



## Bi-Layer Tablet Technology

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### ABSTRACT

Bilayer 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 improved beneficial technology to overcome the short coming of the single layer tablet. The primary objective of bi-layer tablet is to ensure safety and improved efficacy of drug as well as patient compliance. Bilayer tablet have enabled the development of controlled delivery of Active Pharmaceutical Ingredients (API) with predetermined drug release profile by combining layers with various release pattern or by combining slow release with immediate release layer. The technology is appropriate for combination of two drugs and also for biphasic release in which one layer is an initial dose and other layer is maintenance dose. By using bi-layer tablet technology we can administer incompatible drugs in combination as well as same drug with different release rate. The concept avoids frequent administration of dosage form in diseases like diabetes, hypertension, inflammation, asthma to offer better patients compliance. The review article discusses all possible aspects of techniques, presses used to produce bi-layer tablet ranging from simple single sided machines to highly sophisticated machines. The role of material properties, compression forces and effect of lubricant on the heterogeneity of both layers are described. In addition, the impact of layer ratio, layer sequence and layer weight control on the overall characteristics of the bilayer products are also reviewed.

**Keywords:** Bi-layer Tablet, tablet presses, OROS push pull technology, DUREDAS™ technology, layer weight, etc.

### INTRODUCTION

Day-by-day various developed and developing countries are moving towards combination therapy for treatment of various disease and disorders requiring long term therapy such as hyper tension and diabetes.

Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissue with consequent undesirable toxicity and poor efficiency. The goal of designing controlled or sustained delivery system is to reduce the frequency of dosing or to increase effectiveness of drug by localizing at the site of action, reducing dose required or providing uniform drug delivery e.g., sustained, timed, immediate drug delivery.

Bi-layer tablet is improved beneficial technology to overcome the short coming of the single layer tablet. The primary objective of bi-layer tablet is to ensure safety and improved efficacy of drug as well as patient compliance. Bilayer tablet have enable the development of controlled delivery of Active Pharmaceutical Ingredients (API) with predetermined drug release profile by combining layers with various release pattern or by combining slow release with immediate release layer.

“Bi-layer tablet are the solid oral dosage form, usually round, spherical, oval or biconcave in shape and consist of one or more than one medicaments designed in a two layer system which can be suitable for combination therapy and biphasic release therapy”. In case of combination therapy the two layers of the tablet is consist of two different medicaments and in case of

biphasic release bi-layer tablet both the layer content same medicament but the drug release pattern are different.

Bi-layer formulation carry more than one drug and deliver each of them without any pharmacokinetic or pharmacodynamic interaction, with their individual rate of delivery. Bi-layer tablets are tablet, made by compressing two different granulations fed into a die succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet press can be set up for two layers. More layers are possible but the design becomes very special.

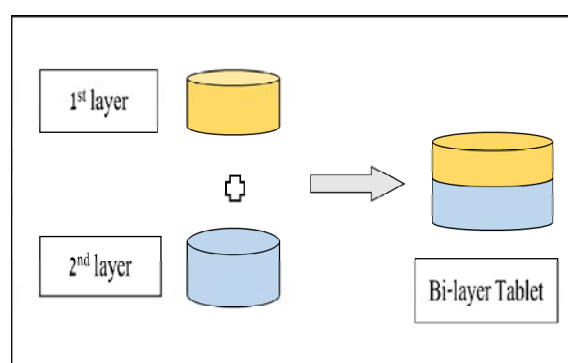


Figure 1: Bilayer Tablet

### Advantages<sup>1-3,5-7,14</sup>

1. Cost is lower compared to all other oral dosage form.
2. Greatest chemical and microbial stability over all oral dosage form.



3. Unpleasant odor and bitter taste can be masked by coating technique.
4. 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 pilot plant scale up technology.
8. The tablet can be easily used for combination therapy.
9. In case of drugs having a low half-life, each of the two layers of the tablet respectively content a loading dose and maintenance dose of the same and thus increase the bioavailability of the drug.
10. Improved patient compliance.
11. Bi-layer execution with optional single-layer conversion kit.

#### Disadvantages<sup>1-3,5-7</sup>

1. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
2. Bitter tasting drugs, drugs with an objectionable odor 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.
5. Lack of sufficient bonding and adhesion at the interface between the adjacent compacted layers which is often the result of an interfacial crack and layer separation.
6. Other challenges during development include establishing the order of layer sequence, layer weight ratio, elastic mismatch of the adjacent layers, first layer tamping force, and cross contamination between layers.
7. The physician has a less flexibility on adjusting the dose regimens.

#### Various Techniques for Bi-Layer Tablet

##### **Osmotic-controlled Release Oral Delivery System**

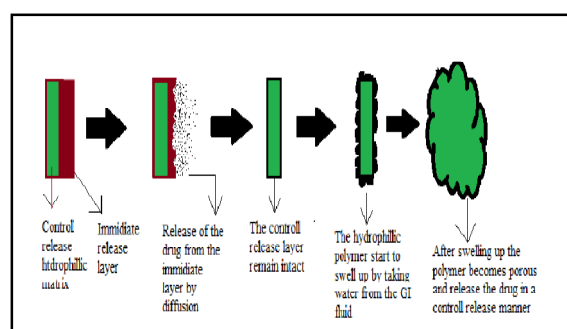
The system consists of mainly two or three layer among which one or more layer are of the drug and other layer are consists of push layer. The drug layer mainly consists of poorly soluble drug along with diluents, low molecular weight polymer, suspending agent and osmotic agent. The push layer is constructed of a higher molecular weight osmopolymer and an osmagent. A semi

permeable membrane surrounds the tablet core. In this technology the medication is sandwiched with an osmotic agent that swells when it takes up water. The sandwich is then coated with a semi permeable membrane. Then laser is used to drill a tiny hole through the membrane. In the stomach, water passes through the membrane into the pill, causing the osmotic material to swell, which pushes the drug out of the hole. This delivers the drug to the body at a constant rate instead of all at once, as happens when a traditional pill dissolves. Products manufactured using this technology are Glucotrol XL and procardia XL both of which are composed of a Bi-layer tablet core and Concerta is composed of a trilayer tablet core.<sup>3</sup>

#### **Elan Drug Technology (DUREDAS™ Technology)**

DUREDAS™ or Dual Release Drug Absorption System (Elan Corporation) utilizes Bi-layer tableting technology, which has been specifically developed to provide two different release rates or dual release of a drug from a single dosage form. The tablets are prepared by two separate direct-compression steps that combine an immediate-release granulate (for rapid onset of action) and a controlled-release hydrophilic matrix complex within one tablet. The immediate release layer, release the drug immediately after going into the GIT (stomach or intestine) in a diffusion and dissolution manner and the controlled-release matrix remains intact and slowly absorbs fluid from the GI tract, which causes the matrix to expand and transforms the hydrophilic polymers into a porous, viscous gel that serves as a barrier between the drug and the surrounding fluid. As the gel continues to expand, fluid penetrates further into the dosage form, dissolving the drug and allowing the resulting solution to diffuse out in a controlled manner.

A further extension of the DUREDAS™ technology is the production of controlled-release combination dosage forms whereby two different drugs are incorporated into the different layers, and the drug release of each is controlled to maximize therapeutic effect of the combination. Again both immediate release and controlled release combinations of the two drugs are feasible. The DUREDAS™ technology was initially employed in the development of a number of over the counter controlled release analgesics.<sup>1-4,9,14</sup>



**Figure 2:** DUREDAS™ technology consists of control release and immediate release layer.

### Geminex

Geminex is a dual drug delivery technology that can deliver one or more drugs at different times. The Geminex technology controls the release rate of the two drugs to maximize their individual therapeutic effect and minimize side effects. The benefit of Geminex to the pharmaceutical industry, and ultimately to patients, is that two different actives or the same active can be delivered at differing rates in a single tablet. Penwest is actively applying its Geminex technology to the following therapeutic areas: cardiovascular disorders, diabetes, cancer, and disorders of the central nervous system.<sup>1,9</sup>

### EN SO TROL Technology

Solubility enhancement of an order of magnitude or to create optimized dosage form Shire laboratory use an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies.<sup>1,2,5,11,14</sup>

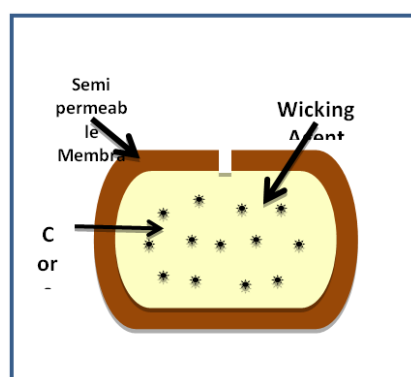


Figure 3: EN SO TROL Technology

### PRODAS or Programmable Oral Drug Absorption System

Prodas or Programmable Oral Drug Absorption System (Elan Corporation) is a multi particulate drug delivery technology that is based on the encapsulation of controlled release mini tablets in the size range of 1.5 to 4 mm in diameter. The technology represents a combination of multi particulate and hydrophilic matrix tablet technologies and thus provides the benefits of both these drug delivery systems in one dosage form. Mini tablets with different release rates can be combined and incorporated into a single dosage form to provide the desired release rates. The combinations may include immediate-release, delayed-release, and/or controlled-release mini tablet. In addition to controlled absorption over a specified period, PRODAS technology enables targeted delivery of drug to specified sites of absorption throughout the GI tract. Combination products also are possible by using mini tablets formulated with different active ingredients.

### OROS® Push Pull Technology

The system consist of mainly two or three layers among which one or more layers are essential of the drug and other layers are consist of push layer. The drug layer mainly consists of drug along with two or more different

agents. The drug layer comprises of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core.<sup>1,2,5,11,14</sup>

### Bi-layer and Tri-layer OROS Push Pull Technology

L-OROS technology is used for the solubility issue, Alza developed the L-OROS system where a lipid soft gel product containing drug in a dissolved state is initially manufactured and coated with a barrier membrane, respectively osmotic push layer and a semi permeable membrane, drilled with an exit orifice.<sup>11,14</sup>

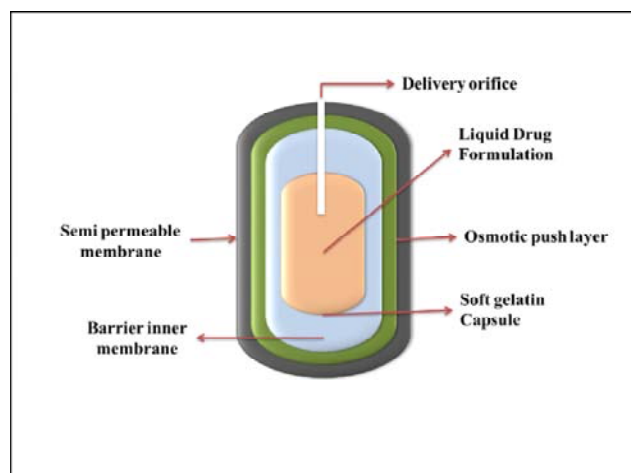


Figure 4: Bi-layer and tri-layer OROS Push Pull Technology

### Erodible Molded Multilayer Tablet

Egalet erodible molded tablets are an erosion-based platform. It has the advantage of delivering zero-order or delayed release with minimal impact from the gastrointestinal conditions. Egalet erodible molded multilayered tablets are prepared by injection molding. Egalet technology contains a coat and a matrix. Drug release is controlled through the gradual erosion of the matrix part.

The mode and rate of release are designed and engineered by altering the matrix, the coat, and the geometry to achieve either a zero-order release or a delayed release. For a zero-order release, a drug is dispersed through the matrix. The coat is biodegradable but has poor water permeability to prevent its penetration.

The matrix tends to erode when in contact with available water. The erosion of the matrix is caused by GI fluids and promoted by gut movements in the GI tract. The drug release is mediated almost wholly by erosion because the dosage form is designed to slow down the water diffusion into the matrix.

It is definitely more desirable for drugs with chemical and physical stability issues after contacting with water.

Egalet delivery technology is developed based on standard plastic injection molding to ensure accuracy, reproducibility, and low production cost.<sup>1,9</sup>

## Various Approaches used in the Bi-Layer Tablet<sup>1,6,9,11,14</sup>

### **Floating Drug Delivery System**

The system is designed to have a low density and thus float on gastric contents after administration until the system either disintegrates or the device absorbs fluid to the point where its density is such that it loses buoyancy and can pass more easily from the stomach with a wave of motility responsible for gastric emptying.

The Bi-layer tablet is designed in such a manner that, one layer gives the immediate dosing of the drug which gives faster onset of action while other layer is designed as a floating layer which floats in the stomach (GI-fluid).<sup>1,17</sup>

### **Polymeric Bioadhesive System**

The system is designed to imbibe fluid following administration such that the outer layer becomes viscous, tacky material that adheres to the gastric mucosa/mucus layer.

Thus encouraging gastric retention until the adhesive forces are weakened. The tablet consist of an immediate dosing and bioadhesive layer.<sup>1</sup>

### **Swelling System**

The system designed to be sufficiently small on administration so as not to make ingestion of the dosage form difficult (e.g., less than approximately 23 mm long and less than 11 mm wide for an oval or capsule shaped tablet whereas 10-12mm in diameter for round tablets).

On ingestion they rapidly swell or disintegrate or unfold to a size that precludes passage through the pylorus until after drug release has progressed to a required degree.

Gradual erosion of the system or its breakdown into smaller particles enables it to leave the stomach. The simple Bi-layer tablet may contain an immediate release layer whilst the other layer is extended release or conventional release.<sup>1</sup>

## **Bi-Layer Tablet Presses<sup>9-11</sup>**

### **Single Sided Press**

Various types of Bi-layer presses have been designed over the years. The simplest design is a single sided press with both chambers of the double feeder separated from each other.

Each chamber is gravity- or forced-fed with a different powder, thus producing the two individual layers of the tablet.

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 (two pre- and main compression).

The two layers in the die mix slightly at their interface and in most cases bond sufficiently so that no layer-separation occurs when the tablet is formed.<sup>1,6</sup>

### **Double Sided Tablet Press**

Offers significant technical advantages that permit higher output and increased efficiency in production. Special emphasis has been given on durability while designing so that the machine can be used in a 24/7 production environment.

The higher load bearing capacity of Adept tablet press makes it suitable for bigger tablets. The machine also offers flexibility to produce both single-layer and Bi-layer tablets on the same platform.<sup>6</sup>

### **Bi-layer Tablet Press with Displacement Monitoring**

Tablet weight control using 'displacement' is based on the measurement of thickness variations under constant force and is measured at pre-compression. This measurement is possible when using the so-called 'pneumatic compensator'.

The displacement-tablet weight control principle is fundamentally different from the principle based upon compression force.

When measuring displacement, the control system's sensitivity does not depend on the operating point on the graph (i.e. it 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 sensitive the monitoring system and this is ideal for good interlayer bonding of the Bi-layer tablet, as explained above.<sup>6</sup>

### **Manufacturing Process**

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.

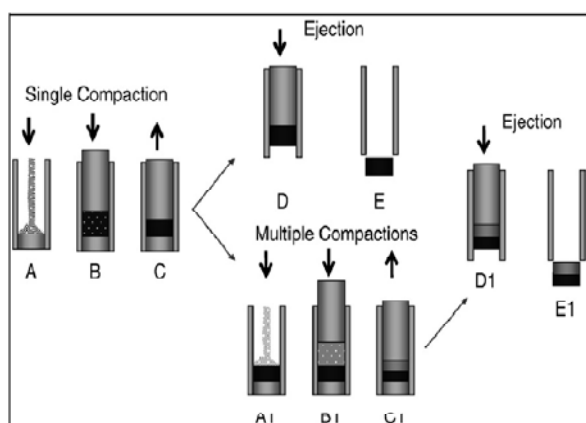
The level of pre-compression force, punch velocity, consolidation time (time when punches are changing their vertical position in reference to the rolls as the distance between the punch tips are decreased), dwell time (time when punches are not changing their vertical position in reference to the rolls), 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.





It was demonstrated that increase in the punch velocity between of 50 and 500mm/s decreased the porosity reduction on individual layers.<sup>4,8,11,14</sup>



**Figure 5:** Schematic Diagram Showing the Manufacture of Single and Bilayer Tablets Utilizing Uniaxial Compaction. A-Die Filling, B-Compression, C-Decompression, D-Lower Punch Removal And Reapplication of Load to the Upper Punch, E-Tablet Fully Ejected. 1 Refers To the Final Compaction Conditions.<sup>3</sup>

### 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 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.

### Evaluation of Bi-Layer Tablet<sup>5-7,23,24</sup>

#### General Appearance

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

#### 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. Thickness of tablet should be recorded by using digital vernier caliper. It is expressed in mm.

#### Size and Shape

The size and shape of the tablet can be dimensionally described, monitored and controlled.

#### Hardness (Crushing Strength)

Hardness indicates the ability of the tablet to withstand mechanical shocks while handling. Hardness of the tablet recorded by Monsanto hardness tester. It is expressed in kg/cm<sup>2</sup>.

#### Friability

The ability of the tablet to withstand abrasion in packaging, handling and shipping. Friability is determined by the use of the Roche friabilator. A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight.

The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked up. Friability is expressed in percentage as:

$$\% \text{ Friability} = 1 - \left( \frac{\text{loss in weight}}{\text{Initial weight}} \right) \times 100$$

#### Drug Content and Release

To evaluate tablets potential for efficacy, the amount of drug per tablet needs to be monitored from tablet to tablet and batch to batch, and a measure of the tablet's ability to release the drug needs to be ascertained.

#### Weight Variation

**Table 1:** Acceptance criteria for Weigh Variation Test as per USP<sup>6,24</sup>

Average weight of tablet	Percentage Deviation
130mg less	10
>130mg or < 324mg	7.5
324mg or more	5

Twenty tablets are selected randomly from each batch and weighed individually to check weight variation. Calculate average weight and comparing the individual tablet weights the average.

The tablet meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. A little variation

is allowed in weight of a tablet according to U.S. Pharmacopoeia. The following percentage deviation shown in Table No. 2 in weight variation is allowed.

### ***In-vitro Dissolution Study***

Dissolution study is done in simulated gastric and intestinal fluids to assess their ability in providing the desired controlled drug delivery. In vitro drug release studies are carried out using USP dissolution test apparatus at 37°C temperature at specific RPM or as mentioned in monograph.

### ***Stability Study (Temperature Dependent)***

The Bi-layer tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies. The

tablets were withdrawn after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability and Dissolution etc.) and drug content.

The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25°C.

**Table 2:** ICH Stability Study Condition<sup>6,23</sup>

Study	Storage Condition	Minimum Time
Long	25°C±2°C/60%±5RH OR 30°C±2°C/65%±5RH	12 Months
Intermediate	30°C±2°C/65%±5RH	6 Months
Accelerated	40°C±2°C/75%±5RH	6 Months

**Table 3:** Troubleshooting of processing problems in Bi-layer Tablet Compression<sup>6</sup>

Trouble	Possible cause	Remedies
Tablet weight variation	a) Poor flow characteristics of material	1. Wrong setting of hopper. 2. Material bridging in hopper 3. Too much recirculation
	b) Dies not filling	1. Press running too fast 2. wrong feeder paddle speed or shape
	c) Material loss or gain after proper die fill	1. Recirculation band leaking 2. Excessive vacuum or nozzle improperly located
Product yield	a) Incorrect feeder fit to die table	1. Feeder bases incorrectly set (too high or not level)
	b) Incorrect action on recirculation band	1. Gap between bottom edge and die table 2. Binding in mounting screw 3. Too little hold down spring pressure
	c) Die table scraper action insufficient	1. Scraper blade worn or binding 2. Outboard edge permitting material to escape
	d) Loss at compression point	1. Compressing too high in the die 2. Excessive or misdirected suction on exhaust nozzle
Low hardness	a) Factors related to machine	1. Tablet press having pre-compression and main compression facilities
	b) Lubricant level	1. Press speed is reduced to increase total compression time 2. Over mixing can reduce tablet hardness
Capping and lamination	a) Non-optimized formulation	1. Incorporate plastically deforming matrix
	b) High compression force	1. Reduced compression force 2. Reduced press speed
	c) Ratio of pre-compression to main d) compression is insufficient	1. Pre-compression force high can be harmful 2. Use large compression roller diameter
	e) Curled or damaged punches	1. Tools should be rewashed or replaced
	Picking and sticking	a) Excessive heat generation during compression
b) Fouling the punch faces		1. Startup should always be close to optimum conditions
Separation of two individual layers	a) Insufficient bonding between the two layers during final compression of bi-layer tablet	1. First layer should be compressed at a low compression force so that this layer can still interact with second layer during final compression of the tablet
Mottling	a) Improper setting of both feed frame	1. Both feed frame should set properly.
	b) Due to weak suction	1. Suction capacity should be such that, all waste material is sucked.

## Challenges in the Formulation of Bi-Layered Tablets<sup>11</sup>

1. Lack of sufficient bonding and adhesion at the interface between the adjacent compacted layers which is often the result of an interfacial crack driven by residual stresses in the tablet propagating a finite distance within the tablet and leads to delamination (layer-separation) which may not always be apparent immediately after compaction (e.g., during storage, packaging, shipping).
2. If the compacted layers are too soft or too hard, they will not bond securely with each other which can lead to compromised mechanical integrity.
3. Other challenges during development include establishing the order of layer sequence, layer weight ratio, elastic mismatch of the adjacent layers, first layer tamping force, and cross contamination between layers. These factors, if not well controlled/optimized, in one way or another will impact the Bi-layer compression per sure (inefficient or uncontrolled process) and the quality attributes of the Bi-layer tablets (sufficient mechanical strength to maintain its integrity and individual layer weight control).
4. Impact of high temperature and humidity on layer adhesion upon storage.
5. Therefore, it is critical to obtain an insight into the root causes to enable design of a robust product and process.

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,
- (v) assessment of the impact of layer sequence and layer weight ratio,
- (vi) development of techniques for small scale material characterization tools that can be applied during bilayer tablet design, and
- (vii) selection of appropriate bilayer tablet press alternatives with consistent weight control delivering system.

### Material Properties

Understanding the fundamental material properties (API and excipients) like brittleness (lactose, di-calcium phosphate), plasticity (microcrystalline cellulose) and visco elasticity (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. To understand the impact of different material properties on the strength of bilayer tablets. It was demonstrated that bilayer tablets prepared with brittle/brittle material in both layers exhibited stronger interfacial strength compared to other material combinations (e.g. brittle/plastic or plastic/brittle or plastic/plastic). In other words, the bonding strength between the two layers was higher than that of the individual layers. Furthermore, if brittle materials are present in both layers, the elastic mismatch between the adjacent layers will be minimal as the mechanism of consolidation of brittle material is by fragmentation. Moreover, the interfacial strength was weakest for compacts made with plastic material (MCC) in both layers and tablets delaminated coming off the tablet press.<sup>18-22</sup>

### 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. 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 reported that 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. 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.<sup>18-22</sup>

### Lubricant

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 bilayer configuration, a greater interfacial interaction between the layers can be achieved with low lubricant level for the first layer. The impact of lubricant level when tested (0.25%, 0.5% and 0.75%, w/w magnesium stearate) on tablet strength is more pronounced for plastic materials compared to brittle material. The tablet surface smoothness increases as the level of lubricant (magnesium stearate) is increased thereby impacting the interfacial interaction between the first and second layers.<sup>18-22</sup>

### Layer Ratio and Layer Sequence

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. 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. The sequencing of layers with distinct compatibility characteristics controls the interface roughness; hence interface strength.<sup>18-22</sup>

### **Environmental Conditions**

The effect of moisture on the strength of bilayer 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, rospovidone, 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.<sup>18-22</sup>

### **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 available bilayer 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 off the press solid enough to weigh. Bilayer presses (Kilian, Fette and Korsch) 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.<sup>18-22</sup>

### **CONCLUSION**

Bi-layer tablet technology is appropriate for combination of two drugs and also for biphasic release in which one layer is an initial dose and other layer is maintenance dose. By using bi-layer tablet technology we can administer incompatible drugs in combination as well as

same drug with different release rate. This technology avoids frequent administration of dosage form in diseases like diabetes, hypertension, inflammation, asthma to offer better patients compliance. Conventional solid oral dosage forms are a traditional, but bi-layer tablet is a novel approach which requires new machinery for manufacturing. For good quality bi-layer tablet the machines should be essentially built as per GMP. This technique is cost effective, safe and reproducible.

This article explains different types of techniques, presses used to produce bi-layer tablet ranging from simple single sided machines to highly sophisticated machines. The role of material properties, compression forces and 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.

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