AN OVERVIEW ON BILAYERED TABLET TECHNOLOGY

Chintan R Dhorajia*, Jaymin M Patel, Kaushika S Patel, Shreeraj Shah and Pratik Upadhyay


ABSTRACT
Over the past 30 years stated that the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. 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. Controlled release dosage forms have been extensively used to improve therapy with several important drugs. Bilayer 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. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet.

KEYWORDS: Bilayer tablet, Bilayer tablet press, GMP requirements, OROS push pull technology, DUROS technology.

INTRODUCTION[1,2]
Now a day’s various developed and developing countries are moving towards combination therapy for treatment of various diseases and disorders requiring long term therapy such as hypertension, Diabetes and Rheumatoid arthritics. The problem of dose dependent side effects is minimized by combination therapies and is advantageous over monotherapy. From last few years, interest in developing a combination of two or more active pharmaceutical ingredients in a single dosage form has increased in pharmaceutical industry.[1]
Bi-layer tablets can be a primary option to avoid incompatibilities between APIs by physical separation. 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.\(^1\)

Bi-layer tablets are tablets made by compressing two different granulations fed into a die succession, one on top of another, in layers. Each layer comes from a separate feed frame within individual weight control. Rotary tablet press can be setup for two layers. They have the appearance of a sandwich because the edges of each layer are exposed. General concept of bi-layer tablet is shown in figure.\(^2\)

![General Concept of bilayer tablet](image)

**Fig.1 General Concept of bilayer tablet**

Generally conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with undesirable toxicity and poor efficiency. This repetitive dosing and unpredictable absorption led to concept of controlled drug delivery system.\(^2\)

The goal in designing sustained or controlled delivery systems is to reduce frequency of dosing or to increase effectiveness of the drug by localization at the site of action. Primary objective of sustained release delivery is to insure safely and to improve efficacy of drugs as well as patient compliance.\(^2\)

1. **Advantages**
   - 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.
Cost is lower compared to all other oral dosage form.
- Lighter and compact.
- Easiest and cheapest to package and strip.
- Easy to swallowing with least tendency for hang-up.
- Objectionable odour and bitter taste can be masked by coating technique.
- Suitable for large scale production.
- Greatest chemical and microbial stability over all oral dosage form.
- Product identification is easy and rapid. Requiring no additional steps when employing an embossed and/or monogrammed punch face.

2. Disadvantages
- Bilayer rotary press is expensive.
- Inaccurate individual layer weight control.
- Some drugs resist compression into dense compact, due to amorphous nature, low density nature.
- Insufficient hardness, layer separation, reduced yield.

3. Types of bilayer tablet\(^{3,4}\)

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

3.1. Homogenous type

![Fig.2 Bilayer tablets (same drug with different release pattern-homogenous)](image)

- 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.

3.2. Heterogenous type

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

![Fig.3 Bilayer tablets (with two different drugs-heterogenous)](image)

4. Need of bilayer tablets\(^5\)

- 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.
- To modify the total surface area available for active pharmaceutical ingredient layer either by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release.
- For the administration of fixed dose combinations of different active pharmaceutical ingredient, prolong the drug product life cycle, buccal/mucoadhesive delivery system, fabricate novel drug delivery system such as chewing device and floating tablet for gastro-retentive drug delivery.

5. General properties of bilayer tablet dosage form\(^6,7\)

- Bilayer tablet should have the chemical and physical stability to maintain its physical attributes over time.
- Bilayer tablet should have sufficient strength to withstand mechanical shock during its production, packaging, shipping and dispensing.
• Bilayer tablet should have elegant product identity while free of defect like chips, cracks, discoloration and contamination.
• Bilayer tablet must be able to release the medicinal agents in a predictable and reproducible manner.

6. Various techniques involved in formulation\textsuperscript{[8,9,10]}

6.1. OROS® push pull technology

![Fig.4 OROS Push Pull Technology](image)

• 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.

6.2. L-OROS® technology

• The L-OROS® system was designed to provide continuous delivery of liquid drug formulations and improve bioavailability of the drugs. L-OROS system consists of two types i.e., soft gelatin capsule (SoftcapTM) and hard gelatin capsule (HardcapTM). Both have a drug layer, barrier layer and a push layer surrounded by a semipermeable membrane with a delivery orifice. The L-OROS hardcap system was designed to accommodate more viscous suspensions with higher drug loading than softcap design.
6.3. 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.

6.4. DUREDASTM technology

- DUREDAS or Dual Release Drug Absorption System (Elan Corporation) utilizes bilayer tableting technology, which has been specifically developed to provide two different release rates or dual release of a drug from a single dosage form. The tablets are prepared by two separate direct compression steps that combine an immediate release granulate (for rapid onset of action) and a controlled release hydrophilic matrix complex within one tablet. The controlled release matrix remains intact and slowly absorbs fluid from the GI tract, which causes the matrix.
To expand and transforms the hydrophilic polymers into a porous, viscous gel that serves as a barrier between the drug and the surrounding fluid. As the gel continues to expand, fluid penetrates further into the dosage form, dissolving the drug and allowing the resulting solution to diffuse out in a controlled manner. A further extension of the DUREDAS technology is the production of controlled release combination dosage forms whereby two different drugs are incorporated into the different layers, and the drug release of each layer is controlled to maximize therapeutic effect of the combination. Again both immediate release and controlled release combinations of the two drugs are feasible.

6.5. DUROS technology

DUROS (Alza Corporation) is based on implant technology, which provides an alternative for the delivery of a wide range of therapeutic compounds, including peptides, proteins, and other bioactive macromolecules. These implants are miniature titanium cylinders designed to provide continuous osmotically driven delivery of drugs within the body for up to one year. Following implantation, DUROS implants enable continuous, precise delivery of the therapeutic compound at rates as low as 1% of a drop of water per day. The cylinder is manufactured from titanium because of the material’s tolerability to human tissue and its long use in medical devices such as implantable defibrillators and joint replacements. The cylinder protects therapeutic agents from degradation in the body and enables a drug to remain stable for extended periods of time. Recently, Viadur (leuprolide acetate implant), which is based upon this technology, has been approved for once yearly palliative treatment of advanced prostate cancer.
6.6. PRODAS technology

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

7. Various approaches for layered tablets\textsuperscript{[11,12]}

7.1. 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.

![Fig.8 Bilayer tablets, Tri layer tablets](image-url)
7.2. Compression coated tablet

- This type of tablet has two parts, internal core and surrounding coat. The core is a small porous tablet and prepared on one turret. For preparing the 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 lends itself into a repeat action tablet as the outer layer provides the initial dose while the inner core releases the drug later on. But, when the core quickly releases the drug, entirely different blood level is achieved with the risk of overdose 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 the 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.

![Core coated tablets]

**Fig.9 Core coated tablets**

7.3. Inlay tablet

- 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. To reduce capital investment quite often existing but modified tablet presses are used to develop and produce such tablets. The development and production of quality bilayer tablets needs to be carried out on purpose-built tablet presses to overcome common bi-layer problems. Using a modified tablet press may therefore not be your best
approach to producing a quality bi-layer tablet under GMP conditions. Especially when in addition high production output is required.

Fig. 10 Inlay tablets

8. Quality and GMP requirements\textsuperscript{[13]}

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

9. Types of bilayer tablet press\textsuperscript{[14,15,16]}

9.1. Single sided press

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

Limitation of single sided press

- No weight monitoring/control of the individual layers.
• No distinct visual separation between the two layers.
• Very short first layer-dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping and hardness problems.

Dwell time
• Dwell time is defined as the time during which compression force is above 90% of its peak value. Longer dwell times are a major factor in producing a quality tablet, especially when compressing a difficult formulation.

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

Limitations of compression force controlled system
• Many bilayer formulations require less than 100 daN to compress first layer in order to retain the ability to bond with the second layer.
• Above 100 daN, 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.

10.3 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.

10. Preparation of bilayer tablet\textsuperscript{[16,23,24]}

- Bilayer tablets are prepared with one layer of drug for immediate release with the second layer designed to release drug later, either as a second dose or in an extended release form. The bilayer tablets with two incompatible drugs can also be prepared by compressing separate layers of each drug so as to minimize area of contact between two layers. An additional intermediate layer of inert material may also be included.

Compression: It is defined as reduction in bulk volume by eliminating voids and bringing particles into closer contacts.

Consolidation: It is the property of the material in which there is increased mechanical strength due to interparticulate interaction (bonding). The compression force on layer 1 was found to be major factor influencing tablet delamination.

![Fig.11 Preparation of bilayer tablet Compaction](image)

11. Characterization of bilayer tablet\textsuperscript{[17,18]}

Particle size distribution
The particle size distribution was measured using sieving method.
Photo microscope study

Photo-microscope image of TGG and GG was taken (×450 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.

LBD \( \frac{1}{4} \) weight of the powder = volume of the packing
TBD \( \frac{1}{4} \) weight of the powder = tapped volume of the packing

Compressibility

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

12. Evaluation of bilayer tablet\textsuperscript{[17,18,19]}

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. Other tester used to check tablet hardness are strong-cubb tester, Pfizer tester the Erweka tester and Schleuniger tester.

**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. \[
\% \text{ loss} = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100
\]

**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.

**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.

13. **Various approaches used in the bilayer tablet**[20,21,22]

**Floating drug delivery system**
- From the formulation and technological point of view, the floating drug delivery systems are considerably easy and logical approach in the development of Gastro retentive dosage forms (GRDFs).

**Approaches to design floating drug delivery system**
**Intra gastric bilayer floating tablets**: These are also compressed tablet as shown in figure and contain two layers i.e. Immediate and sustained release.
Multiple unit type floating pills: 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 temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density.

Polymeric bio adhesive system
- These are designed to imbibe fluid following administration such that the outer layer becomes a viscous, tacky material that adheres to the gastric mucosa/mucus layer. This should encourage gastric retention until the adhesive forces are weakened. These are prepared as one layer with immediate dosing and other layer with bio adhesive property.

Swelling system
- These are designed to be sufficiently small on administration so as not to make ingestion of the dosage form difficult (e.g., less than approximately 23 mm long and less than 11 mm wide for an oval or capsule–shaped tablet whereas 10-12 mm in diameter for round tablets). On ingestion they rapidly swell or disintegrate or unfold to a size that precludes passage through the pylorus until after drug release has progressed to a required degree. Gradual erosion of the system or its breakdown into smaller particles enables it to leave stomach. The simple bilayer tablet may contain an immediate release layer with the other layer as extended release or conventional release.

SUMMARY
Bi-layer tablets provide one of the important design approaches where incompatible drugs, with different indication, and same drug with different release rate (e.g. IR and ER) can be incorporated in a single unit. 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. Bilayer tablet quality and GMP-requirements can vary widely. This explains why many different types of presses are being used to produce bi-layer tablets, ranging from simple single sided presses to highly sophisticated machines.

REFERENCES
