

## Bi-Layer Tablet - A New Ways in Oral Drug Delivery System

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**Abstract:** Over the past 30 years, the expenses and complications involved in marketing new drug entities have increased with concomitant recognition of therapeutic advantages of controlled drug delivery. Now a days greater attention has been focused on development of controlled & immediate release drug delivery systems. Several pharmaceutical companies are currently developing bi-layer tablets, for a variety of reasons: patent extension, efficient pharmacological effect, better patient compliance etc. Bilayer tablet is becoming new approach for the successful development of controlled & immediate release formulation along with various features to provide a way of successful drug delivery system. Bi-layer tablet is suitable for sequential release of two drugs in combination and/or to incorporate two incompatible substances in same tablet. This approach can be utilized for fabrication of sustained release dosage form (tablet) consisting of outer immediate and inner layer as a maintenance dose. To overcome the short comings of single layered tablet approach like bilayered tablet (immediate and sustained release) can be satisfactorily used. 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. Present review mainly focuses on fundamentals of bilayer tablets and it's applications in Pharmaceutical industries

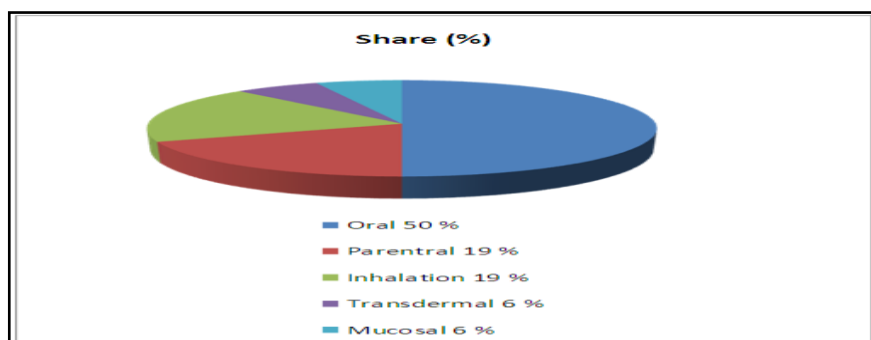
Key Words : Bilayer tablet, Incompatibilities, Sustained release, Immediate release, GMP requirements, Bilayer tablet presses

### Introduction

There are many ways to deliver drugs into the body like oral (through swallowing), sub mucosal (through buccal and sublingual mucosa), parenteral (through injection), transdermal (through skin), pulmonary (through inhalation) etc<sup>(1,2)</sup>. Tablets ("Pharmaceutical powder compacts") are the most common, convenient and preferred means of the existing administration methods for the systemic delivery of drugs<sup>(2)</sup>. It provides, ease of dose administration, patient compliance and flexibility in formulations. The effective oral drug delivery practice depends upon various factors like gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs<sup>(3)</sup>. Conventional dosage form produce wide rang of fluctuation in drug concentration in the blood stream and tissues with undesirable toxicity and poor efficiency. Factors 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<sup>(4)</sup>. In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bilayer tablet) has increased. The main objective of combination therapy is to encourage the utilization of lower doses of drugs to treat patients and also to minimize dose dependent side effect and adverse reactions<sup>(5)</sup>. To overcome the drawbacks of single layer combination tablet this concept was came into force<sup>(6)</sup>. 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)<sup>(7)</sup>.

**Figure. 1 Share of different dosage forms in percentage**



### Type of Tablets & Class of Tablets<sup>(8)</sup>

**Table No.1 Type of tablets & class of tablets**

<p><b>1. Oral Tablets for Ingestion</b></p> <p>I. Standard compressed tablets</p> <p>II. Multiple compressed tablets :</p> <p>a) Layered tablets</p> <p>b) Compression coated tablets</p> <p>c) Inlay tablets</p> <p>III. Modified release tablets</p> <p>IV. Delayed action tablets</p> <p>V. Targeted tablets :</p> <p>a) Floating tablets</p> <p>b) Colon targeted tablets</p> <p>VI. Chewable tablets</p>	<p><b>2. Tablets Used In the Oral Cavity</b></p> <p>I. Buccal tablets</p> <p>II. Sublingual tablets</p> <p>III. Troches and lozenges</p> <p>IV. Dental cones</p> <p><b>3. Tablets Administered By Other Routes</b></p> <p>I. Implantation tablets</p> <p>II. Vaginal tablets</p> <p><b>4. Tablets Used To Prepare Solution</b></p> <p>I. Effervescent tablets</p> <p>II. Dispersible tablets</p> <p>III. Hypodermic tablets</p> <p>IV. Tablet triturates</p>
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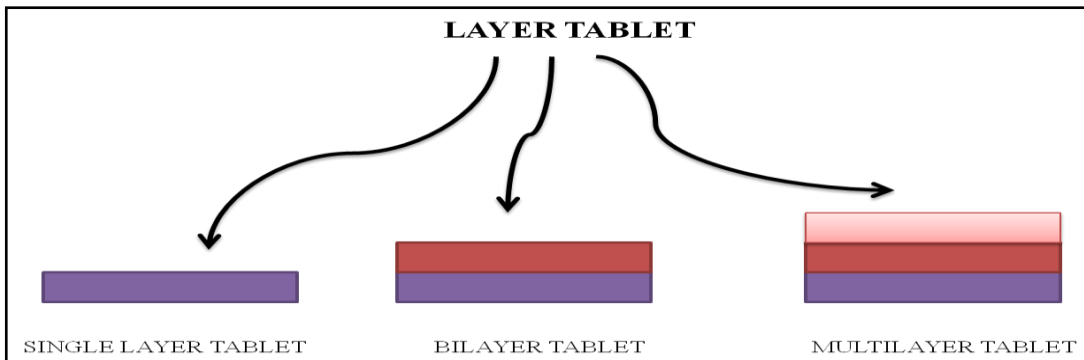
### Layer Tablets

Layer tablets are composed of two or three layers of different materials compressed together. Final tablet have the look like a sandwich. Fig:2 shows various types of layered tablets. It makes possible sustained-release preparations with the immediate-release quantity in one layer and the slow release portion in the second. A third layer with an intermediate release might be added<sup>(9)</sup>.

### Layer Tablet Dosage Forms are Designed for Variety of Reasons

1. To control the delivery rate of either single or two different active pharmaceutical ingredient(s)<sup>(10,11)</sup>.
2. 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.
3. 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<sup>(12, 13)</sup>.
4. To administer fixed dose combinations of different APIs,<sup>(14)</sup> prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device,<sup>(15)</sup> buccal/ mucoadhesive delivery systems,<sup>(16)</sup> and floating tablets for gastro-retentive drug delivery<sup>(17)</sup>.

Figure. 2 Layer Tablet (Single Layer, Bilayer , Multilayer Tablet.)



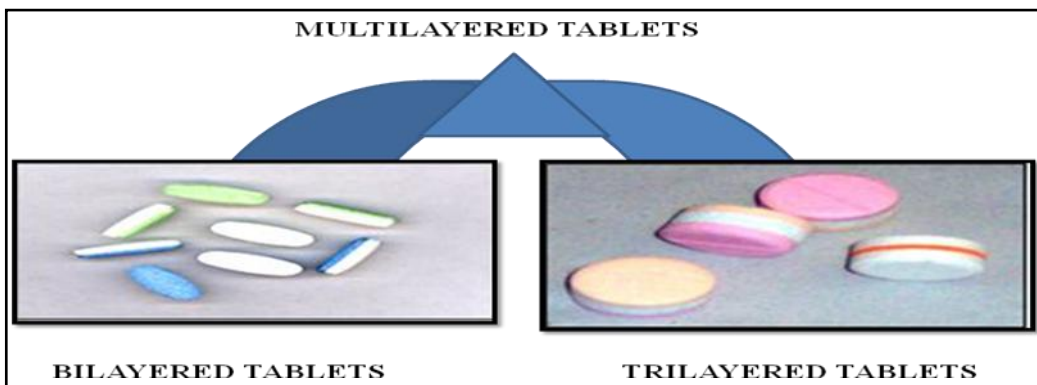
Approaches for Layered Tablets<sup>(5,31)</sup>

1. Multi Layered Tablets – Two To Three Component Systems.
2. Inlay Tablet – Coat Partially Surrounding The Core.
3. Compression Coated Tablets – Tablet Within A Tablet.

1. Multilayered Tablets (Bi, Tri)

“Multilayered Tablets consist of two or more active pharmaceutical ingredients in One unit”. It is the best option to administer two or more incompatible API’s in same unit. Distinct look is obtain for a tablet when fabricated by multi-layers. Dust extraction is essential during compression to avoid contamination.

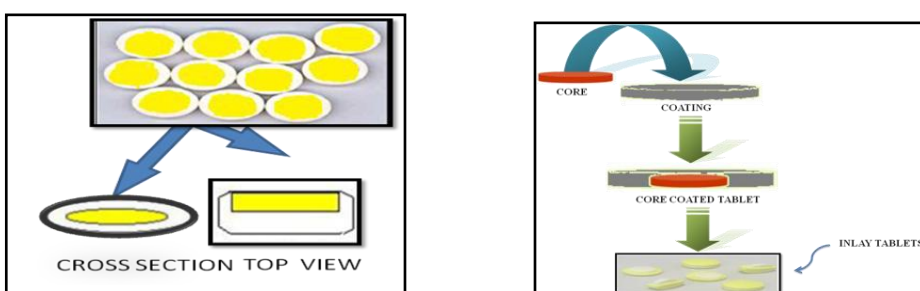
Figure. 3 Multi-layered Tablets ( Bi-layered & Tri-layered Tablets.)



2. Inlay Tablets

Inlay Tablet is defined “As a type of layered tablet in which the core tablet being not completely surrounded by coating instead that only top surface is expose”. During preparation, 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. The development and production of quality bilayer tablets needs to be carried out on purpose-built tablet presses to overcome common bi-layer problems.

Figure. 4 Inlay Tablets



### 3. 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. 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. Sometimes, inner core may be of liquid formulation to provide immediate release of core after the coat gets dissolved.

#### Bilayered Tablets

Bi-layer tablets require fewer materials than compression coated tablets weigh less and may be thinner. Coloring the separate layers provides many possibilities for unique tablet identity. Separation of the layers prior to assay may simplify the analytical work. Since there is no transfer to a second set of punches and dies, as with the dry-coating machine, odd shapes (such as triangles, squares, and ovals) present no operating problems except for those common to keyed tooling. Several pharmaceutical companies are currently developing bilayer tablets for a variety of reasons viz. patent extension, therapeutic, marketing to name a few. Various problems are associated with the formulation of bilayer tablets, such as layer-separation, insufficient hardness, inaccurate individual layer weight control, cross contamination between the layers reduced yield etc.<sup>(18)</sup>

#### Types of Bilayer Tablets

**TableNo.3 Prior study done on bilayer tablets. (ref.no. 50-73)**

Author	Drug(S)	Dosage Form	Rationale	Method	Year
Purohit et al.	Nebivolol & Indapamide	Bilayer tablets	Synergistic effects against Hypertension	Wet granulation	2013
Indhumathi et al.	Paracetamol & Diclofenac Na	Bilayer tablets	Synergistic effect in pain	Wet granulation	2013
Kotta et al.	Pioglitazone Hcl & Metformin Hcl	Bilayer matrix tablet	synergistic effects or biphasic drug release profile	Direct & Wet Compression	2013
Mohan et al.	Tramadol Hydrochloride	Bilayer tablets	strong analgesic action	Direct compression	2013
Arunprasad et al.	Levofloxacin & Ambroxol Hcl	Bi-layer tablets	Treating respiratory tract infections	Wet granulation	2013
Kasid et al.	lisinopril and gliclazide	Bilayer tablets	Management of diabetes along with diabetic hypertension	Direct compression	2013
Karthikeyini et al.	Fluoxetine and Vitamin E	Bilayer tablets	To achieve multi benefits in depression associated with sexual dysfunction	Direct compression	2013
Shirsand et al.	Nebivolol	Buccal Bilayer tablets	To improve drug residence time on buccal mucosa	Direct compression	2013
Wakade et al.	Glipizide	Bilayer Floating Tablets	Sustained-release of Glipizide & Reduce the glucose level of blood in human	Direct compression	2013

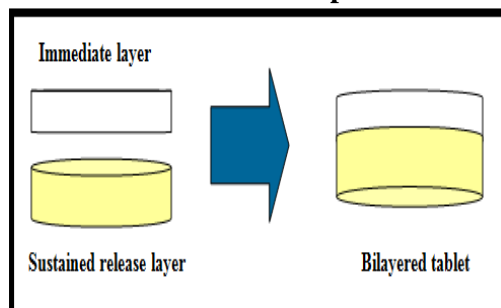
#### a. Homogenous Type

Bilayer tablets are preferred when the release profiles of the drugs are different from one another. It allows designing and modulating the dissolution and release characteristics. This are prepared with one layer being immediate release and other layer is designed to give second dose or extended release.<sup>(19)</sup>

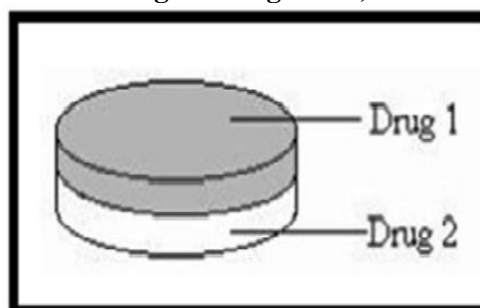
## b. Heterogenous Type

Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances.<sup>(19)</sup>

**Figure.5 Bilayer Tablets (same drug with different different release pattern-homogenous)**



**Figure.6 Bilayer Tablets (with two drugs heterogenous )**



### Need of Developing Bi-Layer Tablets<sup>(20, 21, 22,)</sup>

For the supervision of fixed dose combinations of drugs, prolong the drug product life cycle, buccal /mucoadhesive delivery systems, manufacture novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery systems.

- Controlling the delivery rate of either single or two different API'S.
- To adapt the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable / erodible barriers for controlled release.
- To separate incompatible API's with each other, to control the release of one layer by utilizing the functional property of the other layer (such as osmotic property).

### Advantages of Bi-Layer Tablets<sup>(21, 23)</sup>

1. Greatest chemical and microbial stability compared to other oral dosage forms.
2. Objectionable odor and taste can be masked by coating technologies.
3. Offer greatest precision and the least content uniformity.
4. Fit for large scale production.
5. It is prevent direct contact of two drugs and thus, maximize the efficacy of combination.
6. It 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.
7. Patient compliance is improved and lead to improvement in dose regimen.

### Disadvantages Of Bi-Layer Tablets<sup>(21,23)</sup>

1. Adds complexity and bi-layer rotary presses are expensive.
2. Insufficient hardness, layer separation, reduced yield.
3. Cross contamination between the layers.
4. Difficult to swallow in case of children and unconscious patients.
5. Some drugs resist compression into dense compacts, due to amorphous nature, low density nature.

### Applications<sup>(24-26)</sup>

1. Bi-layer tablets are suitable for sequential release of two drugs in combination.
2. It is improved technology to overcome the shortcoming of the single layered tablet.
3. Bilayer tablets are used to deliver the loading dose and sustained dose of the same or different drugs.
4. Bilayer tablets are used to deliver the two different drugs having different release profiles.

### Quality and GMP Requirements<sup>(27-31)</sup>

To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the selected press is capable of:

1. Preventing capping and separation of the two individual layers that constitute the bi-layer tablet, Providing sufficient tablet hardness.
2. Preventing cross-contamination between the two layers .
3. Producing a clear visual separation between the two layers & give high yield .
4. Accurate and individual weight control of the two layers is not so easily accomplished.

### Compression Cycle for Bilayer Tablet<sup>(32, 33)</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 or three layers. More are possible but the design becomes very special and complicated.

### Various Types of Bilayer Tablet Press

1. Single Sided Tablet Press.
2. Double Sided Tablet Press.
3. Bilayer Tablet Presses With Displacement Monitoring.

#### 1. Single Sided Tablet Presses :

- ❖ There are many different types of bi-layer tablet presses have been designed over the years.
- ❖ The simplest design is a single sided press which have two 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 feeder fed the die with the powders (drugs), 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.

#### The Limitations of Single-Sided Press are

- 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 result 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.

**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. To eliminate these limitations, a double-sided tablet press is preferred over a single-sided press.

### Compression Force

Many bilayer formulations requires a first layer compression force of less than 100 daN in order to retain the ability to bond with the second layer. Above 100daN, this ability may be lost and bonding between both layers may not be sufficient, resulting in low hardness of the bilayer tablet and separation of the two layers.

#### 2. Double Sided Tablet Press or “Compression Force” Controlled Tablet Presses

- ❖ It is one of the best system of tablet press to eliminate the limitations of single-sided press, due to that A double-sided tablet press is preferred over a single-sided press.
- ❖ It offers an individual fill station, pre-compression and main compression for each layer.
- ❖ In fact the bi-layer tablet will go through four compression stages before being ejected from the press.

- ❖ 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 tablet and correct the die fill depth when mandatory.

### Advantages

- Displacement weight monitoring for accurate and independent weight control of the individual layer.
- Low compression force exerted on the first layer to avoid capping and separation of the individual layer.
- 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 two layers.
- A clear visual separation between the two layers.
- Maximized yield.

### Limitations

- Separation of the two individual layers is due to insufficient bonding between the two layers during final compression of bi-layer tablet.
- Correct bonding is only obtained when the first layer is compressed at a low compression force so that this layer can still interact with the second layer during final compression.
- Most of the double sided tablet presses is provided with automated controller for monitoring compression force and control tablet weight, but compression force control system is always based on measurement of compression force at main compression but not at pre compression.
- At higher production speed, the risk of separation and capping increases, but It can be reduced by sufficient dwell time at compression stages.

### 3. Bilayer Tablet Press with Displacement

- ❖ “The displacement tablet weight control principle is basically different from the principle based upon compression force. When measuring displacement the control system sensitivity does not depend on the operation point but depends on the applied pre-compression force”.
- ❖ In fact the lower the pre-compression force, the more the monitoring control system and this ideal for good interlayer bonding of the bi-layer tablet.
- ❖ The upper pre-compression roller is attached to an air-piston which can move up and down in air cylinder and at that time the air pressure in the cylinder is set as a product parameter at initial product set-up and is kept at a constant value by the machine's control system.
- ❖ This pressure multiplied by the piston surface is the constant force at which the piston and consequently the roller is pushed downwards against affixed stop.
- ❖ The lower pre-compression roller is mounted on a yoke and its vertical position can be adjusted through the control system by means of a servomotor.
- ❖ The position of the lower pre-compression determines the pre-compression height, At every pre-compression the upper punch hits the upper roller and is initially pushed downwards into the die.
- ❖ As the lower punch is pushed upwards by the lower roller the power is being compressed, while the exerted compression force increases.
- ❖ At a certain point the reaction force exerted by the power on the upper punch equals the force exerted by the air pressure on the piston.
- ❖ The punch has to continue its way under the roller because the turret is spinning.

### Advantages

- Weight monitoring 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.
- 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.

## Manufacturing Process of Bilayer Tablet<sup>(34)</sup>

Manufacturing processes such as wet granulation/roller compaction and addition of binders increases the level of complexity in understanding the critical factors governing compression and tablet breaking force. Thus, the tablet breaking force and the tablet's susceptibility for delamination /capping either during manufacturing or during storage need to be carefully observed. Apart from the critical material attributes of individual components and final blend, the tablet press has large influence on the manufacture of multilayer tablets. The level of pre-compression force, punch velocity, consolidation time (time when punches are changing their vertical position in reference to the rolls as the distance between the punch tips are decreased), dwell time (time when punches are not changing their vertical position in reference to the rolls), relaxation time (time when both punches are changing their vertical position in reference to the rolls as the distance between the punch tips increases before losing contact with the rolls), and the applied force can have significant effect on the critical quality of the tablet. The extent of compact densification and resistance to compressibility within the die cavity was impacted by compaction pressure and the punch velocity.

## Evaluation of Bilayer Tablets

### pre-compression evaluation :

- 1. Particle size distribution:** The particle size distribution was measured using sieving method. <sup>(35,36)</sup>
- 2. Photo-microscope study:** Photo-microscope image of TGG and GG was taken (X450 magnifications) by Photomicroscope. <sup>(35,36)</sup>
- 3. Angle of repose:** In order to determine the flow property, the Angle of repose was determined. It is the maximum angle that can be obtained between the free standing surface of the powder heap and the horizontal plan. <sup>(37,38)</sup>

$$\tan^{-1} (h/r)$$

Where, h= height, r = radius

- 4. Determination of bulk density and tapped density:** A quantity of 5g of the powder (W) from each formula was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using the following formulas. <sup>(39,40,41)</sup>

$$\text{Bulk density} = W / VO$$

$$\text{Tapped density} = W / Vf$$

Where, W = weight of the powder, VO = initial volume, Vf = final volume

- 5. Compressibility index (carr's indices):** Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. A material having values of less than 20 to 30% is defined as the free flowing material. <sup>(39,40,41)</sup>

$$CI = 100 (VO - Vf)/V$$

Where, CI = Compressibility index, VO = initial volume, Vf = final volume.

- 6. Hausner's ratio:** It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density. <sup>(39,40,41)</sup>
- 7. 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. <sup>(36,37)</sup>

### Post-Compression Evaluation :

- 1. General Appearance:** The general appearance of a tablet, its visual identity and overall "elegance" is essential for consumer acceptance. Includes in are tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking. <sup>(42,43)</sup>
- 2. Size And Shape:** The size and shape of the compressed tablets were examined under the magnifying lens. <sup>(42,43)</sup>



3. **Tablet Thickness:** Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer. <sup>(44)</sup>
4. **Friability Test:** The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed ( $w_0$  initial) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again ( $w$ ). <sup>(45)</sup>

The % friability was then calculated by : **Percentage of Friability = 100 (1-w/w<sub>0</sub>)**

Percentage friability of tablets less than 1% is considered acceptable.

5. **Weight Variation Test:** Twenty tablets were selected at random and the average weight was determined. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation shown in table and none deviates by more than twice the percentage. USP official limits of percentage deviation of tablet are presented in the table. <sup>(35)</sup>
6. **Swelling Studies:** Swelling property of tablet was determined by placing it in the dissolution test apparatus, in 900 ml of 0.1 N HCl at  $37 \pm 2$  °C. The weight and volume reached by the matrix tablets over time was determined by withdrawing the tablets periodically from dissolution medium. The tablets were weighed on an analytical balance after slight blotting with tissue paper to remove the excess test liquid. The volume of the tablets was obtained by measuring the thickness and diameter, considering a right circular cylinder form. The determined weight and volume were used to calculate the tablet density over the dissolution study. Swelling characteristics were expressed in terms of percentage water uptake (WU %) according to the equation: <sup>(46)</sup>  
**WU % = Wt. of swollen tablet – Initial wt. of tablet / Initial wt. of tablet × 100.**
7. **Hardness (Crushing Strength):** The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. Monsanto hardness tester measures the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet. The Strong-Cobb Pfizer and Schleuniger apparatus measures the diametrically applied force required to break the tablet. Hardness, which is now more appropriately called crushing strength determinations are made during tablet production and are used to determine the need for pressure adjustment on tablet machine. If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specifications; if it is too soft, it may not be able to withstand the handling during subsequent processing such as coating or packaging and shipping operations. The force required to break the tablet is measured in kilograms and a crushing strength of 4 Kg is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10 kg; however, hypodermic and chewable tablets are usually much softer (3 kg) and some sustained release tablets are much harder (10 -20 kg). Hardness generally increases with normal storage of tablets and depends on the shape, chemical properties, binding agent and pressure applied during compression. <sup>(47)</sup>
8. **Disintegration Test:** Disintegration test apparatus is generally used to measure disintegration time of tablet. For Disintegration time, one tablet is placed in each tube and the basket arch is positioned in 1 L beaker containing water at  $37^\circ\text{C} \pm 2^\circ\text{C}$ . A standard motor driven device is used to move the basket assembly up and down. To comply with USP standard, all tablets must disintegrate and all particles must pass through the 10 mesh in the time specified. <sup>(48)</sup>
9. **Dissolution Studies:** Drug release studies are carry out using USP dissolution test apparatus I at 100 rpm,  $37 \pm 0.5^\circ\text{C}$ , 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 (900ml) and experiment continued for another 10 hours. The samples withdrawn during dissolution test are analyzed by UV spectrophotometer using multi component mode of analysis. <sup>(45)</sup>
10. **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 plotting according Arrhenius equation to determine the shelf life at  $25^\circ\text{C}$ . <sup>(49)</sup>

**Table No.2 ICH guideline for stability study**

Study	Storage Condition	Minimum time period covered by data at submission
Long term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

\*It is up to the applicant to decide whether long term stability studies are performed at 25± 20C/60% RH ± 5% RH or 300C ± 20C/65% RH ± 5% RH. \*\*If 300C ± 20C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

## Conclusion

Bilayer tablet is improved beneficial technology to overcome the shortcomings of the single layered tablet. There is various application of the bi-layer tablet it consist of monolithic partially coated or multilayered Matrices. 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. 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. Present review mainly emphasizes, why bilayer tablet is considered as better option than conventional tablet.

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