs to be assessed during the stability studies to confirm that aging and environment have not negatively influenced the adhesion of the layers.

6.3. Effect of lubrication

Since the first layer surface is uniform and perhaps relatively less rough due to the first layer compression, the interfacial interactions between the first layer and the second layer may be impacted by the level of lubricant. The tablet surface smoothness increases as the level of lubricant, such as magnesium stearate is increased (Sugisawaa et al., 2009). For example, Dietrich et al. (2000) have concluded that in order to achieve a better interfacial interaction between the layers, relatively low lubricant concentration (practically possible) and low compression forces are required for first layer tabletting. However, the level of lubricant needed for avoiding picking and sticking of the first layer must be assessed as part of the product development.

The blended lubricant in the granules bulk distributes throughout the mixture, or "coats" on the surface of the granules and this provides lubricity and reduces the friction when the granules come in contact with dies and punches during compression. However, the lubrication can also reduce the extent of inter-granular adhesion and potentially affects the critical quality attributes such as tablet breaking force and dissolution. Thus, adding lubricant to the dies and punches, instead of adding directly to the granules, has

been investigated to understand the impact of lubricant on the critical quality attributes of the tablet. This process is referred to as external lubrication in the literature. In external lubrication, the lubricant is sprayed onto the die and punches for each compression cycle instead of adding it to the bulk powder mixture. Yamamura et al. (2009), have shown that the external lubrication can increase crushing strength by 40% without prolonging the tablet disintegration. The authors have confirmed their finding by observing a layer of magnesium stearate on the tablet through scanning electron microscope. Though this new technology appears advantageous for the mono-layer tablets, it can potentially be used to better understand the impact of lubricant on the quality attributes of bi-layer tablets.

6.4. Coating

Often multi-layered tablets are coated to improve elegance, to protect the cores from ambient conditions or to control the release profile. In either case, exposure of the multi-layered tablets to solvents, high temperatures and affect of loads must be considered in the product development. To avoid layer-separation during the coating process it is important to know the coefficients of thermal expansion of the tablet layers and the impact of this difference on the tablet integrity. Breech et al. (1988) have explained that during the coating process of bi-layered tablets, cracks appeared on the surface of only one layer within few minutes of the coating process, leaving the other layer intact. Upon testing, the authors found that the thermal expansion coefficient of two different layers of the tablet were significantly different. When the authors ran a control, coating the individual layers separately at 40–55 °C, no evidence of cracking was found. To alleviate the cracking, the product was reformulated with each layer having almost the same coefficient of thermal expansion. Thus, multi-layer drug products that are intended to undergo coating process require additional scrutiny that may not be needed for drug products that do not require coating.

Though cracking is reported for bi-layer tablets that undergo coating, it is possible that the cracking and/or separation of layers could also occur upon extended storage of the drug product.

Thus, it is imperative that the excipients are not only screened for their physical properties such as particle size and compressibility during the pharmaceutical development stage, but also, tested to ensure the individual layers are similar in terms of their thermal expansion coefficient.

7. Stability

In the stability studies, these drug products need to be observed closely and tested periodically to ensure that their integrity is preserved throughout their shelf life and they perform in a predictable manner. Bi-layer tablets prepared with the combination of two therapeutic agents are certainly convenient, and thus simplifies the treatment regimen. The use of a combination of two active pharmaceutical ingredients or the same active pharmaceutical ingredient (API) with different release rate to optimize therapy and to improve patient compliance has increased steadily over the years (Bangalore et al., 2007).

To achieve this objective it is imperative that the quality and the performance of the bi-layer tablets be maintained over the expiration period. The stability studies must be performed under conditions as per ICH guidelines and the supportive stability data generated during the product development phase and on the exhibit (clinical and/or BA/BE) batches to demonstrate the product quality and performance must be included in the filing. It is recommended that the sponsor perform the drug–drug, drug–excipient interaction, studies the impact of manufacturing process, and the impact of heat and humidity on the integrity of the bi-layer and drug release over the expiration period. The selection of the container/closure system must be based on the ability of the system to protect the drug product and maintain the integrity of the bi-layer under use condition over the shelf life.

The study done by Aryal and Skalko-Basnet (2008) demonstrated that the bi-layer tablets prepared with amlodipine besylate and atenolol had a better stability profile than the mono-layer matrix tablets consisting both the APIs. This strategy, although improving the stability of one drug component, did not completely prevent the interaction. A significant decrease (more than 5%) in the assay was observed in the other drug component. In such scenarios, if alternate approaches are used to improve the product stability of the layered tablets they must be adequately supported by the stability studies.

8. *In vitro* performance

The *in vitro* dissolution testing requirement of the bi-layer tablets will vary based on the intended dosage design and the physico-chemical characteristics of the drug in each layer. This variability poses special challenges in the development of a meaningful dissolution procedure for bi-layer drug products, especially if drugs with different water solubility are incorporated in the bi-layer tablets. In general, attributes such as rate of swelling and rate of water uptake need to be assessed for the bi-layer tablets. For example, if the goal of bi-layer immediate tablet is to deliver two incompatible API, then the separation of these layers in the dissolution media may be of no significance as this would not have any impact on the product performance (*in vivo*). However, if the bi-layer tablet is a modified release product, with the design feature to control the release rate of the API layer by compacting with placebo layer, the integrity of the layers in the dissolution media is critical to the performance of the drug product (*in vivo*).

In the case of bi-layer drug products, a bio-relevant dissolution test conditions would be more meaningful in evaluating product quality and product performance. For example, *in vitro* dissolution testing of bi-layer tablet made with water insoluble APIs need extensive use of simulated fluids on both fresh tablets and the long-term stability samples. Having a sensitive, reliable and discriminating *in vitro* dissolution procedure to determine the product quality and to predict bioavailability is of primary interest to the Agency (Meyer et al., 1992). It is recommended that all studies done for the development of the dissolution method be included in the filing to support the final method that will be used for release and stability of the drug product.

In general, development of a meaningful dissolution procedure for APIs with limited water solubility is more challenging than for the drug product with a high water solubility API. Having both classes of drugs in the same unit presents additional challenges to both the pharmaceutical industry and the regulatory agency.

To measure the *in vitro* drug release performance of the bi-layer drug product, well established techniques can be used to achieve adequate dissolution by understanding the solubility differences of the APIs (where applicable), use of relevant and appropriate amount of surfactants (Schott et al., 1982), composition and volume of dissolution test medium, pH, type of apparatus and rate of agitation (http://www.accessdata.fda.gov/scripts/cder/dissolution/).

9. Conclusion

Bi-layer tablets provide one of the important design approaches where incompatible drugs, drugs with different indication, and same drug with different release rate (e.g. IR and ER) can

be incorporated in a single unit. To develop a robust bi-layer tablet a complete mechanistic understanding must be developed through the application of scientific and quality risk management tools (www.ich.org, ICH Q8(R2): Pharmaceutical Development; www.ich.org, ICH Q9: Quality Risk Management). The knowledge gained by applying these scientific principles and risk management tools during the pharmaceutical developed must be fully discussed and functional relationship linked to the product performance must be clearly presented in the regulatory submission (www.ich.org, ICH M4Q (R1): The Common Technical Document: Quality).

The objective of the dosage form is to ensure that the drugs available to its citizen are not only safe and effective, but are also properly manufactured and packaged to meet the established quality target product profile over it shelf life. A well-developed product will effectively address these issues by including appropriate control strategies and establishing the functional relationships of the material attributes and process parameters critical to the bi-layer tablet quality as discussed in the article.

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