BILAYER TABLET: A 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. Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles (immediate release with extended release). Article provides an overview of the state-of-the-art of bilayer tablet technology, highlighting the main benefits of this type of oral dosage forms while providing a description of current challenges and advances toward improving manufacturing practices and product quality. There is various application of the bilayer tablet it consist of monolithic partially coated or multilayered matrices. This review explains fundamentals of bilayer tablet system along with its fabrication techniques, different approaches, characterization, challenges in Bilayer tablet manufacturing, Quality & GMP requirements, for their production and recent developments in the field of bilayer technology.

KEYWORDS: immediate release with extended release.

INTRODUCTION
Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. The primary
objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance.

Bi-layer tablets can be a primary option to avoid chemical incompatibilities between APIs by physical separation, and to enable the development of different drug release profiles (immediate release with extended release). Bi-layer tablet is suitable for sequential release of two drugs in combination it is also capable of separating 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. Bilayer tablets contain immediate and sustained release layers. The immediate release layer delivers the initial dose, it contains superdisintegrants which promotes drug release rate and attains the onset of action quickly( loading dose ) whereas sustained release(maintenance dose) layer releases drug in sustained manner for prolonged time period.

Need Of Bilayer Tablet

• For the administration of fixed dose combinations of different APIs, prolong the drug product life cycle, buccal / mucoadhesive delivery systems, fabricate novel drug delivery systems such as chewing divice and floating tablets for gastro-retentive drug delivery.
• 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 modified release.
• Controlling the delivery rate of either single or two different active pharmaceutical ingredients.
• To separate incompatible active pharmaceutical ingredient ( APIs) 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).
Advantages of the Bilayer Tablet
1. Bi-layer execution with optional single layer conversion kit.
2. Low cost compared to other dosage forms.
3. Greatest chemical and microbial stability compared to other oral dosage forms.
4. Objectionable odor and taste can be masked by coating technology.
5. Offer greatest precision and the least content uniformity
6. Easy to swallow with least hang up problems.
7. Bi-layer tablet is suitable for preventing direct contact of two drugs and thus to maximiz the efficacy of combination of two drugs.
8. 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.

Disadvantages Of Bi-layer Tablet
- Adds complexity and bi-layer rotary presses are expensive.
- Insufficient hardness, layer separation, reduced yield.
- Imprecise individual layer weight control
- Cross contamination between the layers.
- Difficult to swallow in case of children and unconscious patients.
- Some drugs resist compression into dense compacts, due to amorphous nature, low density nature.
- 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.

Ideal Characteristics Of Bilayer Tablet
- A bi-layer tablet should have elegant product identity while free of defects ike chips, cracks, discoloration and contamination.
- It should have sufficient strength to with stand mechanical shock during its production packaging, shipping and dispensing.
- It should have the chemical and physical stability to maintain its physical attributes over time. The bi-layer tablet must be able to release the medicinal agents in a predictable and reproducible manner.
- It must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.
Applications

- Bi-layer tablets are used to deliver the two different drugs having different release profile.
- Bi-layer tablets are used to deliver the loading dose and maintenance dose of the same or different drug.
- 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 and another one is immediate release layer of the drug.

Types Of Bilayer Tablet

The term bilayered tablets containing subunits that may be either the same (homogeneous) or different (heterogeneous).

Homogenous type

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

Heterogenous type

Bilayer tablet is suitable for sequential release of two drugs in combination, separate two Incompatible substances.

Approaches For Layered Tablet

1. Multi Layered tablets – two to three component systems.
2. Compression coated tablets – tablet within a tablet.
3. Inlay tablet – coat partially surrounding the core.

Multilayered tablets (Bi, Tri)

When two or more active pharmaceutical ingredients are needed to be administered simultaneously and they are incompatible, the best option for the formulation pharmacist would be to formulate multilayered tablet. It consists of several different granulations that are compressed to form a single tablet composed of two or more layers and usually each layer is of different colour to produce a distinctive looking tablet. Dust extraction is essential during
compression to avoid contamination. Therefore, each layer undergoes light compression as each component is laid down. This avoids granules intermixing if the machine vibrates.

Compression coated tablets
This type of tablet has two parts, internal core and surrounding coat. The core is small porous tablet and --prepared on one turret. For preparing final tablet, a bigger die cavity in another turret is used in which first the coat material is filled to half and then core tablet is mechanically transferred, again the remaining space is filled with coat material and finally compression force is applied. This tablet readily lend itself in to a repeat action tablet as the outer layer provides the initial dose while the inner core release the drug later on. But, when the core quickly releases the drug, entirely different blood level is achieved with the risk of over dose toxicity. To avoid immediate release of both the layers, the core tablet is coated with enteric polymer so that it will not release the drug in stomach while, the first dose is added in outer sugar coating. Even so, coating operation requires interpretation while manufacturing and dawdling the manufacturing process. Sometimes, inner core may be of liquid formulation to provide immediate release of core after the coat gets dissolved.
Inlay tablets
A type of layered tablet in which instead the core tablet being completely surrounded by coating, top surface is completely exposed. While preparation, only the bottom of the die cavity is filled with coating material and core is placed upon it. When compression force is applied, some coating material is displaced to form the sides and compress the whole tablet.

Types of Bilayer Tablet Press
A. Single sided tablet press
B. Double sided tablet press
C. Bilayer tablet press with displacement monitoring.

• Single-sided Press
Ø The simplest design is a single-sided press with both chamber of the double feeder separated from each other.
Ø Two individual layers of the tablet produced as each chamber have gravity or forced fed with a different powder.
Ø When the die passes under the feeder, it is at first loaded with the first-layer powder followed by the second-layer powder.
Ø Then the entire tablet is compressed in one or two (pre and main-compression) steps.
Ø 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 produced.


Limitations of single-sided press are
Ø No weight control/monitoring of the individual layer.
Ø No distinct visual separation between the two layers.
Ø Very short first layer dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping and hardness problem.
Ø Very difficult first-layer tablet sampling and sample transport to a test unit for in-line quality control and weight recalibration.

B) Double sided tablet Press
Ø A double-sided press have an individual fill station, pre-compression and main compression for each layer.
Ø Most of the double sided tablet presses with automated production control use compression force to monitor and control tablet weight.
Ø The effective peak compression force exerted on each individual tablet or layer is measured by the control system at main-compression of that layer.
Ø Measured peak compression force(under constant thickness) is the signal used by the control system to reject out-of-tolerance tablet and correct the die fills depth when required.

Limitations of compression force controlled system
Ø A compression force-controlled system requires a minimal compression force of several hundreds of da N.
Ø However, many bilayer formulations require less than 100 da N to compress first layer in order to retain the ability to bond with the second layer.
Above 100 da N, this ability may be lost, bonding between both layers may not be sufficient, resulting in low hardness of the bilayer tablet and separation of the two layers.

At higher production speed, the risk of separation and capping increases but can be reduced by sufficient dwell time at compression stages.

C) Bilayer tablet press with displacement monitoring
The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied pre compression force. This double-sided tablet press has been specifically designed and developed for the production of quality bilayer tablets and provides.
‘Displacement’ weight monitoring/control for accurate and independent weight control of the individual layers.
Low compression force exerted on the first layer to avoid capping and separation of the two individual layers.
Increased dwell time at pre-compression of both first and second layer to provide sufficient hardness at maximum turret speed.
Maximum prevention of cross-contamination between the two layers - a clear visual separation between the two layers – maximized yield.

Various Techneques for Bilayer Tablet
A) OROS® push pulls 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.

Bilayer and trilayer OROS push pull technology

B) L-OROSTM 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.

L-OROSTM Technology

C) 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.
EN SO TROL Technology

D) DUREDAS™ Technology
This system is also known as 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 tableting 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.

E) 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 release minute quantity of concentrated form in continues and consistent from over months or year.

DUROS Technology
Various steps of bi-layer tablet formulation are as follow
Ø Filling of first layer.
Ø Compression of first layer.
Ø Ejection of upper punch.
Ø Filling of second layer.

Compression steps of bilayered tablets

**Challenges in bilayer manufacturing**
Conceptually, bilayer tablets can be seen as two single-layer tablets compressed into one. In practice, there are some manufacturing challenges.

Ø **Delamination:** Tablet falls apart when the two halves of the tablet do not bond completely. The two granulations should adhere when compressed.

Ø **Cross-contamination:** When the granulation of the first layer intermingles with the granulation of the second layer or vice versa, cross-contamination occurs. It may conquer the very purpose of the bilayer tablet. Proper dust collection goes a long way toward preventing cross contamination.

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

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

These factors, if not well controlled/optimized, in one way or another will impact the bilayer compression per se and the quality attributes of the bilayer tablets (sufficient mechanical strength to maintain its integrity and individual layer weight control).

**Characteristics of bilayer tablets**
- **Particle size distribution**

The particle size distribution was measured using sieving method.
• **Photo-microscope Study**

Photo-microscope image of TGG and GG was taken (X450 magnifications) by photomicroscope.

• **Angle of Repose**

The diameter of the powder cone was measured and the angle of repose was calculated using the following equation.

\[ \tan \theta = \frac{h}{r} \]

where \( h \) and \( r \) are the height and radius of the powder cone.

• **Moisture Sorption Capacity**

All disintegrates have capacity to absorb moisture from atmosphere which affects moisture sensitive drugs. Moisture sorption capacity was performed by taking 1 g of disintegrate uniformly distributed in Petri-dish and kept in stability chamber at 37±1°C and 100% relative humidity for 2 days and investigated for the amount of moisture uptake by difference between weights.

• **Density**

The loose bulk density (LBD) and tapped bulk density (TBD) were determined and calculated using the following formulas.

\[ \text{LBD} = \frac{\text{weight of the powder}}{\text{volume of the packing}} \]

\[ \text{TBD} = \frac{\text{weight of the powder}}{\text{tapped volume of the packing}} \]

• **Compressibility**

The compressibility index of the disintegrate was determined by Carr’s compressibility index.

\[ C = 100 \times (1 - \frac{P_B}{P_T}) \]

**Evaluation of bilayered tablets**

• **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 Hardness**
The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in kg/cm².

• **Friability**
Friability is the measure of tablet strength. Electrolab EF-2 friabilator (USP) was used for testing the friability using the following procedure. 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.

\[
\% \text{ loss} = \left[ \frac{(\text{Initial wt. of tablets} - \text{Final wt. of tablets})}{\text{Initial wt. of tablets}} \right] \times 100
\]

• **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.

**CONCLUSION**
Bi-layer tablet is improved beneficial technology to overcome the limitation of the single layered tablet. 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. The preparation of tablets in the form of multi layers is used to provide systems for the administration of drugs, which are incompatible and to provide controlled release tablet preparations by providing surrounding or multiple swelling layers. Bi-layer tablet quality and GMP-requirements can vary widely.

**REFERENCES**