A REVIEW: BILAYR TABLET TECHNOLOGY

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Abstract

Bi-layer tablet could be a new era for the successful development of controlled release formulation together with various features to produce some way of successful drug delivery system. Therapeutic strategies supported oral delivery of bilayer (and multilayer) tablets are gaining more acceptance among brand and generic products due to a confluence of things including advanced delivery strategies, patient compliance and combination therapy. Successful manufacturing of those ever more complex systems must overcome a series of challenges from formulation design to tablet press monitoring and control. this text provides an outline of the state-of-the-art of bilayer tablet technology, highlighting the foremost benefits of this kind of oral dosage forms while providing an outline of current challenges and advances toward improving manufacturing practices and products quality. Several aspects relevant to bilayer tablet manufacturing are addressed including material properties, lubrication, layer ordering, layer thickness, layer weight control, additionally as first and final compression forces. a bit is additionally dedicated to bilayer tablet characterization that present additional complexities related to interfaces between layers. The available features of the manufacturing equipment for bilayer tablet production are described indicating the numerous strategies for sensing and controls offered by bilayer tablet press manufacturers. Finally, a road map for bilayer tablet manufacturing is advanced as a suggestion to formulation design and selection of process parameters and equipment.

Key word: Bilayer tablet, Challenges in manufacturing, Characterization, Bilayer compression machines.

Introduction

Solid oral dosage forms are the preferred route for many drugs and are still the most widely used formulations for new and existing complex-configuration dosage forms such as controlled-release, osmotic pumps, and compression-coated tablets. The controlled-drug delivery systems typically require more demanding mechanical testing, characterization, and monitoring techniques with faster response times than those possible with traditional measurement approaches In recent years, pharmaceutical drug product manufacturers have oriented their product development activities to fixed dose combinations (FDCs) for treatments like type 2 diabetes, hypertension, pain and HIV/AIDS to mention a few. Several different approaches are employed to deliver the FDC products to the patients such as multilayer tablets compression coating, active coating, bilayer floating tablet and buccal/mucoadhesive delivery systems. Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The

goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery.[1] Among these approaches, the multilayer tablets drug delivery is gaining popularity and particularly the bilayer technology has attracted manufacturers' attention for the development of products for life cycle management (LCM). If bilayer tablets are inadequately manufactured, the tablets could split apart leading to a very critical defect since it could potentially result in a patient not receiving one of the intended drug component. The residual stress distribution in the tablet is suspected to be a major cause of the resultant tablet in homogeneity causing the tablet to fracture and split apart The fracture of multi layered tablets is often the result of an interfacial crack driven by residual stresses in the tablet and propagating a finite distance within the tablet. This leads to capping and lamination, which may not always be immediately apparent after compaction. It is known that occurrence of the fracture/crack at the interface causes a reduction in the overall elastic stiffness (Young's modulus) and layered tablets become fragile and develop a tendency to fail. Therefore, while the therapeutic (chemical/pharmaceutical) functions of multi layered tablets are crucial, they need to have sufficient mechanical strength and ruggedness to survive normal processing, handling, packaging, and shipping stresses.[1,3] Understanding what influences the stress state and mechanical properties of a multi layered tablet and developing specialized techniques for measuring those properties will assisting the understanding of how, and why, defects such as capping, delamination, and cracking occur. Understanding and predicting the mechanical strength of bilayer tablets is of commercial significance since bilayer tablet failures (delamination) due to weak mechanical strength can lead to enormous financial loses. This review mainly focuses on the advantages and the main challenges associated with bilayer compaction technology including impact of material mechanical properties, characterization techniques for interface between layers, compression parameters, as well as features offered by commercial bilayer compression machines.[4,5]

2. Advantages & Disadvantages of bilayer tablets[1-11]

Advantages:

1) Bi-layer execution with optional single-layer conversion kit.
2) Cost is lower compared to all other oral dosage form
3) Greatest chemical and microbial stability over all oral dosage form.
4) Objectionable odour and bitter taste can be masked by coating technique. Flexible Concept.
5) They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
6) Easy to swallowing with least tendency for hang up.
7) Suitable for large scale production.

Disadvantages:

1) Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
2) Bitter tasting drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require

encapsulation or coating.

3) Difficult to swallow in case of children and unconscious patients.

4) Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability

3 Challenges in Bilayer Manufacturing:

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

Delamination: Tablet falls apart when the two halves of the tablet do not bond completely. The two granulations should adhere when compressed [12,13]

Cross-contamination: When the granulation of the first layer intermingles with the granulation of the second layer or vice versa, cross-contamination occurs. It may conquer the very purpose of the bilayer tablet. Proper dust collection goes a long way toward preventing cross contamination [12,13] Production yields: To prevent cross contamination, dust collection is required which leads to losses. Thus, bilayer tablets have lower yields than single-layer tablets. [12,13]

Cost: Bilayer 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 bilayer mode. Third, development of two compatible granulations is must, which means more time spent on formulation development, analysis and validation. These factors, if not well controlled/optimized, in one way or another will impact the bilayer compression per se and the quality attributes of the bilayer tablets (sufficient mechanical strength to maintain its integrity and individual layer weight control). Therefore, it is critical to obtain an insight into the root causes to enable design of a robust product and process. [12,13]

Overcoming all these challenges requires a focused effort toward addressing the following areas related to material properties and bilayer processing parameters:

i. Determination of mechanical properties of each layer,

ii. Maximization of inter-facial adhesion between the layers,

iii. Optimization of the first layer compression force,

iv. Quantification/understanding of factors contributing to delamination, assessment of the impact of layer sequence and layer weight ratio,

v. Development of techniques for small scale material characterization tools that can be applied during bilayer tablet design.

vi. Selection of appropriate bilayer tablet press alternatives with consistent weight control delivering system.

3.1 Material properties

Understanding the fundamental material properties (API and excipients) like brittleness (lactose, di-calcium phosphate), plasticity (microcrystalline cellulose) and viscoelasticity (pre-gelatinized starch) is key in the successful development of bilayer tablets. Depending on the drug load in the formulation, either the API property and/or the excipients property will predominantly impact the compaction property of the formulation. It has been reported in the pharmaceutical literature that plastically deforming and brittle materials have a significant impact on the compression process. The compression of a plastic material is by virtue of the plastic flow as long as the stress developed by the elastic recovery does not exceed the bond strength. On the application of a compression force, a brittle material will fracture and fill the voids. In addition, due to differences in the elastic Young's modulus, materials relax at different rates during decompression. Elastic mismatch of the adjacent layers in a bilayer configuration is due to differences in the Young's modulus and deformation histories of the respective individual layers. This generates radial stresses, which in turn causes the bilayer tablets to delaminate. Propagation or transmission of compression force through the materials also changes with the material properties. A greater particle deformation in the lower central region of the die than at the outer radial regions can be attributed to the applied compression stress, which acts primarily in a downward central direction. This phenomenon is due to the wall friction, which retards the vertical movement of the particles in contact with the die. The expansion of a tablet continued over several days after ejection from a die(elastic recovery), and the amount of expansion was demonstrated to be different depending on the materials evaluated (e.g. micro-crystalline cellulose, dicalcium phosphate, hydroxypropyl methylcellulose) concluded that the nature of materials played a critical role on the strength of bilayer compacts and also on their mode of fracture. [1,14]

3.2. Compression forces

Compression forces applied on the first layer and the second layer significantly impact the interfacial strength and the adhesion between the adjacent layers thereby contributing to the mechanical integrity of the resultant bilayer tablet. To address this major concern, the compression force requires very close attention. The delamination of bilayer tablets is due to the development of various mechanical stresses during compression and particularly during the unloading phase and tablet ejection if the material forming the first layer of a bilayer tablet was more elastic, the tension introduced into the system weakened the strength of the bilayer tablets. It has been revealed that the way in which failure of a rectangular beam (bilayer tablet) crossed the interface between different layers was an important factor in determining the tensile strength of bilayer tablets. The compression of the first layer was the most critical factor, which affected layer adhesion. 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 an increase in the punch velocity between 50 and 500 mm/s decreased the porosity reduction on individual layers. [1,15] A decrease in axial tensile strength of bilayer tablets observed with increasing first layer compression force for several mechanically different materials, e.g. plastically deforming materials and brittle fragmenting materials, was attributed to the reduction of bonding surface area and adhesion between the layers. It was suggested that stresses caused from compaction and elastic material mismatch between layers can result in tablet delamination. In addition, a fracture toughness test was utilized to examine the fracture behaviour of the bilayer interface. The interfacial strength of bilayer tablets composed of plastic material (MCC in first and second layers) decreased with the increase of the first

layer force while maintaining constant the second layer force. To further strengthen the criticality of compression forces in a bilayer configuration ,the authors suggested that the bilayer tablets with a diameter of 9.5 mm compressed with first layer force of 0.25 kN fractured in the second layer (though very close to the interface), while tablets pre-pared with 0.5 and 1 kN first layer compression forces, the bilayer tablets fractured along the interface. On the other hand, bilayer tablets compressed using MCC in first and second layers at a constant first layer force of 2 kN and varying (15–25 kN) second layer force led to an increase in the interface with an increase of the second layer force. These findings support that the interfacial strength.[16]

3.3. Lubricant

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. In order to achieve a better interfacial interaction between the layers, relatively low lubricant concentration and low compression forces are required for first layer tableting. 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 lubrication 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 external lubrication, the lubricant is sprayed onto the die and punches for each compression cycle instead of adding it to the bulk powder mixture, have shown that the external lubrication can increase crushing strength by 40% without prolonging the tablet disintegration. It is confirmed 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 bilayer tablets.[17]

3.4. Layer ratio and layer sequence

There are a very limited number of publications on the impact of layer ratio and layer sequence in a bilayer configuration on the mechanical strength and other quality attributes of bilayer tablets. In general, it is a common practice to have a 1:1 or 1:2 weight ratio between the two layers. In most cases, a layer ratio of 1:3, 1:4 can be encountered and even sometimes a disproportionate ratio of up to 1:6 can be evaluated during development. It is more challenging to maintain a consistent second layer weight when the first layer weight is large as com-pared to the second layer weight (for example, ratio of 1:5 or 1:6). In such circumstances, it is preferred to compress the smaller layer weight in the first layer. However, due to mechanical limitations, the features of the current commercially available bilayer presses do not offer the possibility of compressing the smaller weight in the first layer. Therefore, the formulators have no option than placing the material with a larger weight in the first layer with all its associated challenges. Upper punch penetration depth during the first layer compression force and during the second layer

compression force impacted the potency of the second layer API. It was argued that a deeper upper punch penetration into the die might minimize any sort of splashing out of the second layer mate-rial from the die during compression thereby providing potency values close to 100% of label claim. The impact of layer weight ratio on the mechanical strength of the bilayer tablets, which were prepared with MCC and lactose at ratios of 1:3, 1:1 and 3:1 was investigated. There was no significant impact on the breaking force of the bilayer tablets for the materials and ratio ranges studied.[18]

3.5 Environmental Conditions:

The effect of moisture on the strength of bilayer tablets was studied by few authors. Compacts made from hygroscopic mate-rials will respond to the relative humidity of the surrounding air by absorbing/desorbing of moisture into/out of their pore structure. In addition, if the compacts have been made from, for example, starches, microcrystalline cellulose, crospovidone, hydroxypropyl methylcellulose, polyvinylpyrrolidone, sodium starch glycolate, and colloidal silicon dioxide, moisture can also penetrate the bulk of the particles of these materials. The uptake of moisture into the porous compacts and/or particles leads to layer expansion and to changes in the Young's modulus of elasticity. Any change in layer dimensions will weaken the interface between the layers and might hence contribute to time-dependent delamination extensively studied changes in the Young's modulus of elasticity and their effects on strength and delamination.[19] In general, an increase in moisture results in a decrease in Young's modulus, and very small differences and changes in Young's modulus can lead to adhoc delamination. It was recommended that materials should be pre-conditioned to ensure that they are at equilibrium with the moisture of the air in the manufacturing area and the com-pacts should be packaged into air-tight, moisture protective blisters. Thermal diffusion is a rapid process, thermally induced changes in deformation and stresses are usually momentous and can lead toad-hoc delamination. On the other hand, hygroscopic effects are quite slow (can take anything from days to weeks or even months before moisture equilibrium inside a compact have been achieved as they depend on the moisture diffusion inside the compact. Apart from the formulation design and manufacturing process considerations, physical stability of bilayer tablets during storage is a key factor for consideration during product development as this may impact the quality attributes of the bilayer tablets such as ten-sile strength, layer adhesion, friability and dissolution. The strengths of bilayer tablets composed of plastic/brittle, brittle/plastic and brittle/brittle were compared upon storage. For bilayer tablets prepared with MCC in the first layer/lactose in the second, and lactose in the first layer/MCC in the second, the tablet interfacial strength decreased with the increase in humidity and storage time while for those prepared with lactose/lactose, an increase in tablet strength was observed due to the formation of solid bridges upon storage. Transient in moisture diffusion into bilayer tablets with significant differential moisture absorption characteristics are responsible for the reduction of strength in both high and low moisture environments. The authors suggested that the insight gained from their studies will be useful for material selection and packaging of bilayer tablet systems.[20]

3.6. Layer weight control

The materials particle size distribution, flow property and the ability of the bilayer press to accurately control the layer weight are very critical in assuring acceptable content uniformity of the APIs composing the bilayer tablets.

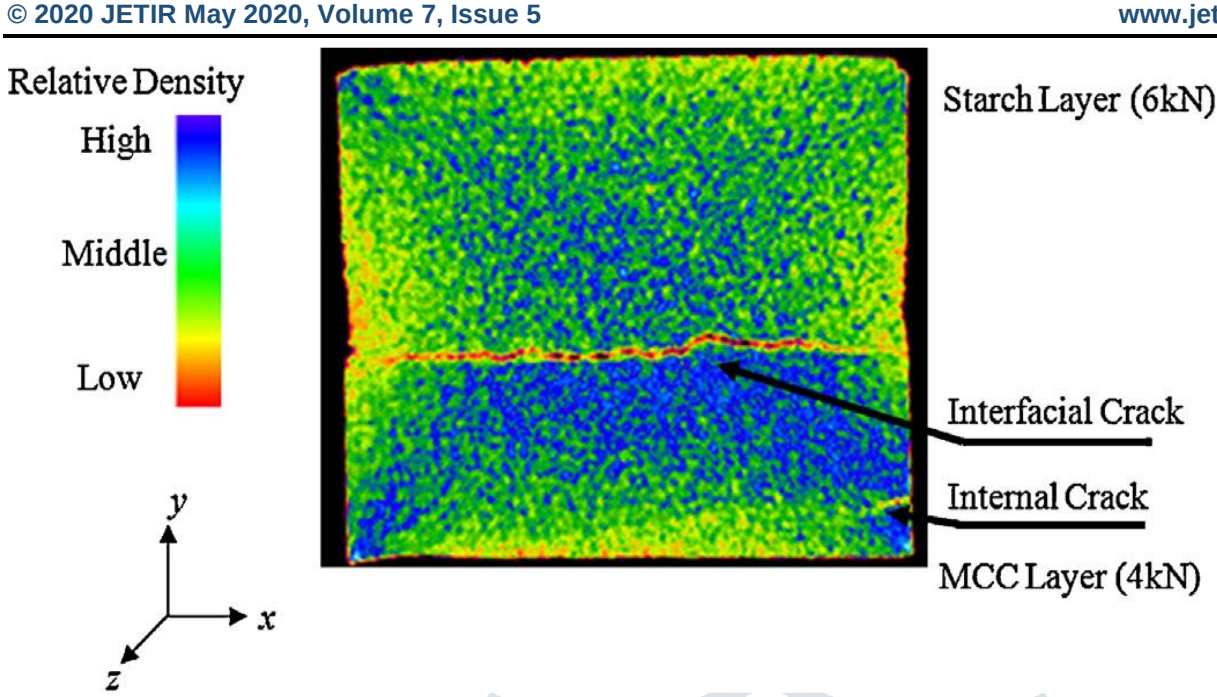
Each instrumented bilayer press from different vendors has its own weight control mechanism. The available development and commercial presses offer the possibility of monitoring the first layer weight and the second bilayer weight. To make situations more complex, no commercially avail-able bilayer press is equipped with a device to sample separately the second layer weight. In general, a minimal precompression force is applied on the first layer, which makes sampling more challenging as the tablets do not come of the press solid enough to weigh. Bilayer presses are equipped with a sampling device for first layer compact, which allow applying an additional compression force on the first layer material and there by hardening the compact and rendering it more suitable for weight check.[1]

3.7. Bilayer tablet characterization

The bilayer tablet formulations used for each individual layer should be compressible (i.e., the ability of a material to undergo are duction in volume as a result of an applied pressure) and compactable (i.e., the ability of a powdered material to be transformed into tablets with strength during densification) on their own, that is, they should show satisfactory reduction in volume and form mechanically strong and coherent solid bodies. Some benefits of bilayer tablet characterization in early formulation development are (i) quantitatively determine the interfacial strength in bilayer tablets, (ii) detect unusual or extreme proper-ties of compacted layers, (iii) ensure lot-to-lot consistency of the resultant tablets, (iv) rationale strategy to guide formulation development and for the selection of compatible product formulations and manufacturing processes, (v) explain material failure mechanisms during tablet manufacturing, (vi) understand the effect of the factors specific to tableting equipment (e.g., speed of operation, applied forces, etc.), (vii) reduction in energy consumption by minimization of faulty tablet production, and (viii) environmental issues and concerns related to the management of waste materials.[21]

3.7.1. 3D characterization tools

X-ray micro-computed topography is a volumetric imaging technique, which enables non-invasive determination of the density of a material in space on the principle of attenuation of X-rays as it pass through. The specimen is placed on a rotating stage between a micro-focal mono-energetic source and a charge couple detector (CCD) array based detector. A phosphor plate between the specimen and the detector is used to intensify the image. Most modern industrial CT systems are capable of attaining resolutions of less than 50m. Projection images (radio-graphs) of the object are obtained in slices at specified angular rotational steps; from which horizontal slices are reconstructed utilizing Fourier based Filtered Back Projection (FBP) algorithms. The attenuation values calculated as a function of space obeys the Beer–Lambert's Law. Upon normalizing by the mass density, the mass attenuation coefficient is found to be constant for most materials over a range of energies, leaving the attenuation values (CT or HU) as a function of density and path alone. By means of calibration, it is quantitatively possible to determine the density of the sample as a function of space at a sufficiently high resolution. The individual slices can be stacked up and a 3D volumetric reconstruction of the specimen can be obtained using standard interpolation techniques such as marching cubes or adaptive rendering. The interfacial cracks between the adjacent layers can be detected. This nucleation of the cracks was attributed to the weak bonding between adjacent layers consist of two different materials.[22]



3.7.2. Interface characterization tools

The number of compressions in manufacturing of multilayer tablets is equal to the number of layers in the multilayer 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 com-pressed 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 but also visually assures that there is no cross-contamination. The material response of the con-strained particles to an applied load within the initial compaction layer has shown to have a detrimental effect on the resistance to fracture of a bilayer tablet [1].This indicates the importance and quality of the bonding produced at the interface. Knowledge of the morphology and surface properties of pharmaceutical particles commonly utilized in tableting applications, in a free or a consolidated state, can assist with the characterization of a material mechanical response to an applied load. The determination of the inherent structure of single particles obviously requires a topographical methodology which can accurately operate at relatively small length scales, such as atomic force microscopy. At larger operating length scales, as commonly employed with an optical profilometer, the 'waviness' or form and roughness of a surface can be determined. It is the form of a surface which may provide information regarding the elastic recovery of a compacted material (Poon and Bhushan, 1995). Previous applications of optical profilometers to investigate the properties of compacted materials have involved the generation of both 2D and 3D profiles of surfaces to be analysed. Generally, for tablet analysis where the samples are relatively large and are considered isotropic, a repeatable line profile provides an adequate analysis (1). The stress distribution caused during the loading of the particles and the resultant tablet inhomogeneity are, therefore, postulated to be the cause of the tablet fracture. The fracture of tablets is the result of a crack propagating a finite distance within the sample and is commonly grouped under two dominant components: lamination (also referred as delamination) and capping. Lamination occurs when the strength of the compact is reduced by internal cracks within the tablet. Capping is where the upper part of the compact dislocates from the bulk

assembly. If the delamination is due to rapid relaxation of the peripheral regions of the bilayer compact due to air entrapment during ejection from the dies, it is strongly recommended to have dies tapered either at one end or at both sides to enable air to escape from the compact.

4. Evaluations of Bilayer Tablets [23]

General Appearance

The general appearance of a tablet, its visual identity and overall "elegance" is essential for consumer acceptance. Includes in are tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

Tablet Thickness and Size

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter was measured using venire calliper.

Tablet thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micro meter.

Friability

Friability is the measure of tablet strength. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed and the percentage loss in tablet weight was determined.

% loss = [(Initial wt. of tablets – Final wt. of tablets)/ Initial wt. of tablets] ×100

Uniformity of weight

Twenty tablets were selected at random and the average weight was calculated. Weight Variation was calculated and was compared with I. P. standards.

Dissolution Studies

Bilayer tablets were subjected to in vitro drug release studies in simulated gastric and intestinal fluids to assess their ability in providing the desired controlled drug delivery. Drug release studies were carried out using USP dissolution test apparatus I at 100 rpm, 37±0.5°C and pH 1.2 buffer (900 ml) (i.e. 0.1 N HCl) for 2 hours, since the average gastric emptying time is about 2 hours. The dissolution medium was replaced with pH 6.8 phosphate buffer

(900 ml) and experiment continued for another 10 hours. At different time intervals, 5ml of the samples were withdrawn and replaced with 5ml of drug-free dissolution medium. The samples withdrawn were analysed by UV spectrophotometer using multi component mode of analysis.

Stability Study

In order to determine the change on storage, stability study is carried out a 25°C / 60% RH and 40°C / 75% RH in a stability chamber. Samples are withdrawn at regular intervals. Formulation is evaluated for changes in Hardness, Thickness, Disintegration time and in vitro release studies.

5. Bilayer tablet compression machines:

Several bilayer presses such as Kilian, Oystar Manesty, Hata, Korsch, Courtoy, Fette, Kilian and Piccola are commercially available for formulators and process development scientists. Most instrumented bilayer presses are equipped with control systems to automatically evaluate compression forces and punch displacements on the presses. Recent advances in the compression machine design and its accessories have provided opportunities to choose the features (first layer sampling, sealed feeders, precompression rolls, sensitivity of layers strain gauge, maximum upper punch penetration) as per the requirements of the product under question. The level of precompression force, punch velocity, consolidation time, dwell time, relaxation time, and the applied compression force have significant effect on the critical quality attributes of the tablet [1,24]. As detailed in the previous sections, separation of the two individual layers is the consequence of insufficient bonding between the two layers during final compression of the bilayer tablet. Correct bonding is only obtained when the first layer is compressed at a low compression force so that this layer can still interact with the second layer during final compression of the tablet. Bonding is severely restricted if the first layer is compressed with high compression force. The low compression force required when compressing the first layer unfortunately reduces the accuracy of the weight control mechanism since it relies on “compression force measurement” using a weight-force curve as a surrogate, indirect measurement of weight. More sensitive compression transducers may have to be installed for first layer compression to accurately detect small compression forces allowing optimum layer adhesion, as well as weight control. Applying a low compression force on the first layer is problematic from weight control stand point as the force versus weight sensitivity decreases as the force decreases. In other words, changes in weight will have less impact on the force when it is low and leads to less sensitive control over weight. Most double-sided tablet presses with automated production control use compression force to monitor and control tablet weight. The effective peak compression force exerted on each individual tablet or layer is measured by the control system at main compression of that layer. This measured peak compression force [F] (under constant thickness) is the signal used by the control system to reject out-of-tolerance tablets and correct the die fill depth when required. The compression force control system is always based on measurement of compression force at main-compression and not at pre-compression since a higher compression force is required to obtain sufficient sensitivity, thus allowing a more accurate control. A weight control system based on compression force monitoring is not the best solution for first layer weight control in a bilayer tableting process. A compression force-controlled system requires a minimal compression force of several hundreds of Newtons (N). However, many bilayer formulations require a first layer compression force of less than 1000 Nin order to retain the ability to bond with the

second layer. Beyond1000 N, this ability may be lost, bonding between both layers may not be sufficient, resulting in low hardness of the bilayer tablet and separation of the two layers (unpublished data). To overcome such basic problem, which is inherent to the principle of com-pression force monitoring, Courtoy solved the challenge by using a different weight monitoring system based upon 'displacement' control system. "Displacement measurement" as the alternative to "compression force measurement" has the advantage that accuracy increases with reduced compression force. At higher production speed, the risk of separation and capping increase but can be reduced by sufficient dwell time at all four compression stages (pre-compression force and main com-pression force for each of the layer). Weight monitoring based upon 'displacement' also provides increased dwell-time in addition to good bonding between the two layers, with improved and accurate weight monitoring/control of the first layer. As claimed by Courtoy, a double-sided tablet press with "displacement measurement" can be the preferred press to produce bi-layer tablets. To compensate for a decreased dwell time (at higher press speeds) during com-pression, larger compression rolls and punches with special head design, extended dwell bars are available. Incorporation of sensors in the compression work flow have provided insight into the potential challenges and facilitated a better control and monitoring of the compression process: ejection sensor (will help to evaluate the sticking potential in the die), take off sensor (will help to evaluate the sticking potential on the punch face, torque sensor (to measure the work required to move the powder in the feed turret), and pre and main compression force sensors (will help to reject the tablets outside the specification).Some recent model versions of presses include automated sampling and integrated multi-tester. The feedback loop will adjust the press parameters based on the weight, hardness, and thickness data determined by the tester. In the new Courtoy–Modul series press, tablet weight control is based on displacement of the punch into the die rather than the main compression force, which the manufacturer claims to have a better weight control when one of the layers has a relatively lower weight in a bilayer tablet. New model presses are equipped with software packages for data acquisition, calculate results compare parameters within and among the batches, correlate material properties to product quality, and to monitor and control the critical bilayer compression parameters. The precision needed for controlling the individual layer weight demands consistent behaviour of the final blend such as flow property and particle size distribution.[25]

6. CONCLUSIONS

Bilayer and monolayer tablet manufacturing share many com-mon technological features as both products are formed by powder compaction. While significant advances in compaction area have brought improvements to quality and efficiency of pharmaceutical tableting in general, there are still a number of scientific and technological challenges ahead to bring bilayer design and manufacturing to similar levels of robustness as encountered in monolayer tablets. These issues range from product characterization, to material/parameters/equipment selection, as well as modelling. Bilayer tablets by design are heterogeneous systems composed of two (or more for multilayers) different layers separated by a discrete interface. This heterogeneity is the main source for the additional challenges in the design and manufacture of bilayer tablets. The properties of compacted products such as hard-ness and lamination tendency depend not only on the formulation but also on the deformation history of each layer during tablet manufacturing. While for monolayer tablets the impact of deformation history is reasonably well characterized and understood, for bilayer tablets it requires further studies due to the interdependency between first and second layer interactions,

including thickness, weight and force. Variations in one single parameter result in changes in the properties of both layers and also the interface. In this article, some key issues were identified for bilayer tablet manufacturing attendant to the need for understanding heterogeneous systems while providing an overview of prior and current strategies to address them. More specifically, the following critical aspects were reviewed. The role of material properties on the competition between layer and interface strength, the impact of first layer and second layer compression forces on the patterns and mechanisms of bilayer failure including the appearance of an optimal region for the selection of the first layer force and the effect of lubricant on the heterogeneity of both layers were described. In addition, the impact of layer ratio, layer sequence and layer weight control on the overall characteristics of the bilayer products were also reviewed. Bilayer tablet characterization is a key aspect toward better understanding and design, which requires additional techniques such as 3D characterization tools and interface characterization tools. A discussion of the equipment/devices available for both R&D and manufacturing environments is also included. Bi-layer tablets provide one of the important design approaches where incompatible drugs, with different indication, and same drug with different release rate can be incorporated in a single unit. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. 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. To develop a robust bi-layer tablet a complete mechanistic understanding must be developed through the application of scientific and quality risk management tools. Bilayer tablet quality and GMP requirements can vary widely.

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