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## **Sustained Release Bilayered Tablets: An Overview**

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### **Abstract**

Bi-layer tablet is a new era for going development of Controlled Release Drug Delivery System (CDDS) along with various features to formulate powerful Novel Drug Delivery System (NDDS). Greater attention and better attempts have been focused on fabrication of bi-layered tablets of sustained or controlled release drug delivery systems for last 30 years. So many pharmaceutical industries are currently developing bi-layer tablets, for a variety of reasons: patent extension, therapeutic efficacy, marketing to name a few. Conventional 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 obstacles. In this overview, it is emphasized that Duredas or Dual Release Drug Absorption System (DUROS Technology) uses bilayer tableting technology, which has been specifically targeted to provide two different release rates or dual release of a drug from a single dosage form. It is prepared by two separate direct-compression steps that combine and immediate-release granulate and a controlled-release hydrophilic matrix complex within one tablet. L-OROS™ Technology is also used for the solubility issue to produce 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 than a semi permeable membrane, drilled with an exit orifice. Bi-layered tablets are fabricated to have a low density and thus float on gastric premises after swallowing until the system either disintegrates in the biological system.

**Key words:** controlled release, L-OROS™ Technology, tablet press, floating lag time, dissolution.

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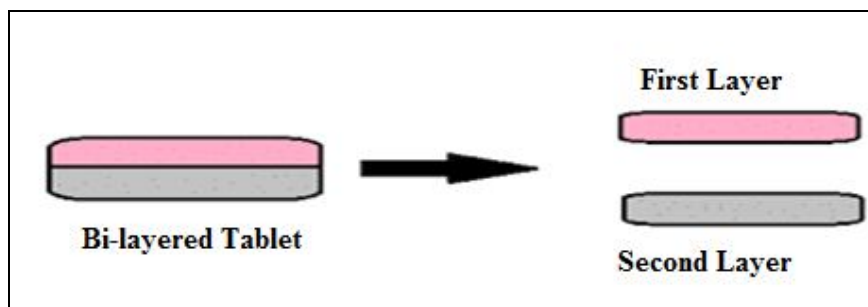
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## **Introduction**

Over the past 30 years higher and effective attempts have been focused on development of sustained or controlled release of drug delivery systems. The development of combination of two or more active pharmaceutical ingredients (API) in a single dosage form has increased in the pharmaceutical industry, promoting patient convenience & compliance<sup>[1]</sup>. 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<sup>[2]</sup>. 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<sup>[3]</sup>.



**Figure1:** Bi-layered 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, cross contamination 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<sup>[4]</sup>.

### **Objective behind Designing Bi-layered tablet**

- ❖ To control the delivery rate of either single or two different active pharmaceutical ingredient(s)
- ❖ 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).
- ❖ 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
- \* 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.

### **Advantages of Bi-layered tablet**

- When the two different layers of the tablet content two different drugs, then the tablet can be easily used in combination therapy.
- Cost is subordinate compared to all other oral dosage form.
- Maximum chemical and microbial stability over all oral dosage form.
- In case of drugs having a low half life, each of the two layers of the tablet respectively content a loading dose and maintenance dose of the same and thus increase the bioavailability of the drug.
- Objectional odour and bitter taste can be masked by coating technique.
- Greatest chemical and microbial stability over all oral dosage form.
- Easy to swallowing with least tendency for hang up.
- Suitable for large scale production.<sup>[5]</sup>

### **Disadvantages of Bi-layered tablet**

- ✓ Difficult to swallow in case of children and unconscious patients.
- ✓ Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
- ✓ Bitter tasting drugs or drugs that are sensitive to oxygen may require coating.
- ✓ Difficult to swallow in case of children and unconscious patients.
- ✓ Drugs with poor wetting, slow dissolution properties may be difficult to formulate.<sup>[5]</sup>

### **Various Techniques for Bi-layered tablet**

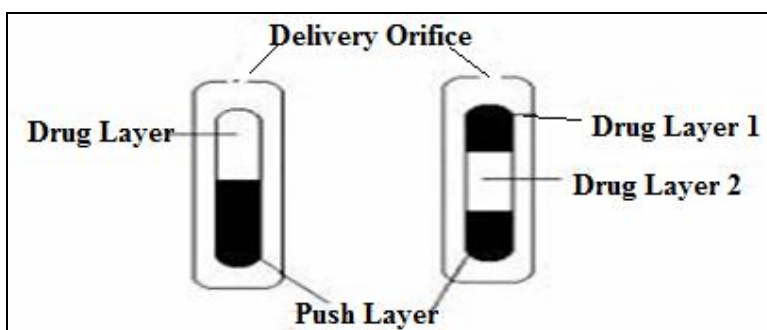
**Duredas Technology:** Duredas or Dual Release Drug Absorption System (Elan Corporation) utilizes bilayer tableting technology, which has been specifically developed to provide two different release rates or dual release of a drug from a single dosage form. The tablets are prepared by two separate direct-compression 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.<sup>[6]</sup>

### **Benefits offered by the Duredas technology**

- Bilayer tableting technology.
- Tailored release rate of two drug components.
- Capability of two different CR formulations combined.
- Capability for immediate release and modified release components in one tablet.
- Unit dose, tablet presentation.

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 is controlled to maximize therapeutic effect of the combination. Again both immediate- release and controlled-release combinations of the two drugs are feasible.<sup>[6]</sup>

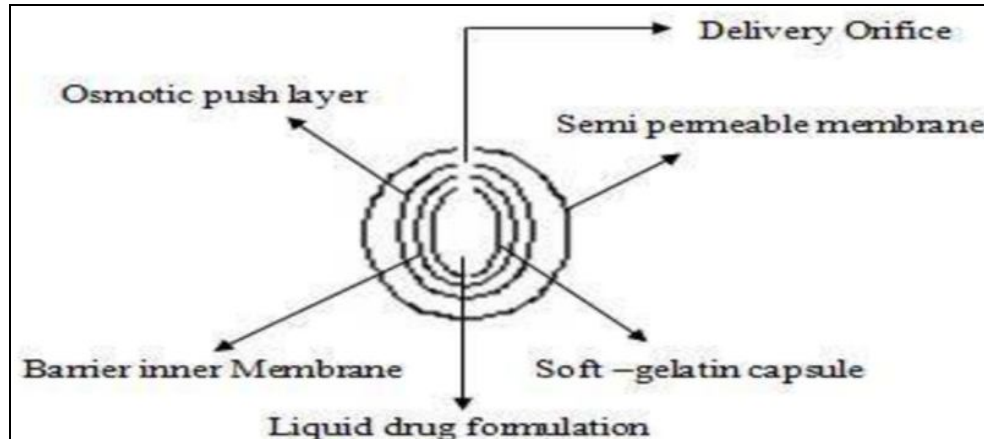
**OROS® Push Pull Technology:** This system consists of mainly two or three layers among which one or more layers are essential for the drug and other layers consist of push layers. The drug layer mainly consists of drug along with two or more different agents. So this drug layer comprises of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent<sup>[6]</sup>.



**Figure2:** Bilayer and trilayer OROS Push Pull technology

### **L-OROS™ Technology**

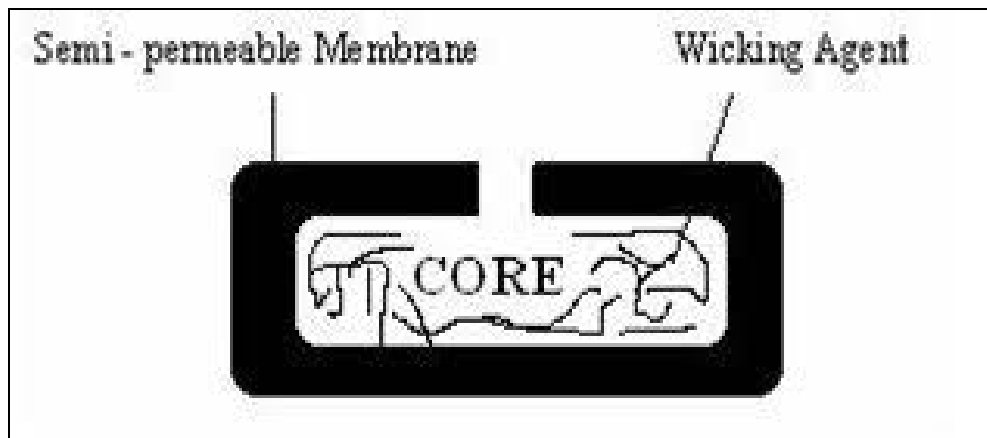
This system used for the solubility issue. Alza developed the L-OROS system where a lipid soft gel Product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, than osmotic push layer and than a semi permeable membrane, drilled with an exit orifice<sup>[7]</sup>.



**Figure3:** L-OROS tm Technology

### **EN SO TROL Technology**

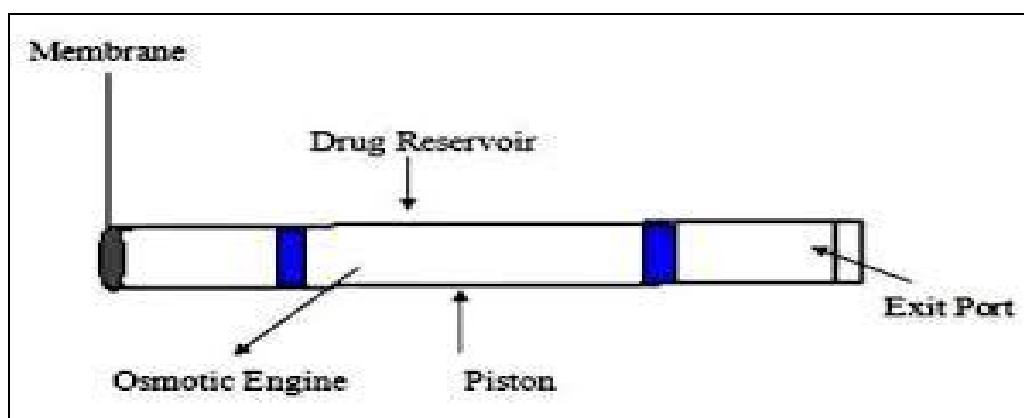
Solubility enhancement of an order of magnitude or to create optimized dosage form Shire laboratory use an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies.



**Figure4:** EN SO TROL Technology

### **DUROS Technology**

DUROS 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<sup>[7]</sup>.



**Figure5:** DUROS technology

### **Geminex Techonology**

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<sup>[8]</sup>.

**Prodas or Programmable oral Drug absorption system:** Prodass or Programmable Oral Drug Absorption System is a multiparticulate drug delivery technology that is based on the encapsulation of controlled-release minitables 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 minitables. 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 minitables formulated with different active ingredients<sup>[7]</sup>.

### **Various approaches used in bi-layer tablet**

#### **a) Floating Drug Delivery System**

These are designed to have a low density and thus float on gastric contents after administration until the system either disintegrates or the device absorbs fluid to the point where its density is such that it loses buoyancy and can pass more easily from the stomach with a wave of motility responsible for gastric emptying. The bilayer tablet is designed in such a manner that, one layer gives the immediate dosing of the drug which gives faster onset of action while other layer is designed as a floating layer which floats in the stomach (GI-fluid)<sup>[9]</sup>.

#### **Disadvantages**

It may not have the controlled loss of density alternatively required for it to eventually exit from the stomach. Floating tablets are not applicable to higher dose levels of highly water soluble drugs where large amounts of polymer are needed to retard drug release, as in case of water soluble drugs. The performance of floating formulation may also be posture dependant. A patient sitting upright may ensure prolonged gastric residence of a buoyant dosage form, whereas a supine patient might allow ready presentation of the floating dosage form to the pylorus and thus allow rapid exit of the dosage form from the stomach. Hence, floating dosage forms might be expected to only have limited applications.

#### **b) 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<sup>[9]</sup>.

#### **Disadvantages**

The success is seen in animal models with such system has not been translated to human subjects due to differences in mucous amounts, consistency between animals and humans.<sup>[9]</sup>

#### **c) 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 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.

### **Types of bi-layered tablet press**

#### **➤ 1) Single sided tablet Press**

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 powder, 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<sup>[10]</sup>.

### **Limitations of single-sided press**

Various types of bi-layer presses have been designed over the years. 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 steps (two = pre- and main compression). 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<sup>[11]</sup>.

This is the simplest way of producing a bilayered tablet. It undergoes certain limitation as follow:

- 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. This may be corrected by reducing the turret-rotation speed (to extend the dwell time) but with the consequence of lower tablet output.
- Very difficult first-layer tablet sampling and sample transport to a test unit for in-line quality control and weight recalibration to eliminate these limitations, a double-sided tablet press is preferred over a single-sided press. A double-sided press offers an individual fill station, pre-compression and main compression for each layer. In fact, the bi-layer tablet will go through 4 compression stages before being ejected from the Press<sup>[12]</sup>.





**Figure6:** Single Sided Tablet Press

➤ **2)Double-sided tablet presses**

Double-sided tablet presses have been specifically designed and developed for the production of quality bi-layer tablets and provide:

- ‘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
- maximised yield<sup>[13]</sup>.

**2.1 ADEPT double sided tablet press**

Offers significant technical advantages that permit higher output and increased efficiency in production. Special emphasis has been given on durability while designing so that the machine can be used in a 24/7 production environment. The higher load bearing capacity of Adept tablet press

makes it suitable for bigger tablets. The machine also offers flexibility to produce both single-layer and bi-layer tablets on the same platform<sup>[14]</sup>.



**Figure7:**Double sided tablet press



**Figure8:**ADEPT double sided tablet press

### **3) Bi-layered 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<sup>[15]</sup>.

#### **❖ Advantages**

1. Weight monitoring / control weight of the individual layers.
2. Avoid capping and separation of the two individual layers.
3. Independence from the machine stiffness.
4. Provide sufficient hardness at maximum turret speed.
5. Maximum prevention of cross-contamination between the two layers.
6. Clear visual separation between the two layers and maximized yield<sup>[16]</sup>.



**Figure9:** Bi-layered tablet press with displacement monitoring

### **3.1 The Courtoy R292F: “bi-layer” tablet press with ‘displacement monitoring’**

This double-sided tablet press has been specifically designed and developed for the production of quality bi-layer 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<sup>[17]</sup>.



**Figure10:** Courtoy R292F Bilayer Press

### **Preparation of bi-layer tablets**

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.

### **Compaction**

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<sup>[18]</sup>.

### **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<sup>[19]</sup>.

## **Evaluation of bi-layered tablet**

### **Pre-compression evaluation**

#### **Particle size distribution**

The particle size distribution is measured using sieving method.

#### **Photo-microscope Study**

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

#### **Angle Of repose**

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

$$\tan\theta = (h/r) \text{ [Where 'h' and 'r' are the height and radius of the powder cone.]}$$

#### **Moisture Sorption Capacity**

All disintegrates have capacity to absorb moisture from atmosphere which affects moisture sensitive drugs. Moisture sorption capacity is performed by taking 1 g of disintegrate uniformly distributed in petri-dish and kept in stability chamber at  $37\pm 1^\circ\text{C}$  and 100% relative humidity for 2 days and investigated for the amount of moisture uptake by difference between weights<sup>[20]</sup>.

#### **Compressibility**

The compressibility index of the disintegrate is determined by Carr's compressibility index.

$$\% \text{compressibility} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

#### **Density**

The bulk density(BD) and tapped density(TD) were determined and calculated using the following formulas.

$$\text{Bulk density} = \frac{\text{Weight of powder}}{\text{Bulk volume}}$$

$$\text{Tapped Density} = \frac{\text{Weight of powder}}{\text{Tapped volume}}$$

#### **Housner's ratio**

It's calculated by a formula: **Hausner's Ratio**=(TD/BD)<sup>[21]</sup>

### **Post-compression parameter**

#### **General Appearance**

The general appearance of a tablet, its visual identity and overall “elegance” is essential for consumer acceptance. Includes tablet size, shape, color, presence or absence of an odor, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

#### **Size and Shape**

The size and shape of the tablet can be dimensionally described, monitored and controlled.

#### **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. Thickness of tablet should be recorded by using digital vernier caliper. It is expressed in mm.

#### **Hardness (Crushing strength)**

Hardness indicates the ability of the tablet to withstand mechanical shocks while handling. Hardness of the tablet recorded by Monsanto hardness tester. It is expressed in kg/cm<sup>2</sup>.

#### **Friability**

Friability is the measure of tablet strength. Friabilator is used for testing the friability using the procedure:

Twenty tablets are 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 is determined<sup>[22]</sup>.

$$\% \text{ loss} = \frac{\text{Initial weight of tablets} - \text{Final weight of tablets}}{\text{Initial weight of tablets}} \times 100$$

**Initial weight of tablets**

#### **Uniformity of weight**

Twenty tablets are selected at random and the average weight is calculated. Weight Variation is calculated and is compared with I. P. standards.

#### **Drug content and release**

To evaluate tablets potential for efficacy, the amount of drug per tablet needs to be monitored from tablet to tablet and batch to batch, and a measure of the tablet's ability to release the drug needs to be ascertained.

### **Stability Study**

The bilayer tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies. The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability And Dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotted according to Arrhenius equation to determine the shelf life at 25°C.

### **In-vitro Dissolution Study**

Dissolution study is done in simulated gastric and intestinal fluids to assess their ability in providing the desired controlled drug delivery. In-vitro drug release studies are carried out using USP dissolution test apparatus at 37°C temperature at specific RPM or as mentioned in monograph<sup>[23]</sup>.

### **Marketed Bi-layered tablets**

Commercially available bi-layer tablets are enlisted in the Table-I.

**Table 1**

<b>Brand Name</b>	<b>Name of the Drug</b>	<b>Manufacture</b>
Clarinet-D	Desloratadine/Pseudoephedrine Sulphate	Merck&Co.
Ditropan XL	Oxybutynin Chloride	Alza Corporation
Augmentin	Amoxicillin/Clavulanate	Janssen Pharmaceuticals
Zyrtec-D	Cetirizine HCL/Pseudoephedrine HCL	Dr.Reddy's Labs
Cipro	Ciprofloxacin	Pfizer Laboratories
Istamet	Sitagliptin, Metformin Hydrochloride	Ranbaxy Laboratories Ltd.
Volise-M	Voglibose, Metformin Hydrochloride	Ranbaxy Laboratories Ltd.
Gluconorm	Glimepiride, Metformin Hydrochloride	Lupin Pharmaceuticals
Pioglu	Pioglitazone, Metformin Hydrochloride	Emcure Pharmaceuticals Ltd.
Alprax Plus	Sertraline, Alprazolam	Torrent Pharmaceuticals Ltd.

### **Conclusion**

Bi-layered 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 its 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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