

## An Overview on Bilayered Tablet Technology

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**Abstract:** Bilayer tablet is new novel of tablet for the successful development of controlled release formulation along with many features to provide a way of successful drugdelivery 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. So use of bi-layer tablets is a very different aspect for anti-hypertensive, diabetic, anti-inflammatory and analgesic drugs where combination therapy is often used. Bi-layer tablets have been developed to achieve modified release of drug. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. In the case of bilayered 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. To reduce capital investment, quite often existing but modified tablet presses are used to develop and produce such tablets. The present article explains why the production and development of quality bi-layer tablets needs to be carried out on purpose-built tablet presses to overcome common bi-layer problems, such as hardness, insufficient, layer-separation, inaccurate individual layer weight control, reduced yield, cross-contamination between the layers, etc. Using a modified tablet press may therefore not be your best approach to producing a quality bi-layer tablet under GMP-conditions.

**Key words:** Approaches • Bilayer tablets • OROS push pull technology • DUROS technology • Immediate release • GMP requirements for bilayer tablet

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### INTRODUCTION

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 many swelling layers. Control release systems that have been proposed for providing controlled release formulations showing how the different designs can be used to control the drug release profile such as constant, delayed pulsatile and multi modal release profiles [1]. In Day-to-day's many developed and developing countries are approaching towards combination therapy for treatment of various diseases and disorders requiring long term therapy such as hypertension and diabetes. The problem of dose dependent side effects is minimized by combination therapies and is advantageous over monotherapy [2, 3, 4, 5, 6]. Now interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bi-layer tablet)

has increased in the pharmaceutical industry, promoting patient convenience and 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) [7, 8, 9].

Bi-layer tablets are prepared with one layer of drug for immediate release with second layer design to release drug later as second dose or in an extended release or for both immediate release. Bi-layer tablets are tablet, 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 with individual weight control. Rotary tablet press can be set up for two layers. More layers are possible but the design becomes very special. Bi-layer tablets are composed of two layers of granulation compressed together. They have the appearance of a sandwich because the edges of each layer are exposed. Five general concept of bi-layer tablet is shown in Figure 1.

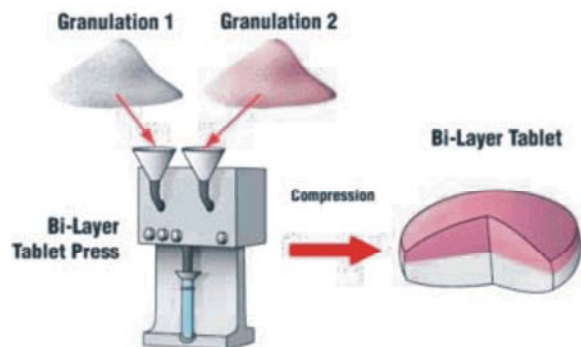


Fig. 1: General concept of Bi-layer tablet

However, these drug delivery devices are mechanically complicated to design/manufacture and harder to predict their long term mechanical properties due to the poor mechanical and compression characteristics of the constituent materials in the compacted adjacent layers, elastic mismatch of the layers, insufficient hardness, inaccurate individual mass control, crosscontamination between the layers, reduced yield and their tendency to delaminate at the interface between the adjacent compacted layers during and after the various stages of production downstream of the compaction process [10]. Formulation of layers from different polymers allows manipulation over more than one rate-controlling polymer, thus enabling different types of drug delivery of one or more drugs, i.e. where the drug may be released with a bolus and then at a controlled rate or by targeted drug delivery in the GI tract using pH dependent polymers [11]. 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. 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 [12].

#### Need of Bilayer Tablets [13, 14, 15]:

- Controlling the delivery rate of either single or two different active pharmaceutical ingredient(s)
- To modify the total surface area available for API layer either by sandwiching with one or two in active layers in order to achieve swellable/erodible barriers for modified release.

- 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 Dosage Form [13-15]:

- 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.
- Greatest chemical and microbial stability over all oral dosage form.
- Objectionable odour and bitter taste can be masked by coating technique.
- Flexible Concept.
- Suitable for large scale production.
- Bi-layer execution with optional single-layer conversion kit.
- Cost is lower compared to all other oral dosage form.
- For chronic condition requiring repeated dosage forms.
- Disadvantages of Bi-Layer Tablet Dosage Form are [16,17,18,19]
- Bitter tasting drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.
- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
- Bitter tasting drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.
- Difficult to swallow in case of children and unconscious patients.
- Administration of sustained release bilayer tablet does not permit the prompt termination of therapy.
- The physician has a less flexibility on adjusting the dose regimens.
- If the compacted layers are too soft or too hard, they will not bind securely with each other which can lead to compromised mechanical integrity and also the separation of the layers.

#### Applications [20]:

- 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 therapy.

- 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.

#### **Challenges in Bilayer Manufacturing [21]:**

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. The two granulations should adhere when compressed.

**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.

**Production Yields:** 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 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). Therefore, it is critical to obtain an insight into the root causes to enable design of a robust product and process.

#### **Types of Bilayer Tablet Press:**

Single sided tablet press.

Double sided tablet press.

Bilayer tablet press with displacement monitoring.

**Single Sided Press: [22]:** The simplest design is a single sided press with both chambers of the doublet feeder separated from each other. Each chamber is gravity or forced fed with different power, producing the two

individual layers of tablets. When die passes under the feeder, it is first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps.

#### **Limitations of the Single Sided Press: [23, 24, 25]:**

- 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 deaeration, capping and hardness problems.
- This may be corrected by reducing the turret rotation speed (to extend the dwell time) but with the consequence of lower tablet output.

**Double Sided Tablet Press: [22]:** In 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 the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance and correct the die fill depth when required.

**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 precompression force.

#### **Advantages:**

- 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.
- Independence from the machine stiffness.
- Increased dwell time at precompression of both first and second layer to provide sufficient hardness at maximum turret speed.
- Maximum prevention of cross-contamination between the two layers.
- Clear visual separation between the two layers and maximized yield.

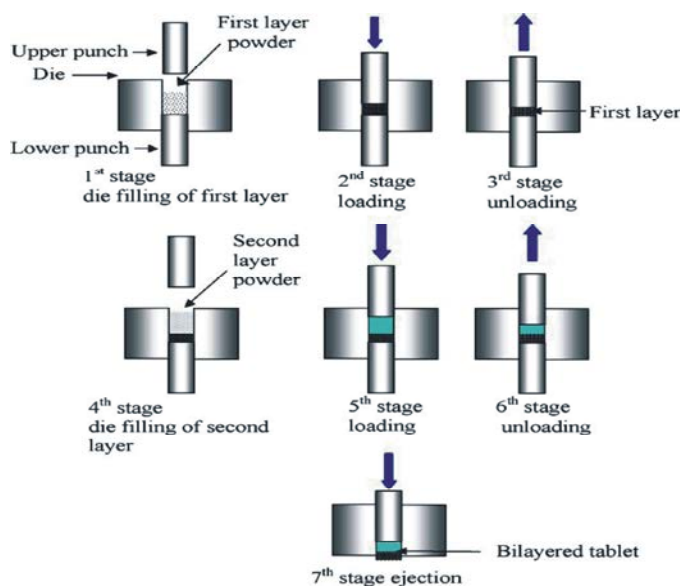


Fig. 2: Process of bilayer tablet Compaction

**Manufacturing Aspect of Bi-Layer Tablet [26, 27, 28, 29]:** The manufacturing process of bi-layer tablets requires special rotary presses where the first layer is fed into the die and partially pressed, but not ejected from the die. Then the second layer is fed followed by compaction and ejection.

To produce adequate tablet formulation, certain requirements such as sufficient mechanical strength and desired drug release profile must be met. At times, this may be difficult task for formulator to achieve these conditions especially in bilayer tablet formulation where double compression technique is involved, because of poor flow and compatibility characteristic of the drug which will result in capping and/or lamination. The compaction of a material involves both the compressibility and consolidation.

**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.

**Quality and Gmp-Requirements [30]:** To produce a quality bi-layered tablet, in a validated and GMP way, it is important to select a bi-layer tablet press 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.
- Accurate and individual weight control of the two layers.
- High yield.

#### Various Techniques for Bilayer Tablet

**Oros® Push Pull Technology [31]:** 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 (Figure 3).

**L-OROS™ Technology [31]:** 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 4).

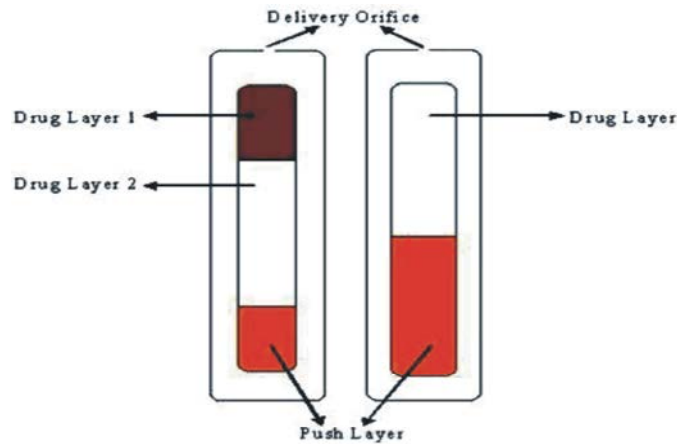


Fig. 3: Bilayer and trilayer OROS push pull technology

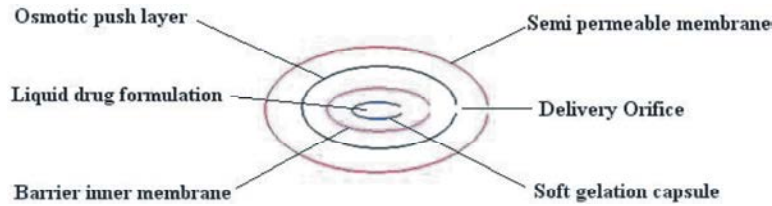


Fig. 4: L – OROS tm technology



Fig. 5: EN SO TROL Technology

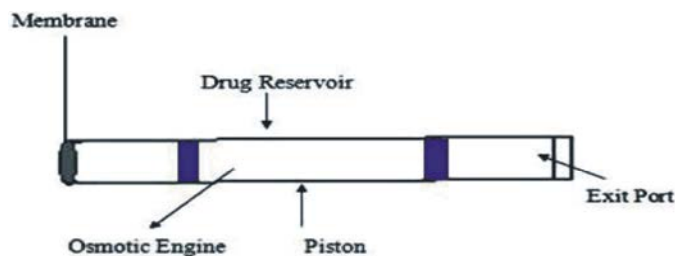


Fig. 6: DUROS Technology

**EN SO TROL Technology [32, 33]:** 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 (Figure 5).

**DUREDAS™ Technology [32, 33]:** 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.

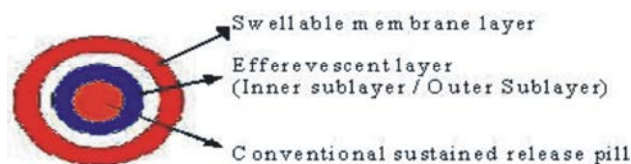


Fig. 7: Multiple units of oral FDDS

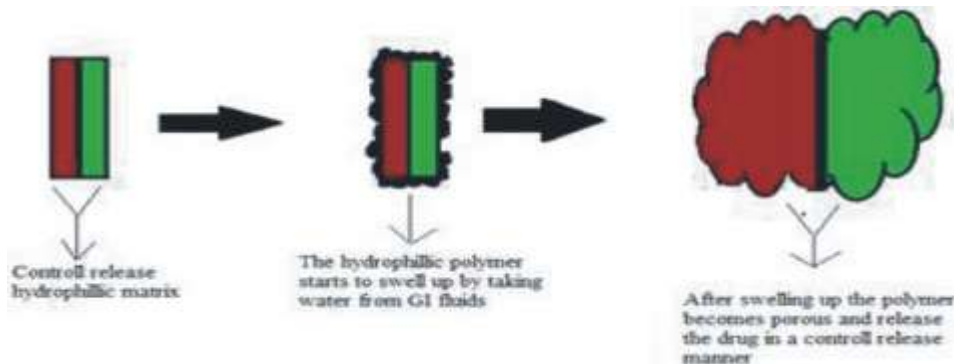


Fig. 8: Bi-layer tablet consist of two controlled release layer

**DUROS Technology [34]:** 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 reglious minute quantity of concentrated form in continues and consistent from over months or year (Figure 6).

#### Various Approaches Used in Bi-Layer Tablet

**Floating Drug Delivery System [33, 35]:** 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:

The following approaches have been used for the design of floating dosage forms of single- and multiple-unit systems.

- Intra gastric bilayered 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 (Figure 7).

**Polymeric Bio Adhesive System [36, 37]:** These are designed to imbibe fluid flowing 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 a one layer with immediate dosing and other layer with bio adhesive property.

**Swelling System [38, 39]:** 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 bi-layer tablet may contain an immediate release layer with the other layer as extended release or conventional release or both as controlled release layer. Such systems are shown in Figure 8 and Figure 9.

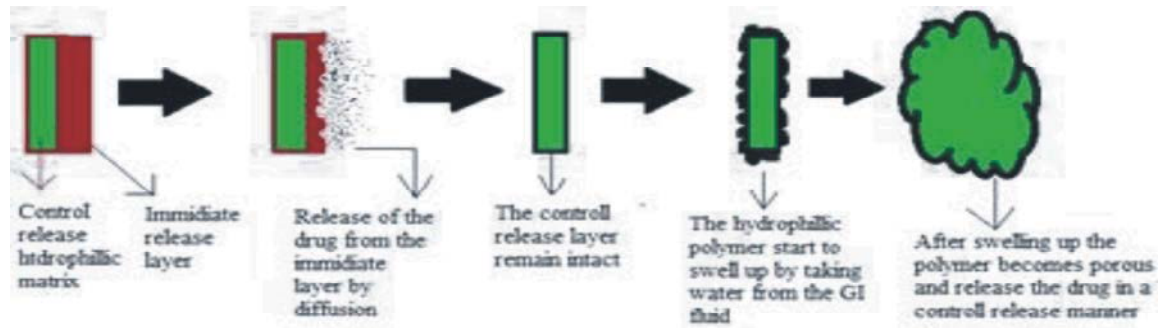


Fig. 9: Bi-layer tablet consist of immediate release and controlled release layer

Table 1: Previous study done on bi-layer tablet

| Drugs             |                   | Super disintegrant used in Immediate release layer | Polymer used in Sustained release layer      | References |
|-------------------|-------------------|--|--|------------|
| First layer       | Second layer      |  |  |            |
| Glimepride        | Metformin HCL     | Sodium starch glycolate                            | HPMC K4M, sodium carboxy methyl cellulose    | 19         |
| Paracetamol       | Acetaminophen     | Microparticles by ethylcellulose                   | Microparticles by ethylcellulose             | 24         |
| Tramadol HCL      | Acetaminophen     | Sodium starch glycolate as superdisintegrant       | Sodium starch glycolate as superdisintegrant | 25         |
| Valsartan         | Metformin HCL     | Crospovidone                                       | HPMC K100M, sodium CMC, PVP K90              | 26         |
| Glipizide         | Glipizide         | Starch   | HPMC, xanthan gum, guar gum, karaya gum,     | 27         |
| Zolpidem tartrate | Zolpidem tartrate | Sodium crosscarmellose                             | HPMC K100M                                   | 28         |
| Ranitidine        | Ranitidine        | Starch   | Carbopol, HPMC                               | 17         |

Table 2: Marketed bi-layer tablet:

| Product Name   | Active Pharmaceutical Ingredients (API) | Manufacturer               |
|----------------|---|----------------------------|
| Pioglu         | Pioglitazone, Metformin hydrochloride   | Emcure Pharmaceutical Ltd. |
| Xilla M- Forte | Glimepride, Metformin hydrochloride     | Emcure Pharmaceutical Ltd. |
| Gluconorm      | Glimepride, Metformin hydrochloride     | Lupin Pharmaceuticals      |
| Volise-M       | Voglibose, Metformin hydrochloride      | Ranbaxy Laboratories Ltd.  |
| Glimeto- MP    | Glimepride, Pioglitazone                | RPG Life Sciences Ltd.     |
| Istamet        | Sitagliptin, Metformin hydrochloride    | Ranbaxy Laboratories Ltd.  |
| Glyrep         | Glyclizide, Metformin hydrochloride     | Emcure Pharmaceutical Ltd. |
| Unistar        | Rosuvastatin, Aspirin                   | Unichem Laboratories Ltd.  |

**Evaluation of Sustain Release Bilyer Tablet [40, 41]**

**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/cm<sup>2</sup>.

**Friability:** Friability is the measure of tablet strength. Electro lab 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.

$$\% \text{ loss} = \frac{[(\text{Initial wt. of tablets} - \text{Final wt. of tablets}) / \text{Initial wt. of tablets}] \times 100}{1}$$

**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.

**Marketed Bi-layer Tablets [3, 4, 42,43, 44, 45, 46]:** Various researcher works on bi-layer tablet, which are shown in table no. 1. Commercially available bi-layer tablets are enlisted in Table 2.

### CONCLUSION

Bi-layer tablet is suitable for sequential release of two drugs in combination and also for sustained release tablet in which one layer is immediate release as an initial dose and second layer is maintenance dose. By using bi-layer tablet technology we can administer incompatible drugs in combination as well as same drug with different release rate. This technology avoids frequent administration of dosage form. Now a day such technology is used for administration of drugs like anti-diabetic, anti-hypertensive, anti-inflammatory, antipyretic, anti-asthmatic to the patients. Conventional solid oral dosage forms are a traditional, but bi-layer tablet is a novel approach. This novel approach requires new machinery for manufacturing. This article explains different types of presses used to produce bi-layer tablet ranging from simple single sided machines to highly sophisticated machines. For good quality bi-layer tablet the machines should be inherently built as per GMP. This technique is cost effective, safe and reproducible.

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