A NEW VENTURE IN DRUG DELIVERY: BILAYERED TABLETS REVIEW

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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 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. Novel technologies with improved performance, patient compliance and enhanced quality have emerged in the recent past. Multilayer tabletting is getting increasing attention for a variety of reasons like patent extension, therapeutic effect, marketing to name. To reduce capital investment, quite often existing but modified tablet presses are used to develop and produce such tablets. While general tablet manufacturing principles remain the same, there is much more to consider because making multi-layer tablets involves multiple-often incompatible products, additional equipment and many formulation and operation challenges. The present article provides a review on types of tablets, and challenges in bilayer tablet manufacturing, quality and GMP requirements for their production and recent developments in the field of bilayer technology.

KEY WORDS
Bilayer Tablet, Manufacturing Aspects of Bilayered Tablets and Various techniques for Bilayer Tablets.

INTRODUCTION
Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease of administration. Conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. The aim in designing sustained or controlled delivery systems is to decrease the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required.
The main objective of sustained release drug delivery is to make sure safety and to improve effectiveness of drugs as well as patient compliance\(^1\). Now a day’s various developed and developing countries move towards combination therapy for treatment of various diseases and disorders requiring long-term therapy such as hypertension, diabetes and Cardio vascular diseases.

Bi-layer tablets are 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\(^2\).

Bi-layer tablets consist of monolithic partially coated or multilayered matrices. In the case of bi-layered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper non-adhesive layer its delivery occurs into the whole oral cavity. The mechanical strength of bi-layered tablets has been observed not to be a controlling factor in drug release.

Challenges during development of bilayer tablets include the order of layer sequence, layer weight ratio, elastic mismatch of the adjacent layers, first layer tamping force and cross contamination between layers. If these factors not well controlled in one way or other will effect the bi-layer compression pressure and the quality attributes like mechanical strength and individual layer weight control. Therefore care must be taken to enable design of a vigorous product and process\(^3,4\).

**NEED OF BILAYERED TABLET**

1. Controlling the delivery rate of either single or two different API’S.
2. To separate incompatible active pharmaceutical ingredient from each other, to control the release of API from one layer by utilizing the functional property of the other layer such as, osmotic property.
3. To administer fixed dose combinations of different APIs, prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device, buccal/ mucoadhesive delivery systems, and floating tablets for gastro-retentive drug delivery.
4. To modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable / erodible barriers for controlled release\(^5\).

**ADVANTAGES**\(^6\)

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. Bi-layer execution with optional single layer conversion kit.
3. Low cost compared to other dosage forms.
4. Greatest chemical and microbial stability compared to other oral dosage forms.
5. Objectionable odor and taste can be masked by coating technologies.
6. Offer greatest precision and the least content uniformity.
7. Easy to swallow with least hang up problems.
8. Fit for large scale production.
9. Bi-layer tablet is suitable for preventing direct contact of two drugs and thus to maximize the efficacy of combination of two drugs.
10. Bi-layer tablets can be designed in such a manner as to modified release as either of the layers can be kept as extended and the other as immediate release.
11. Expansion of a conventional technology.
12. Prospective use of single entity feed granules.
14. Patient compliance is improved leading to improve drug regimen efficiency.
15. Easiest and cheapest to package and strip.

**DISADVANTAGES**

1. Drugs with poor wetting, slow dissolution properties, optimal absorption high in GIT may difficult to manufacture as a tablet that will still provide ample drug bio availability.
2. In accurate individual layer weight control.
3. Adds complexity and bilayer rotary presses are expensive.
4. Difficult to swallow in case of children and unconscious patients.
5. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
6. Cross contamination between the layers.
7. Insufficient hardness, layer separation, reduced yield.

**GENERAL PROPERTIES OF BI-LAYER TABLET DOSAGE FORMS**

1. It should have graceful product identity free of defects like chips, cracks, discoloration, and contamination.
2. Should have sufficient strength to withstand mechanical shock during its production, packaging, shipping and dispensing.
3. Should have physical and chemical stability.
4. The bi-layer tablet must release drug in an expected and reproducible manner.
5. Must have a chemical stability shelf life, so as not to follow alteration of the medicinal agents.

**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 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.

**Skipping first layer compression**

The number of compressions in manufacturing of multi-layer tablets is equal to the number of layers in the multi-layer tablet. If the first layer is not compressed before addition of second layer, there is a possibility of uncontrolled mixing of granules of first layer into second layer at the interface. In addition, if the first layer is not compressed before addition of second layer, due to the centrifugal force during the rotation of the turret, the granules of first layer may shift toward the outer periphery of the die cavity resulting in an angled interface. A clear demarcation between the two layers is desirable since it is not only appealing and but also visually assures that there is no cross-contamination.

**Tablet breaking force**

According to the current USP, tablet breaking force is the force required to cause the tablets to break in a specific plane. The tablets are generally placed between two platens, one of which moves to apply sufficient force to the tablet to cause fracture. For conventional round a tablet loading occurs across their diameter, and fracture occurs in that plane. Tensile strength provides a more fundamental measure of the mechanical strength of the tablet and it considers geometry of the tablet. Tensile strength is calculated by the following:

\[
\text{Tensile strength} = \frac{2F}{\pi Dh}
\]

Where, \(F\) is the load required breaking the tablet diametrically (as opposed to de-laminating or capping), “\(D\)” and “\(h\)” are tablet diameter and thickness, respectively. Thus, tensile strength estimates force per unit area of the tablet at breakage. This equation is applicable only for the tablets that have flat surface. For tablets that do not have flat surface, curvature needs to be considered while calculating the surface area. It is well documented that the mechanical strength of a tablet can be generally characterized by measuring the tensile strength using the compression test introduced by Fell and Newton.

To simplify the process, alternate approaches of determining adhesion strength as a measure of binary
tablet performance have been developed and reported in the literature. An apparatus to measure the shear forces needed to separate the layers in the radial direction and relate these forces as a measure of adhesion strength was reported. Although measurement of tensile strength is appropriate for assessing the tablet strength; pharmaceutical firms tend to measure the tablet breaking force, which is essentially the load to break the tablet. Another measure for mechanical strength is the crushing strength-friability ratio. Regardless of how the tablet is evaluated for its strength, a measure to assess this critical attribute must be fully evaluated and the choice of the test method must be supported by the formulation and the manufacturing process. The integrity of the tablet needs to be assessed during the stability studies to confirm that aging and environment have not negatively influenced the adhesion of the layers.

**Effect of lubrication**

Since the first layer surface is uniform and perhaps relatively less rough due to the first layer compression, the interfacial interactions between the first layer and the second layer may be impacted by the level of lubricant. The tablet surface smoothness increases as the level of lubricant, such as magnesium stearate is increased. In order to achieve a better interfacial interaction between the layers, relatively low lubricant concentration and low compression forces are required for first layer tableting.

However, the level of lubricant needed for avoiding picking and sticking of the first layer must be assessed as part of the product development. The blended lubricant in the granules bulk distributes throughout the mixture, or “coats” on the surface of the granules and this provides lubrication and reduces the friction when the granules come in contact with dies and punches during compression. However, the lubrication can also reduce the extent of inter-granular adhesion and potentially affects the critical quality attributes such as tablet breaking force and dissolution.

Thus, adding lubricant to the dies and punches, instead of adding directly to the granules, has been investigated to understand the impact of lubricant on the critical quality attributes of the tablet. This process is referred to as external lubrication. In external lubrication, the lubricant is sprayed onto the die and punches for each compression cycle instead of adding it to the bulk powder mixture, have shown that the external lubrication can increase crushing strength by 40% without prolonging the tablet disintegration. It is confirmed by observing a layer of magnesium stearate on the tablet through scanning electron microscope. Though this new technology appears advantageous for the mono-layer tablets, it can potentially be used to better understand the impact of lubricant on the quality attributes of bilayer tablets.

**Coating**

Often multi-layered tablets are coated to improve elegance, to protect the cores from ambient conditions or to control the release profile. In either case, exposure of the multi-layered tablets to solvents, high temperatures and affect of loads must be considered in the product development. To avoid layer-separation during the coating process it is important to know the coefficients of thermal expansion of the tablet layers and the impact of this difference on the tablet integrity, have explained that during the coating process of bi-layered tablets, cracks appeared on the surface of only one layer within few minutes of the coating process, leaving the other layer intact.

Upon testing, it was found that the thermal expansion coefficient of two different layers of the tablet were significantly different. When control coating was run, the individual layers separately at 40-55 °C, and no evidence of cracking was found. To alleviate the cracking, the product was reformulated with each layer having almost the same coefficient of thermal expansion. Thus, multi-layer drug products that are intended to undergo coating process require additional scrutiny that may not be needed for drug products that do not require coating. Though cracking is reported for bi-layer tablets that undergo coating, it is possible that the cracking and/or separation of layers could also occur upon extended storage of the drug product. Thus, it is
imperative that the excipients are not only screened for their physical properties such as particle size and compressibility during the pharmaceutical development stage, but also, tested to ensure the individual layers are similar in terms of their thermal expansion coefficient.

Stability
In the stability studies, drug products need to be observed closely and tested periodically to ensure that their integrity is preserved throughout their shelf life and they perform in a predictable manner. Bi-layer tablets prepared with the combination of two therapeutic agents are certainly convenient, and thus simplify the treatment regimen. The use of a combination of two APIs or the same API with different release rate to optimize therapy and to improve patient compliance has increased steadily over the years.

To achieve this objective it is imperative that the quality and the performance of the bi-layer tablets be maintained over the expiration period. The stability studies must be performed under conditions as per ICH guidelines and the supportive stability data generated during the product development phase and on the exhibit (clinical and/or BA/BE) batches to demonstrate the product quality and performance must be included in the filing. It is recommended that the sponsor perform the drug-drug, drug-excipients interaction, studies the impact of manufacturing process and the impact of heat and humidity on the integrity of the bi-layer and drug release over the expiration period. The selection of the container/closure system must be based on the ability of the system to protect the drug product and maintain the integrity of the bi-layer under use condition over the shelf life. The study done, demonstrated that the bi-layer tablets prepared with amlodipine besylate and atenolol had a better stability profile than the mono-layer matrix tablets consisting both the APIs. This strategy, although improving the stability of one drug component, did not completely prevent the interaction. A significant decrease (more than 5%) in the assay was observed in the other drug component. In such scenarios, if alternate approaches are used to improve the product stability of the layered tablets they must be adequately supported by the stability studies.

In vitro performance
The in vitro dissolution testing requirement of the bi-layer tablets will vary based on the intended dosage design and the physicochemical characteristics of the drug in each layer. This variability poses special challenges in the development of a meaningful dissolution procedure for bilayer drug products, especially if drugs with different water solubility are incorporated in the bi-layer tablets. In general, attributes such as rate of swelling and rate of water uptake need to be assessed for the bi-layer tablets. For example, if the goal of bi-layer immediate tablet is to deliver two incompatible API, then the separation of these layers in the dissolution media may be of no significance as this would not have any impact on the product performance.

However, if the bi-layer tablet is a modified release product, with the design feature to control the release rate of the API layer by compacting with placebo layer, the integrity of the layers in the dissolution media is critical to the performance of the drug product (in vivo). In the case of bi-layer drug products, a bio-relevant dissolution test conditions would be more meaningful in evaluating product quality and product performance. For example, in vitro dissolution testing of bi-layer tablet made with water insoluble APIs need extensive use of simulated fluids on both fresh tablets and the long-term stability samples.

Having a sensitive, reliable and discriminating in vitro dissolution procedure to determine the product quality and to predict bioavailability is of primary interest to the agency. It is recommended that all studies done for the development of the dissolution method must be included in the filing to support the final method that will be used for release and stability of the drug product. In general, development of a meaningful dissolution procedure for APIs with limited water solubility is more challenging than for the drug product with a high water solubility API. Having both classes of drugs in the same unit presents additional challenges to both the pharmaceutical industry and the regulatory agency.
To measure the in vitro drug release performance of the bi-layer drug product, well established techniques can be used to achieve adequate dissolution by understanding the solubility differences of the API, use of relevant and appropriate amount of surfactants, composition and volume of dissolution test medium, pH, type of apparatus and rate of agitation.

**Various Techniques for Preparation of Bilayer Tablets**

**Duros Technology**
The system consists from an outer cylindrical titanium alloy reservoir. This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the miniature drug dispensing system that opposes like a miniature syringe and regluous minute quantity of concentrated form in continues and consistent from over months or Year.

**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.

**Elan Drug Technologies Dual Release Drug Delivery System**
(DUREDAS™ Technology) is a bilayer tablet which can provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form. The tab letting process can provide an immediate release granulate and a modified-release hydrophilic matrix complex as separate layers within the one tablet. The modified-release properties of the dosage form are provided by a combination of hydrophilic polymers.

**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.

**Oros® Push Pull Technology**
This system consist of mainly two or three layer among which the one or more layer are essential of the drug and other layer are consist of push layer. The drug layer mainly consists of drug along with two or more different agents. So this 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.

**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.

**Bilayer Tablets**

**Quality and Gmp Requirements**
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 bilayer 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 the two layers.

**Various Aspects used in the Bi-Layer Tablet**

**Floating Drug Delivery Systems (FDDS)**
From the formulation and technological point of view, the floating drug delivery systems are significantly easy and consistent approach in the development of Gastro retentive dosage forms.

**Approaches to design floating drug delivery system**
The following approaches have been used for the design of floating dosage forms of single-and multiple unit systems.
Intra gastric bi-layered floating tablets
These are also compressed tablet contain two layers i.e., i) Immediate release layer ii) Sustained release layer.

Multiple unit type floating pill
These systems consist of sustained release pills as ‘seeds’ surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density.

EVALUATION OF BILAYER TABLET

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

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

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

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

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

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

Dissolution Studies
Bilayer tablets were subjected to in vitro drug release studies in simulated gastric and intestinal fluids to assess their ability in providing the desired controlled drug delivery. Drug release studies were carried out using USP dissolution test apparatus I at 100 rpm, 37±0.5°C and pH 1.2 buffer (900 ml) (i.e. 0.1 N HCl) for 2 hours, since the average gastric emptying time is about 2 hours. The dissolution medium was replaced with pH 6.8 phosphate buffer (900 ml) and experiment continued for another 10 hours. At different time intervals, 5ml of the samples were withdrawn and replaced with 5ml of drug-free dissolution medium. The samples withdrawn were analyzed by UV spectrophotometer using multi component mode of analysis.

Stability Study
In order to determine the change on storage, stability study is carried out at 25°C / 60% RH and 40°C / 75% RH in a stability chamber. Samples are withdrawn at regular intervals. Formulation is evaluated for changes in Hardness, Thickness, Disintegration time and in vitro release studies.
Table No.1: Commercially marketed bilayer tablets

<table>
<thead>
<tr>
<th>S.No</th>
<th>Product Name</th>
<th>Chemical Name</th>
<th>Developer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ALPRAX PLUS</td>
<td>Sertraline, Alprazolam</td>
<td>Torrent Pharmaceuticals Ltd.</td>
</tr>
<tr>
<td>2</td>
<td>DIAMICRON®XRMEX500</td>
<td>Gliclazide, Metformin Hcl</td>
<td>Sedia® Pharmaceuticals Pvt. Ltd.</td>
</tr>
<tr>
<td>3</td>
<td>DIUCONTIN-K®20/250</td>
<td>Furosemide, Potassium chloride</td>
<td>T.C. Health Care Pvt. Ltd.</td>
</tr>
<tr>
<td>4</td>
<td>Glycomet®-GP2Forte</td>
<td>Metformin hydrochloride, Glimepiride</td>
<td>USV Limited</td>
</tr>
<tr>
<td>5</td>
<td>New cold Plus</td>
<td>Levocetirizine Hcl, Phenylpropanolamine Paracetamol</td>
<td>Piramol Healthcare Ltd.</td>
</tr>
<tr>
<td>6</td>
<td>PIOKIND®-M15</td>
<td>Pioglitazone, metformine Hcl</td>
<td>Psychotropics India Ltd.</td>
</tr>
<tr>
<td>7</td>
<td>Revelol®-Am 25/5</td>
<td>Metoprolol succinate, Amlodipine besilate</td>
<td>Ipca Laboratories Ltd.</td>
</tr>
<tr>
<td>8</td>
<td>TRIOMUNE 30</td>
<td>Nevirapine, Lamivudine, Stavudine</td>
<td>Cipla Ltd.</td>
</tr>
</tbody>
</table>

Table No.2: Various Advancements in the Field of Bilayer Tablets

<table>
<thead>
<tr>
<th>S.No</th>
<th>DRUG (s)</th>
<th>RATIONALE</th>
<th>METHOD</th>
<th>AUTHOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Aspirin + Ranitidine</td>
<td>To minimize the contact of two incompatible drugs</td>
<td>Wet granulation &amp; fluidization</td>
<td>Wang et al&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Amlodipine Besilate + Metoprolol Succinate</td>
<td>Synergistic effect in hypertension</td>
<td>Direct compression &amp; wet granulation</td>
<td>Jayaprakash et al&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>Atenolol + Lovastatin</td>
<td>Synergistic effect in hypertension &amp; biphasic release profile</td>
<td>Direct compression</td>
<td>Kulkarni et al&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>Ascorbic acid + Cyanocobalamine</td>
<td>To avoid interaction b/w incompatible vitamins</td>
<td>Using suppository base</td>
<td>Bakuridze et al&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>Artesunate + Amlodipine</td>
<td>To minimize contact b/w drugs</td>
<td>Wet granulation</td>
<td>Godha et al&lt;sup&gt;14&lt;/sup&gt;</td>
</tr>
<tr>
<td>No.</td>
<td>Drug Combinations</td>
<td>Formulation Type</td>
<td>Processing Method</td>
<td>Authors</td>
</tr>
<tr>
<td>-----</td>
<td>-----------------------------------------------------------------------------------</td>
<td>----------------------------------------------</td>
<td>----------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>6</td>
<td>Cefuroxime axetil</td>
<td>Bimodal drug release</td>
<td>Granulation</td>
<td>Dhumal et al(^{15})</td>
</tr>
<tr>
<td>7</td>
<td>Cefixime Trihydrate + Dicloxacilline Sodium</td>
<td>Synergistic effect in bacterial infections</td>
<td>Wet granulation</td>
<td>Kumar et al(^{16})</td>
</tr>
<tr>
<td>8</td>
<td>Cefuroxime Axetil + Potassium Clavulanate</td>
<td>Synergistic effect against microbial infections &amp; to minimize dose dependent side effects</td>
<td>Dry granulation</td>
<td>Parmar et al(^{17})</td>
</tr>
<tr>
<td>9</td>
<td>Diclofenac + Cyclobenzaprine HCl</td>
<td>Synergistic effect in Pain</td>
<td>Wet granulation</td>
<td>Jamunadevi et al(^{18})</td>
</tr>
<tr>
<td>10</td>
<td>Diclofenac Sodium + Paracetamol</td>
<td>Synergistic effect in Pain</td>
<td>Wet granulation</td>
<td>Musle et al(^{19})</td>
</tr>
<tr>
<td>11</td>
<td>Glipizide + Metformin HCl</td>
<td>To avoid interaction b/w incompatible drugs</td>
<td>Wet granulation</td>
<td>Kadam et al(^{20})</td>
</tr>
<tr>
<td>12</td>
<td>Granisetron HCl</td>
<td>To overcome bioavailability problem</td>
<td>Direct compression</td>
<td>Swamy et al(^{21})</td>
</tr>
<tr>
<td>13</td>
<td>Indomethacin</td>
<td>Biphasic drug release</td>
<td>Wet granulation</td>
<td>Jain et al(^{22})</td>
</tr>
<tr>
<td>14</td>
<td>Losartan</td>
<td>Biphasic drug release</td>
<td>Direct compression</td>
<td>Hiremath et al(^{23})</td>
</tr>
<tr>
<td>15</td>
<td>Ibuprofen + Methocarbamol</td>
<td>Synergistic effect of drugs in back pain</td>
<td>Wet granulation</td>
<td>Remya et al(^{24})</td>
</tr>
<tr>
<td>16</td>
<td>Misorostol + Diclofenac</td>
<td>To minimize contact b/w drugs</td>
<td>Wet granulation</td>
<td>Ouali et al(^{25})</td>
</tr>
<tr>
<td>17</td>
<td>Metformin + Glipizide</td>
<td>Synergistic effect of drugs in diabetes</td>
<td>Wet granulation</td>
<td>De-fang et al(^{26})</td>
</tr>
<tr>
<td>18</td>
<td>Metformin HCl + Atorvastatin Calcium</td>
<td>To develop polytherapy for the treatment of NIDDS &amp; hyperlipidemia</td>
<td>Wet granulation</td>
<td>Mohindeen et al(^{27})</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>No.</th>
<th>Drug Combination</th>
<th>Synergistic effect/To minimize interaction</th>
<th>Method of Drug Release</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>Piracetam + Vinpocetin</td>
<td>Synergistic effect in Alzheimer disease</td>
<td>Wet granulation</td>
<td>Jadav et al 28</td>
</tr>
<tr>
<td>20</td>
<td>Paracetamol + Diclofenac</td>
<td>Synergistic effect of drugs in Pain</td>
<td>Wet granulation</td>
<td>Gohel et al 29</td>
</tr>
<tr>
<td>21</td>
<td>Propranolol HCl</td>
<td>Bimodal drug release</td>
<td>Wet granulation</td>
<td>Patra et al 30</td>
</tr>
<tr>
<td>22</td>
<td>Salbutamol + Theophylline</td>
<td>Synergistic effect of drugs in asthma</td>
<td>Wet granulation</td>
<td>Nagaraju et al 31</td>
</tr>
<tr>
<td>23</td>
<td>Statin + Aspirin</td>
<td>To minimize interaction b/w two drugs and side effects due to aspirin</td>
<td>Wet granulation</td>
<td>Ullah et al 32</td>
</tr>
<tr>
<td>24</td>
<td>Telmisartan + Simvastatin</td>
<td>To minimize contact b/w Simvastatin &amp; Telmisartan</td>
<td>Wet granulation</td>
<td>Kohlrausch et al 33</td>
</tr>
<tr>
<td>25</td>
<td>Tramadol + Acetaminophen</td>
<td>Synergistic effect of drugs in pain</td>
<td>Coacervation via temp change</td>
<td>Naeem et al 34</td>
</tr>
<tr>
<td>26</td>
<td>Telmisartan + Hydrochlorothiazide</td>
<td>To minimize contact b/w hydrochlorothiazide and basic component of Telmisartan</td>
<td>Wet granulation</td>
<td>Friedl et al 35</td>
</tr>
</tbody>
</table>

**CONCLUSION**

Bi-layer tablets provide one of the important design approaches where incompatible drugs, with different indication, and same drug with different release rate can be incorporated in a single unit. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. The objective of the dosage form is to ensure that the drugs available to its citizen are not only safe and effective, but are also properly manufactured and packaged to meet the established quality target product profile over it shelf life. To develop a robust bi-layer tablet a complete mechanistic understanding must be developed through the application of scientific and quality risk management tools. Bilayer tablet quality and GMP-requirements can vary widely.

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REFERENCES


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