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Review Article

## The Challenges of Producing Bilayer Tablet: A Review

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### Abstract

Bilayer tablets are the advanced form of conventional immediate release tablet system, which consist of either two similar or different drugs combined in a single dose for effective treatment of the disease improving patient compliance. However, the multilayer tablet technology is demanding. It also necessitates meticulous selection of excipients and manufacturing conditions for each technological stage. The aim of this review is to provide an outline of state of art of bilayer tablet technology and emphasise the difficulties experienced during Bilayer tablet manufacturing along with its intend solutions for these challenges.

**Keyword:** Bilayer tablet, Conventional release, Challenges encountered, Compliance.

## INTRODUCTION

Solid oral dosage forms are most favored over other route of drug administration due to ease of drug administration, better patient compliance and flexibility of the design<sup>1</sup> and still the most extensively used formulation. Almost 90% of the formulation produced today are consumed orally. It demonstrates that this type of formulation is the most widely accepted globally, and the researcher's primary focus is in this area. Bilayer tablet is a fixed dose combination (FDC) and intended for oral use, it contain immediate release as well as sustained release layer and the immediate release layer deliver the initial dose (loading dose), it contain superdinintegrants that hasten the rate of release of the drug and also attains the onset of action promptly. Whereas sustained release (maintenance dose) layer release the drug in a sustained manner for a prolong period of time by using various polymer acting as a release retardants, hydrophilic polymer are mostly employed for this sustained release action<sup>2</sup>. Diabetes, antihypertensive, antihistamines, analgesics, antipyretics and antiallergenic agents are mostly suitable for this type of drug delivery<sup>3</sup>. Conventional dosage form causes a broad range of medication concentration fluctuations in the bloodstream and tissues, resulting in unfavorable toxicity and ineffectiveness. As a result of problems including repeated dosage and uncertain absorption, the idea of developing sustained or controlled drug delivery systems was generated. Much more effort is stress out in research and development for successful development of Bilayer system that involves incompatible products, additional equipment and operation challenges<sup>4</sup>

## CHALLENGES INVOLVED IN MANUFACTURING OF BILAYER TABLET:

Challenges during the development of bilayer tablets might include inadequate hardness, the order of layer sequence, layer weight ratio, and elastic mismatch of the adjacent layers, first layer tamping force and cross contamination between layers. If these elements are not adequately regulated in some way, they will have an adverse effect on bi-layer compression pressure, as well as qualitative characteristics such as mechanical strength and individual layer weight control. Therefore care must be taken to enable design of a vigorous product and process<sup>5,6</sup>.

Bilayer tablets can be thought of as two single-layer tablets compacted into one but in practicality there are several manufacturing problems associated.

## MATERIAL PROPERTIES:

Physicochemical properties of API and excipients are crucial for the success of Bilayer tablet manufacturing<sup>7,8</sup>. The nature of materials plays a key role in the strength of multi-layer tablets and their manner of fracture<sup>9,10</sup>. Material properties such as plasticity, brittleness and visco-elasticity have significant impact on compression process<sup>11</sup>. The plasticity deformation and the brittleness of material have significant role in the compression process. This means that the plasticity would not affect the compression process as long as the elasticity of the plastic material does not go beyond the bond limit. Besides, the particle deterioration in the central area of die is greater in comparison to the outer layer; Hence before using a substance for manufacturing of Bilayer tablets, it's critical to pay attention to its material

characteristics.<sup>12,13</sup> Each layer in multi-layer tablet formulation must exhibit a sufficient volume reduction and ability to form a mechanically strong and coherent solid form. Therefore, they should be characterized by good compressibility (ability of a substance to reduce the volume under pressure) and compatibility (ability of powdered substances to convert into tablets).<sup>14</sup> It is important to optimize the size distribution of the particles, the flow characteristics, and compression ability of material when used in layered tablet manufacturing, so as to ensure accurate control of each layer weight.

### COMPRESSION FORCE:

According to the research conducted by the Li et al.<sup>15</sup>, the most vital parameter in the production process of multi-layer tablet is the assessment of compression force used for the very first layer, which influences the interfacial strength and adhesion between the two layers, resulting in the mechanical attraction among the layers in the tablet. As a result, if the initial layer of the bilayer medication was more elastic, the stress and tension produced in the entire system as a result of it leads the bilayer tablet's strength to deteriorate. This can cause the bond between the two layers at the bilayer tablet's interface to break which directly impact the adherence of layers.<sup>16, 17</sup> The compression pressure and also punch speed significantly affect the compactibility and resistance to compressibility into the die.<sup>18</sup> The job of the initial layer of compression forces (generally in the range of 2-18 KN) is to tamp the powder/granulated substances in order to reduce the volume, smooth the first layer surface and generate a space for depositing the second layer. In general, the application of higher compression force tends to increase tensile strength and decreased surface roughness. Smoothing the surface of the initial layer may augment the delamination by limiting the intermolecular adherence between adjacent layers.<sup>19</sup>

Proper 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.

### LUBRICANT:

Research has showed that substance which is having greater lubricity will have lower friction between its particles and with die when it comes into contact because all the matter will be uniformly distributing. Conversely, when it comes to bilayers substances to achieve greater interaction and strength between the two layers' low lubricant level is obligatory. Because lubricant levels have a greater impact than brittle substances, this characteristic of the material should be considered while dealing with the development of Bilayer tablet.<sup>20, 21</sup>

As part of the product development process, the amount of lubricant necessary to avoid picking and sticking of the first layer must be determined. When the granules come into contact with dies and punches during compression, the blended lubricant in the granular bulk spreads throughout the mixture, or "coats" on the surface of the granules, providing lubrication and reducing friction. Lubrication can also diminish inter-granular adhesion, which can have an influence on key quality parameters including tablet breaking force and dissolution. Thus, the influence of lubricant on the essential quality characteristics of the tablet has been studied by adding it to the dies and punches rather than directly to the granules. This procedure is known as external lubrication in the literature. External lubrication, in which the lubricant is sprayed over the die and punches for

each compression cycle rather of being added to the bulk powder combination, has been demonstrated to enhance crushing strength by 40% without extending tablet disintegration time. The presence of a coat of magnesium stearate on the tablet was confirmed using a scanning electron microscope. Though this new technique tends to be beneficial for monolayer tablets, it may be utilized to better understand the influence of lubricant on bilayer tablet quality features.

### LAYER RATIO AND LAYER SEQUENCE:

The least amount of research has been done in this section. In a bilayer tablet, the weight of the two layers is not always the same during the design of bilayer tablets. In majority of cases, there will be a significant variation in the ratio of their weights. However; it has been shown that in most cases, the ratio between the first and second layers might be 1:1, 1:2, or even 1:3 in rare cases. However, making the weight of the second layer constant with that of the first layer, which is typically heavy, is challenging, and this presents a challenge during the creation of bilayer drugs.<sup>22, 23</sup>

### ENVIRONMENTAL CONDITION:

Environmental condition shall be taken into account while formulating the bilayer tablet, the environmental condition like humidity and moisture have a significant impact on the compactness of bilayer tablets. Despite the fact that only a few authors have looked into the effect of moisture on the strength of bilayer tablets. Bilayer tablet which had been prepared from hygroscopic material will absorb/desorb moisture into/out of their pore structure in response to the relative humidity of the surrounding air.

Furthermore, moisture can penetrate the bulk of the particles if the compacts are composed of starches, microcrystalline cellulose, crospovidone, hydroxypropyl methylcellulose, polyvinylpyrrolidone, sodium starch glycolate, and colloidal silicon dioxide. Layer expansion occurs when moisture is absorbed by porous compacts and/or particles. Any change in layer size weakens the contact between the layers, which might lead to time-dependent delamination<sup>24</sup>. It was recommended that the materials be pre-conditioned to ensure that they are in equilibrium with the moisture content of the air in the manufacturing area, and that the compacts be packaged in airtight, moisture-resistant blisters.

Physical stability of bilayer tablets during storage, in addition to formulation design and manufacturing process considerations, is an important factor to consider during product development because it can affect quality attributes such as tensile strength, layer adhesion, friability, and dissolution. The strengths of bilayer tablets made up of plastic/brittle, brittle/plastic and brittle/brittle were compared upon storage. The tablet interfacial strength of bilayer tablets prepared with MCC in the first layer/lactose in the second, and lactose in the first layer/MCC in the second, decreased with increased humidity and storage time, whereas those prepared with lactose/lactose showed an increase in tablet strength due to the formation of solid bridges during storage.<sup>25</sup>

### LAYER WEIGHT CONTROL:

To make sure the content uniformity of the active pharmaceutical ingredients in the bilayer tablets some precursors play a significant role, such as material flow property, particle size distribution, and the ability of the bilayers to press accurately. Each instrumented bilayer press from different vendors has its own weight control

mechanism. The existing development and commercial presses provide the option of monitoring the first layer weight and the second bilayer weight. However, yet there is no commercially accessible bilayer press with a mechanism to sample the second layer weight independently. This generates a huge challenge while manufacturing the bilayer tablets. Therefore, a way should be developed to minimize this effect<sup>26</sup>.

### BILAYER TABLET COMPRESSION MACHINE:

For formulators and process development scientists working on bilayer tablets, several bilayer presses are commercially available, including Kilian, Oystar Manesty, Hata, Korsch, Courtoy, Fette, Kilian, and Piccola. Most instrumented bilayer presses are equipped with control systems to automatically evaluate compression forces and punch displacements on the presses. Recent advancements in compression machine design and accessories have made it possible to customize features (initial layer sampling, sealed feeders, precompression rolls, layer strain gauge sensitivity and maximum upper punch penetration) to meet the needs of the product. Precompression force, punch velocity, consolidation time, dwell time, and relaxation are all factors to consider. For that reason, Compression machines are critical in the production of bilayer tablets since they can aid in achieving the appropriate dose quality or degrade the tablet's quality. As a result, throughout the development of the bilayer tablet, this region should receive a lot of attention<sup>27,28</sup>.

### BILAYER TABLET CHARACTERIZATION:

It is one of the most important areas which should not be ignored in any case while discussing the bilayer tablets.

While it is theoretically preferable to have a material that can be compressed without deformation and compact on its own when compressed, resulting in a stronger bond between the two layers of a bilayer tablet, there are other factors that influence the formation of the desired quality of bilayer tablets. Particle size distribution, angle of response, photomicroscopic examination, density, compressibility, and moisture sorption capacity are all included in characterization<sup>29,30</sup>.

The following are some of the advantages of bilayer tablet characterization in early formulation development:<sup>31</sup>

- (i) Determination of the interfacial strength of bilayer tablets using quantitative methods.
- (ii) Unusual or severe characteristics of compacted layers must be detected.
- (iii) Ensure that the bilayer tablets produced are consistent from batch to batch.
- (iv) To create a rationale strategy in order to guide formulation development and the selection of suitable product formulations and manufacturing process.
- (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 utilization by minimization of faulty tablet production.
- (viii) Environmental issues and concerns related to the waste management of materials.

**Table 1:** Several breakthroughs in the area of bilayer tablets<sup>32</sup>:

DRUG(s)	DOSAGE FORM	RATIONALE
Atorvastatin, Atenolol	Bilayer gastro retentive matrix Tab	Hypertension and hypercholesterolemia treatment
Nifedipine	Gastro retentive floating Bilayer tablets	Hypertension and angina pectoris treatment
Aspirin, Isosorbide 5-mono-nitrate	Sustained Bilayer tablets	Pain, fever, and other inflammatory disorders are treated.
Pioglitazone HCl, Gliclazide	Bilayer Tablets	Type II Diabetes Treatment
Losartan potassium	Bilayer tablet	Hypertension management
TrimetazidineHCl, Clopidogrelbisulphate	Bilayer tablet	In the treatment of acute coronary syndromes, cytoprotective anti-ischemic platelet inhibitors are used.
Diclofenac, Cyclobenza-prine	Bilayer tablet	In the case of pain, there is a synergistic effect.
Granisetron HC1	Bilayer buccal tablets	To solve the problem of bioavailability while minimising adverse effects
Metformin HC1,Glimipiride	Bilayer tablets	In diabetes, there is a synergistic impact.
Indomethacin	Bilayer floating tablets	Drugs are released in two phases.
Metformin HC1, Atorvastatin Calcium	Bilayer tablets	Polytherapy for the treatment of NIDDS and hyperlipidemia is being developed.
CefiximeTrihydrate, Dicloxacilline Sodium	Bilayer tablets	In bacterial infections, this has a synergistic impact.
Piracetam, Vinpocetin	Bilayer tablets	In Alzheimer's disease, there is a synergistic impact.
Metformin HCl, Pioglitazone	Bilayer tablets	Diabetes mellitus: a synergistic impact
Atenolol	Bilayer buccal tablets	To address the issue of bioavailability while minimising adverse effects and administration frequency.
Cefuroxime Axetil Potassium Clavulanate	Bilayer tablets	Diabetes mellitus: a synergistic impact
Amlodipine Besilate, Metoprolol Succinate	Bilayer tablets	Hypertension: a synergistic impact
Diclofenac Sodium, Paracetamol	Bilayer tablets	In pain, there is a synergistic effect.
Ibuprofen, Methocarba-mol	Bilayer tablets	In case of back pain it has synergistic effect.
Atorvastatin Calcium	Bilayer buccal tablets	To solve the bioavailability issue.

## CONCLUSION

Bi-layer tablets offer one of the most significant design methods is to combine incompatible drug with various indications and the same drug with varied release rates in a single unit. The bilayer tablet is an upgraded technology that overcomes the limitations of single-layered tablets. Bilayer and monolayer tablet production share several common features of technology as both of these pharmaceutical formulation are prepared by compacting powdered/granulated API with or without excipients. Multi-layer tablets have many key benefits compared to conventional immediate-release monolayer tablets. Recently, significant advancement in the manufacturing of tablets has been achieved. This has contributed to the improvement of physicochemical properties of tablets, as well as the possibility of producing tablets with modified/controlled release. However, there are nevertheless, a number of technological obstacles need to be overcome in order to achieve a multilayer tablet with parallel levels of reliability as found in monolayer tablets. A key source of design and manufacturing problems of the multilayer tablets is heterogeneity of adjacent layers. Fluctuations of even one of compression parameters (e.g. the compression strength, ratio of the layers, arrangement of layers, the used excipients) can significantly have an effect on the properties of each layer and the interfacial strength. However, considering the different parameters of the manufacturing process of multi-layer tablets, it is possible to attain the desired release profile. Bilayer formulations are convenience dosage form, safe and possess greater advantages to both patient and clinician that it may be administered as a single tablet once a day.

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