BI-LAYER TABLET: A CONTROLLED RELEASE DOSSAGE FORM

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Abstract:

Bilayer tablets are developed to get an immediate and sustained delivery of various drugs which have pre-defined release. In past few decades, development in combination of active pharmaceutical ingredients (API) in a single fixed dosage form has increased in the pharmaceutical industry, also promotes patient convenience and compliance. Bilayer tablet plays a crucial role for development of controlled release in order to give a successful drug delivery. Bilayer tablets can be said to be a better option to reduce chemical incompatibilities taking place between Active Pharmaceutical Ingredients and to enable the development of various drug release profiles. Bilayer tablet suits for sequential release of two drugs in combination or to incorporate two incompatible substances in same tablet. The bilayer tablets preparing by using different techniques such as OROS® push pulls Technology, L-OROSTM Technology, EN SO TROL Technology. This review article explains about various techniques of bilayer tablet and why the development and production of quality bilayer tablets needs to be carried out and basic challenges faced during production of Bilayer Tablet. This review also describes the rationale for this combination therapy and the clinical trials that have demonstrated that these two agents can be combined without the loss of efficacy for either agent or an increase in the incidence of adverse events.

Keywords: Bilayer tablets, OROS®, API.

Introduction:

Solid oral dosage forms are mostly preferred over other routes for many drugs and are still the most widely used formulations. 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. Over 90% of the formulations manufactured today are ingested orally. It shows that this class of the formulation is the most popular worldwide and the major attention of the researcher is towards this direction. The major aim of controlled drug delivery is to reduce the frequency of dosing. The objective of sustained release is to ensure safety and also to improve efficacy of drugs and patient compliance. Bilayer tablet is a fixed dose combination (FDC) intended for oral application. It consists of two layers first layer have immediate release part of single; next layer is controlled release part of single or multiple actives. They are called as “Bilayer tablets”. For the
identification of two drugs various colors were used. Bilayer tablet is a very improved technique to overcome the single layered tablet. Bilayer tablets contain immediate, sustained release layers, and the immediate release layer delivers the initial dose. It includes super disintegrates, that increases the release rate of the drug and also attains the onset of action quickly. Whereas sustained release (maintenance dose) layer releases the drug in a sustained manner for a prolonged period of time by using various polymers as release in retardants. Diabetes, antihypertensive, antihistamines, analgesics, antipyretics and antiallergenic agents are mainly suitable for this type of drug delivery.

Bilayer tablets have advantage as compared to conventional monolayer tablets. These tablets are commonly used so as there is less use of chemical incompatibilities of formulation components by physical separation. Moreover, bilayer tablets have also enabled the development of controlled delivery of an API by combining slow-release with immediate-release layers.

However, such drug delivery devices are complicated mechanically to manufacture and also difficult to judge their long term properties as they have poor mechanical and compression of the materials in the adjacent layers which is compacted, insufficient hardness, inaccurate individual mass control, reduced yield, cross contamination between the layers and their potency to delaminate at the interface while on various stages of compaction process. The major problem, that has to be overcome, is to find out in detail the sources of these problems at lower scales and to find out remedies to solve them. A major challenge is lack of appropriate bonding at the interface between the adjacent compacted layers. When the compacted layers are beyond a certain limit soft or hard, they might not bond appropriately with each other and that can lead to compromised mechanical integrity. Challenges during development also includes layer weight ratio, establishing the order of layer sequence, first layer tamping force, elastic mismatch of the adjacent layers and cross contamination between layers.

Cardiovascular disease (CVD) has a multifactorial nature and their risk factors accompany various different problems. The combination of risk factors like hypertension and dyslipidemia act synergistically which in turn increases the risk of CVD events. This synergistic action is recognized by the major clinical guidelines currently to help in the management of patients with CVD or at risk of CVD, as they recommend a strategy of treating CVD risk factors simultaneously rather than in isolation. There is an increase in evidence describing the advantages of a combined/multifactorial approach to reducing CV risk vs the older sequential approach of treating risk factors individually. The driving forces for the development of such bilayer tablet were the poor level of control of CV risk factors, despite the widespread availability of efficacious antihypertensive and lipid-lowering mediations. A single tablet combination of an antihypertensive and lipid-lowering medication may address some of the issues thought to hinder the management of CVD, such as poor adherence to multiple treatments due to high pill burden and the reluctance of physicians to manage more than one CV risk factor simultaneously. The antihypertensive component(s) must also be free from drug–drug interactions with other BP-lowering medications due to the frequent need for multiple antihypertensive to achieve BP goals in certain difficult-to-treat populations, such as patients with diabetes. The antihypertensive amlodipine Besylatesatisfies these criteria in that it has been demonstrated to reduce CV events in various patient populations and is effective when combined with other classes of antihypertensive. There are a
number of important requirements for therapies used in a combination medication, regardless of the condition being treated. Firstly, the medications must have a same dosing regimen. There should be no negative pharmacokinetic or pharmacodynamic interactions between the proposed components. Thirdly, from a patient’s perspective, the tablet should be of a reasonable size and the formulations should allow flexible dosing.\textsuperscript{5,6}

<table>
<thead>
<tr>
<th><strong>Drug(s)</strong></th>
<th><strong>Dosage Form</strong></th>
<th><strong>Rationale</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin, Atenolol</td>
<td>Bilayer gastroretentive matrix Table</td>
<td>Treatment of hypertension and hypercholesterolemia</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Gastroretentive floating bilayer tablets</td>
<td>Treatment of hypertension and angina pectoris</td>
</tr>
<tr>
<td>Aspirin, Isosorbide 5-mono-nitrate</td>
<td>Sustained tablets</td>
<td>Treatment of pain, fever and other inflammatory Conditions</td>
</tr>
<tr>
<td>Pioglitazone HCl, Gliclazide</td>
<td>Bilayer Tablets</td>
<td>Treatment of Type II Diabetes</td>
</tr>
<tr>
<td>Losartan potassium</td>
<td>Bilayer tablet</td>
<td>Treatment of hypertension</td>
</tr>
<tr>
<td>TrimetazidineHCl, Clopidogrelbisulphate</td>
<td>Bilayer tablets</td>
<td>Cytoprotective anti-ischemic</td>
</tr>
<tr>
<td>Diclofenac, Cyclobenza-prine</td>
<td>Bilayer tablets</td>
<td>Synergistic effect in pain</td>
</tr>
<tr>
<td>Granisetron HCl</td>
<td>Bilayer buccal tablets</td>
<td>To overcome bioavailability problem</td>
</tr>
<tr>
<td>Metformin HC1,Glimipiride</td>
<td>Bilayer tablets</td>
<td>Synergistic effect in diabetes</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Bilayer floating tablets</td>
<td>Biphasic drug release</td>
</tr>
<tr>
<td>Metformin HC1, Atorvastatin Calcium</td>
<td>Bilayer tablets</td>
<td>To develop polytherapy for the treatment of NIDDS &amp; hyperlipidemia</td>
</tr>
</tbody>
</table>

Table No. 1: Various advancements in the field of bilayer tablets\textsuperscript{7}
<table>
<thead>
<tr>
<th>Combination</th>
<th>Formulation</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefixime Trihydrate, Dicloxacillin Sodium</td>
<td>Bilayer tablets</td>
<td>Synergistic effect in bacterial infections</td>
</tr>
<tr>
<td>Piracetam, Vinpocetin</td>
<td>Bilayer tablets</td>
<td>Synergistic effect in Alzheimer disease</td>
</tr>
<tr>
<td>Metformin HCl, Pioglitazone</td>
<td>Bilayer tablets</td>
<td>Synergistic effect in diabetes mellitus</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Bilayer buccal tablets</td>
<td>To overcome bioavailability problem, reducing side effects and frequency of administration</td>
</tr>
<tr>
<td>Cefuroxime Axetil Potassium Clavulanate</td>
<td>Bilayer tablets</td>
<td>Synergistic effect against microbial infections and to minimize dose dependent side effects</td>
</tr>
<tr>
<td>Amlodipine Besylate Metoprolol Succinate</td>
<td>Bilayer tablets</td>
<td>Synergistic effect in hypertension</td>
</tr>
<tr>
<td>Diclofenac Sodium, Paracetamol</td>
<td>Bilayer tablets</td>
<td>Synergistic effect in pain</td>
</tr>
<tr>
<td>Ibuprofen, Methocarbamol</td>
<td>Bilayer tablets</td>
<td>Synergistic effect of drugs in back pain</td>
</tr>
<tr>
<td>Atorvastatin Calcium</td>
<td>Bilayer buccal tablets</td>
<td>To overcome bioavailability problem, reducing side effects and frequency of administration</td>
</tr>
</tbody>
</table>
Need of bilayer tablet

- For purpose of administration of dual release fixed dose combinations of different APIs.
- For the purpose of developing novel drug delivery system such as buccal/Mucoadhesive delivery system and floating tablets for gastro retentive drug delivery system. It helps in controlling drug delivery rate of single or two APIs.
- To modify bilayer tablet in such way that surface area available for active ingredient layer by placing between one or two in active layers for achieving swellable/erodible barrier for modified release.
- To incorporate two incompatible API in one dosage, this helps in control release of API from one layer by utilizing property of other layer.

General properties of Bi-Layer Tablet Dosage Forms:

1. A bi-layer tablet should posses an elegant product identity and should be free of defects like cracks, chips, contamination and discoloration.
2. Must have sufficient strength which will handle mechanical shock during its production.
3. It must have the chemical and physical stability to maintain its physical attributes over time.
4. Must have a chemical stability shelf-life.

The advantages of the bi-layer tablet dosage form are:

1. 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.
2. Cost is lower compared to all other oral dosage form.
3. Lighter and compact.
4. Easiest and cheapest to package and strip.
5. Easy to swallowing with least tendency for hang-up.
6. Objectionable odour and bitter taste can be masked by coating technique.
7. Suitable for large scale production.
8. Greatest chemical and microbial stability over all oral dosage form.
9. Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.
Disadvantages of Bi-Layer Tablet Dosage Form are:  

1. Difficult to swallow in case of children and unconscious patients.
2. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
3. 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.
4. Bitter testing drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.

Preparation of bilayer tablets  

Quality and Good manufacturing practice (GMP) requirements of bi-layer tablets:

- To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the selected press is capable of:
- Preventing capping and separation of the two individual layers that constitute the bi-layer tablet.
- Providing sufficient tablet hardness.
- Preventing cross-contamination between the two layers.
- Producing a clear visual separation between the two layers.
- High yield.
- Accurate and individual weight control of the two layers.

These requirements seem very obvious but are not very easy to observe in manufacturing a bilayer tablet dosage form as there are several critical factors that are to be taken into consideration while manufacturing bilayer tablets. Bi-layer tablets require fewer materials than compression coated tablets weigh less and may be thinner. These tablets are manufactured where one layer of drug is for immediate release while the second layer is for release of drug afterwards, it can be as a second dose or an extended release form. The bilayer tablets can also be produced taking into account two incompatible drugs which is done by compressing individuallayers of each drug to reduce area of contact between two layers. There are certain requirements to develop a proper tablet formulation, like sufficient mechanical strength and desired drug release profile must be met. This might be a tough task for formulator to achieve these conditions especially in bilayer tablet formulation in which double compression technique is involved, because of poor flow and compatibility characteristic of the drug. The compaction of a material involves compressibility and consolidation.

1. Filling of firstlayer
2. Compression of firstlayer
3. Ejection of upper punch
4. Filling of secondlayer
5. Compression of second layer
6. Ejected fully bilayer tablet

![Diagram showing steps in bilayer tablet formulation](image)

**Figure no.1: Steps in bilayer tablet formulation**

**Various techniques for bilayer tablet**\(^{13,14}\)

**OROS® push pulls Technology**

It includes two or three layer amongst which the one layer is essential of the drug and other layer is push layer. The drug layer consists of drug along with two or more various agents. So this drug layer comprises of drug which is in poorly soluble form. Suspending agent and osmotic agents can also be added. A semi permeable membrane surrounds the tablet core (Figure 2).

![Diagram showing bilayer and trilayer OROS push pull technology](image)

**Figure no. 2: Bilayer and trilayer OROS push pull technology**

**L-OROS\(^{TM}\) Technology**

This system 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 then coated with a barrier membrane, than osmotic push layer and then a semi permeable membrane, drilled with an exit orifice(Figure 3).
EN SO TROL Technology

Enhancement of solubility or to create optimized dosage form uses an approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies.

DUROS Technology

This system is also called “Miniature drug dispensing technology”. Its functioning resembles miniature syringe that releases drug in continues and consistent manner in small concentrated form for long period of time. Drug molecules are protected from enzyme with help of cylindrical titanium alloy reservoir present outside having high impact strength.

DUREDAS™ Technology

This technology gives combination release pattern of drug i.e. immediate or sustained release. This system provides one drug with different release pattern or two drugs of combination release pattern. In this system different release pattern achieved by using combination of hydrophilic polymer. This technology provides number of advantages i.e. combination release in one tablet or another advantage is two drugs incorporated in single dosage form. During process of manufacturing bilayer tablet by using DUREDAS™ Technology immediate release granulate compressed first followed by sustained release layer. DUREDAS™ Technology first used for development of OTC controlled release analgesics.
Geminex Technology

With help of this the therapeutic efficacy of drugs can be increased greatly, also useful in minimizing side effects. This technology delivers one or more drug with different release rate in single dosage form. It is very useful both for industry as well patients. Geminex Technology actively applied by pen west in following areas – diabetes, cardiovascular diseases, cancer and CNS disorders

Various approaches used in the bilayer tablet $^{15,16}$

A. Floating Drug Delivery System

These are designed to have a low density and thus float on gastric contents after administration until the system either disintegrates or the device absorbs fluid until its density is such that it can pass easily from the stomach responsible for gastric emptying. The design of bilayer tablet is such that, one layer gives the immediate dosing of the drug and it gives faster onset of action. The other layer is designed as a floating layer which floats in the stomach (GI-fluid).

Disadvantages:

- It might not control the loss of density required to exit from the stomach.
- These tablets cannot be applicable to high doses of highly water soluble drugs.
- The performance of floating formulation may also be posture dependant. Hence, floating dosage forms might be expected to only have limited applications.

A. Polymeric Bioadhesive System

These are made to imbide fluid after administration in such a way that the outer layer is seen to be viscous which adheres to the gastric mucus layer. It is required that gastric retention increases until the adhesive forces are weakened. These are designed such as one layer has an immediate dosing and the next layer has Bioadhesive property.

Disadvantages:

- The success seen in animal models is not as that of human subjects due to differences in mucous amounts, consistency between animals and humans.
- The system adheres to mucous not mucosa.
- The mucous layer in humans can slough off easily and can carry drug along with it.
B. Swelling System

These systems are small on administration so as ingestion of the dosage form is made easy. Upon ingestion they swell rapidly or unfold to a size that precludes passage through the pylorus until after drug release has progressed to a required degree. Slow erosion or its breakdown into smaller particles allows it to leave stomach. The bilayer tablet might contain an immediate release layer with the other layer as conventional release.

**Challenges in bilayer manufacturing** ¹⁷,¹⁸:

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.

**Cross-contamination**
When the granulation of the first layer intermingles with the granulation of the second layer or vice versa, cross-contamination occurs. Proper dust collection can prevent cross-contamination.

**Production yields**
In order to prevent cross contamination, dust collection is required which leads to losses. Thus, bilayer tablets have lower yields than single-layer tablets.

**Cost**
Bilayer tableting is expensive than single layer tableting for several reasons. The tablet press costs more. The press generally runs slowly in bilayer mode. Third, development of two compatible granulations is mandatory, which means more time spent on formulation development, analysis and validation.

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**Figure no. 5: Drug release from bilayer tablet** ¹⁸

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Evaluation of Bilayer Tablets:

1. **General Appearance**: It includes its visual identity; “elegance” is required for consumer acceptance. Other parameters are tablet’s size, colour, shape, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

2. **Size and Shape**: The size and shape of the tablet can be dimensionally described, monitored and controlled.

3. **Tablet thickness**: Tablet thickness is an important characteristic when it comes to reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism.

4. **Weight variation**: Standard procedures are followed as described in the official books.

5. **Friability**: The friability test relates to hardness of tablet and is planned to test the ability of the tablet to withstand abrasion in all the processes like packaging. It is measured by the Roche friabilator. Tablets are placed in the apparatus after they are weighed where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. It continues for after four minutes or 100 revolutions. The loss occurring due to abrasion is measured by 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. Normally, when capping occurs, friability values are not calculated. A thick tablet may have less tendency to cap whereas thin tablets of large diameter often show extensive capping, thus indicating that tablets with greater thickness have reduced internal stress the loss in the weight of tablet is the measure of friability and is expressed in percentage as:

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

6. **Hardness (Crushing strength)**:

   The hardness of the tablet will be carved out using Monsanto type hardness tester. The hardness of the tablet is measured in Kg/Cm². The hardness is considered as an important parameter which helps to overcome resist the tablets to shipping or breakage under conditions of storage.

7. **Stability Study (Temperature dependent)**: The bilayer tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.
Table No. 2 Recommended Long Term and Accelerated Storage Condition

<table>
<thead>
<tr>
<th>Study</th>
<th>Storage Condition</th>
<th>Minimum Time Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long term</td>
<td>25°C ± 2°C / 60% RH ± 5% RH</td>
<td>12 months</td>
</tr>
<tr>
<td></td>
<td>30°C ± 2°C / 65% RH ± 5% RH</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>30°C ± 2°C / 65% RH ± 5% RH</td>
<td>6 months</td>
</tr>
<tr>
<td>Accelerated</td>
<td>40°C ± 2°C / 75% RH ± 5% RH</td>
<td>6 months</td>
</tr>
</tbody>
</table>

Applications

- Bi-layer tablets deliver two different drugs having different release profile.
- Bi-layer tablets deliver the loading dose and maintenance dose
- Bi-layer tablets are mainly used in combination for modified release.
- Bi-layer tablets are used for bi-layer floating tablets in which one layer is floating layer another one is immediate release layer of the drug.

Conclusion

Bi-layer tablet is selected for sequential release of two drugs in combination or separate two substances which are incompatible, for sustained release tablet where one layer is immediate release and second layer is maintenance dose. Bi-layer tablets give an opportunity for producers to improve their products’ efficacy, and protect against impersonator products. Bi-layer tablet GMP requirements can differ widely. When a bi-layer tablet requires to be developed along with accurate weight control of the two layers, compression force-controlled presses are limited as their insufficient sensitivity and thus lack of accuracy at low compression forces required to secure interlayer bonding. 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. Bilayer tablet has been done with various or various combination, which is useful for various ailments. Thus bilayer formulation is convenience dosage form, safe and possesses greater advantages to both patient and clinician that it may be administered as a single tablet in once a day. Bilayer tablet is quality and GMP requirements can vary widely.
References:


