ABSTRACT
In recent times, various developed and developing countries move towards combination therapy for treatment of multiple diseases and disorders requiring long term therapy. Combination therapy have various advantages over mono therapy such as problem of dose dependent side effects is minimized, a low dose combination of two different agents reduces the dose related risk, the addition of one agent may potentiate effects of other agent. In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form has increased in the pharmaceutical industry, promoting patient convenience and compliance. Bi-layer tablet is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. Bi-layer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. Several pharmaceutical companies are currently developing bi-layer tablets. This article explains about types of bi-layer tablets, potential reasons for considering bi-layer dosage form, challenges related to bi-layer tablet technology and about various bi-layer tablet press.

KEY WORDS: Combination therapy, Bi-layer tablet, Bi-layer tablet press.

INTRODUCTION
Bi-layer tablets are novel drug delivery systems where combination of two or more drugs in a single unit having different release profiles improves patient compliance, prolongs the drugs
action, avoid saw tooth kinetics resulting in effective therapy along with better control of plasma drug level. Bi-layer tablet are very common dosage form for drugs such as captopril, metoprolol, amoxicillin and potassium clavulanate, propranolol hydrochloride, bambuterol hydrochloride. Joint National Committee VI (JNC VI) recognized the value of combination therapy and suggested that combining drug with different modes of action will often allow smaller doses of drugs to be used to achieve control and minimize the potential dose dependent side effects. JNC VI recommended that the combination of a low dose of two drugs in fixed dose combination is an appropriate choice for initial treatment of any chronic disease. Hence management of multiple diseases can be effectively and better done by bi-layer tablet or layering in tablet.

Types of Bi-Layer Tablets
The term bi-layered tablets containing subunits that may be either the same (homogeneous) or different (heterogeneous).

A) Homogenous type
Bi-layer tablets are preferred when the release profiles of the drugs are different from one another. Bi-layer tablets allows for designing and modulating the dissolution and release characteristics. Bi-layer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug, later, either as second dose or in an extended release manner.

B) Heterogeneous type
Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances.
Advantages of Bi-layer tablets over conventional tablets

1. Blood level of a drug can be held at consistent therapeutic level for improved drug delivery, accuracy, safety and reduce side effects. Reduction of adverse side effect can be accomplished by targeting the drug release to the absorption site as well as controlling the rate of release, enabling the total drug content to be reduced.

2. Patient convenience is improved because fewer daily doses are required compared to traditional systems. Patient compliance is enhanced leading to improved drug regimen efficacy.

3. Bi-layer tablets readily lend themselves to repeat action products; where in one layer on layered tablet provides the initial dose, rapidly disintegration in the stomach, the other layer are insoluble in gastric media but are released in the intestinal environment.

4. Separate physically or chemically incompatible ingredients.

Challenges Related To Bi-Layer Technology

In spite of the aforementioned advantages provided by the bi-layer technology, several issues associated with the mechanisms and compression of bi-layer tablets have been reported in the literature in recent years. The formulators and process scientists need to overcome the challenges to deliver a robust bi-layer tablet and manufacturing process. Some of the key challenges are

1. Inaccurate individual layer weight control

2. Cross contamination between the layers

3. Elastic modulus mismatch between the adjacent layers. High elastic modulus ratio between adjacent layers could cause insufficient layer bonding and relatively low
Reduced production yield and the propensity to delaminate (distinct layers separation) at the non-planer interface between the adjacent compacted layers
4. Disproportionate layers weight ratio coupled with low drug load
5. Insufficient bi-layer tablet hardness
6. Long term physical and chemical integrity throughout shelf life.
7. Large tablet size, which can impact the swallow ability of the unit dose.
8. Impact of high temperature and humidity on layer adhesion upon storage

Overcoming all these challenges requires a focused effort toward addressing the following areas related to material properties and bi-layer processing parameters:
1. Determination of mechanical properties of each layer,
2. Maximization of inter-facial adhesion between the layers,
3. Optimization of the first layer compression force,
4. Quantification/understanding of factors contributing to delamination,
5. Assessment of the impact of layer sequence and layer weight ratio,
6. Development of techniques for small scale material characterization tools that can be applied during bi-layer tablet design, and
7. Selection of appropriate bi-layer tablet press alternatives with consistent weight control delivering system.

A) Material properties
Understanding the fundamental material properties (API and excipients) like brittleness (lactose, dicalcium phosphate), plasticity (microcrystalline cellulose) and visco elasticity (pre-gelatinized starch) is key in the successful development of bi-layer 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 materials 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 bi-layer 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 bi-layer
tablets to delaminate. Propagation or transmission of compression force through the materials also changes with the material properties.

B) Compression force for bi-layer tablets
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 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. Thus, understanding the interaction and adhesion behavior between different layers composed of various ingredients with differing physicochemical 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.

C) Optimization of Layer Adhesion in Bi-layer Tablets
Lubricant system was found to have a significant impact on interlayer adhesion. Increased lubricity of a powder blend will reduce the friction between the powder particles that contact with each other or with dies and punches during compression because the lubricant will be distributed uniformly throughout the blend and coat the surface of the particles. In a bi-layer configuration, a greater interfacial interaction between the layers can be achieved with low lubricant level for the first layer. Elevated temperature and humidity during storage caused layers to separate in some tablets that appeared to be well adhered after compression. In
general, physical stability on storage for tablets of different composition tracked with the tamping force that caused delamination at the time of compression, giving a simple measure of bi-layer tablet robustness. Separation of the tablet layers will occur if the tamping force (defined as the force that is applied to the first layer prior to fill of the second layer) is greater than some critical value.

D) Layer ratio and layer sequence
There are a very limited number of publications on the impact of layer ratio and layer sequence in a bi-layer configuration on the mechanical strength and other quality attributes of bi-layer 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 compared 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 bi-layer 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.

E) Environmental conditions
The effect of moisture on the strength of bi-layer tablets was studied by few authors. Compacts made from hygroscopic materials 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, polyvinyl pyrrolidone, 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.

F) Layer weight control
The materials particle size distribution, flow property and the ability of the bi-layer press to accurately control the layer weight are very critical in assuring acceptable content uniformity.
of the APIs composing the bi-layer tablets. Each instrumented bi-layer 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 bi-layer weight. To make situations more complex, no commercially available bi-layer press is equipped with a device to sample separately the second layer weight. In general, a minimal pre compression 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. Bi layer presses are equipped with a sampling device for first layer compact, which allow applying an additional compression force on the first layer material and thereby hardening the compact and rendering it more suitable for weight check.

G) Bi-layer tablet characterization
The bi-layer tablet formulations used for each individual layer should be compressible (i.e., the ability of a material to undergo a reduction 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. From this point of view, the interface between the layers should weld together during compaction and strong adhesion forces should hold the layers together after tablet ejection. However, this is not always the case, and as compressibility and compactability of the individual layers should not be the cause for delamination, other physical mechanisms need to be identified that can explain the problems with delamination.

Quality and GMP-Requirement of Bi-Layer Tablets press.
To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the selected press is capable of the following requirements
1. It should be Prevent capping and separation of the two individual layers that comprise the bi-layer tablet.
2. It should be produce a clear visual separation between the two layers.
3. It should maintains the accurate and individual weight control of the two layers
4. It should provide sufficient tablet hardness.
5. It should prevent cross-contamination between the two layers.
6. It is capable of producing high yield.
Types of Bi-Layer Tablet Press\textsuperscript{5}
2. Double sided tablet press or “compression force” controlled tablet press.

A) Single sided tablet press
The simplest design is a single sided press with both chambers of the doublet feeder separated from each other. Each chamber is gravity or force fed with different powers, thus producing the two individual layers of the tablets. When the die passes under the feeder, it is at first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps.

Limitations of Single sided tablet press
1. No weight monitoring/ control of the individual layers.
2. No distinct visual separation between the two layers.
3. Very short first layer dwell time due to the small compression roller, possibly resulting in poor de aeration, capping and hardness problems. This may be corrected by reducing the turret- rotation speed (to extend the dwell time) but with the consequence of lower tablet output.
4. Very difficult first-layer tablet sampling and sample transport to a test unit for in-line quality control and weight recalibration.

B) Double sided tablet presses
A double sided press offers an individual fill station, pre – compression and main compression for each layer. In fact the bi-layer tablet will go through four compression stages before being ejected from the press. 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 the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance tablet and correct the die fill depth when required.

Advantages
1. Displacement weight monitoring for accurate and independent weight control of the individual layer.
2. Low compression force exerted on the first layer to avoid capping and separation of the individual layer.
3. Increased dwell time at pre compression of both first and second layer to provide sufficient hardness at maximum turret speed.
4. Maximum prevention of cross contamination between two layers.
5. Maximized yield.

Limitations
Separation of the two individual layers is due to insufficient bonding between the two layers during final compression of bi-layer 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. Bonding is too restricted if first layer is compressed at a high compression force. The low compression force required when compressing the first layer unfortunately reduces the accuracy of the weight monitoring/control of the first layer in the case of tablet presses with “compression force measurement”. Most of the double sided tablet presses with automated production control use compression force to monitor and control tablet weight. Compression force control system is always based on measurement of compression force at main compression but not at pre-compression.

C) Bi-Layer Tablet Press With Displacement Monitoring
The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied pre compression force. In fact the lower the pre-compression force, the more the monitoring control system and this ideal for good interlayer bonding of the bi-layer tablet.

Advantages
1. Weight monitoring/ control for accurate and independent weight control of the individual layers.
2. Low compression force extends on the first layer to avoid capping and separation of the two individual layers.
3. Increased dwell time at pre compression of both first and second layer to provide sufficient hardness at maximum turret speed.
4. Maximum prevention of cross contamination between the two layers.
Manufacturing Process of Bi-Layer Tablet

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 delamination/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 multilayer 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. For instance, the extent of compact densification and resistance to compressibility within the die cavity was impacted by compaction pressure and the punch velocity.

Compaction

To produce adequate tablet formulation, certain requirements such as sufficient mechanical strength and desired drug release profile must be met. At times, this may be difficult task to achieve these conditions especially in bi-layer tablet formulation where double compression technique is involved, because of poor flow and compatibility characteristic of the drug of the drug which will result in capping and/or lamination. The compaction of a material involves both the compressibility and consolidation.

Compression

It is defined as reduction in bulk volume by eliminating voids and bringing particles into closer contacts.

Consolidation

It is the property of the material in which there is increased mechanical strength due to inter particulate interaction (bonding). The compression force on layer one was found to be major factor influencing tablet delamination.
CONCLUSION

Bi-layer tablets offer an excellent opportunity for manufacturers to separate themselves from their competitors, improve their products efficacy, and protect against impersonator products. Bi-layer tablet quality and GMP requirements can vary widely. This explains why many different types of presses are being used to produce bi-layer tablets, ranging from simple single-sided presses to highly sophisticated machines. When a quality bi-layer tablet needs to be produced in conjunction with accurate weight control of both layers, compression force-controlled presses are clearly limited because of their insufficient sensitivity and hence lack of accuracy at low compression forces required to secure interlayer bonding. Such problems become even more apparent when the tableting speed is high or increased. Accurate individual layer weight monitoring/control at high speed and in combination with reduced layer separation risk can be achieved with the displacement weight control system based presses.

REFERENCES


