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Bilayer tablet technology: An overview

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Abstract : Bi-layer tablet is a new era for successful development of controlled release formulation along with various features to provide successful drug delivery. Bi-layer tablets can be primary option to avoid chemical incompatibilities between APIs by physical separation and to enable the development of different drug release profiles. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. Several pharmaceutical companies are currently developing bi-layer tablets. For a variety of reasons: patent extension, therapeutic, marketing to name a few. To reduce capital investment, quite often existing but modified tablet presses are used to develop and produce such tablets. Bi-layer tablet is suitable for sequential release of two drugs in combination and also for sustained release of tablet in which one layer is for immediate release as loading 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. Several pharmaceutical companies are currently developing bi-layer tablets, for a variety of reasons: patent extension, therapeutic, marketing to name a few. General 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 challenges.

Keywords : Bi-layer tablet, API (active pharmaceutical ingredient), Sustained release, Immediate release. Incompatibilities.

Introduction

In the last decade, 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).[1,2] 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[3]. To overcome the drawbacks of single layer combination tablet this concept was came into force[4]. 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)[5] .

Need of Bilayer Tablet [6,7,8]

1. For the administration of fixed dose combinations of different APIs, prolong the drug product life cycle, buccal/mucoadhesive delivery systems; fabricate novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery.
2. Controlling the delivery rate of either single or two different active pharmaceutical ingredient(s)
3. 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.
4. 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 Bilayer Tablet-

1. Bi-layer execution with optional single-layer conversion kit.
2. Cost is lower compared to all other oral dosage form.
3. Greatest chemical and microbial stability over alloral dosage form.
4. Objectionable odour and bitter taste can be masked by coating technique.
5. Flexible Concept.
6. 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.
7. Easy to swallowing with least tendency for hangup.
8. Suitable for large scale production.

Disadvantages of Bilayer Tablet -

1. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
2. Bitter tasting drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.
3. Difficult to swallow in case of children and unconscious patients.
4. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.

Quality and GMP-Requirements [9]

To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the Selected press is capable of 5:

1. Preventing capping and separation of the two individual layers that constitute the bi-layer tablet
2. Providing sufficient tablet hardness
3. Preventing cross-contamination between the two layers
4. Producing a clear visual separation between the two layers
5. High yield Accurate and individual weight control of the two layers.

These requirements seem obvious but are not so easily accomplished.

TYPES OF BI-LAYER TABLET PRESSES:

1. Single sided tablet press.
2. Double sided tablet press.
3. Bi-layer tablet press with displacement.

(1) Single sided tablet press [10-12]

The simplest design is the single sided press with both chambers of the double feeder separation from each other. Each chamber is gravity or forced fed with different powder, thus producing the two individual layers of the tablets. When the die passes under the feeder, it is first loaded with the first-layer powder followed by the second layer powder. Then the intact tablet is compressed in one or two steps.

Limitations of the single sided press [13,14]

- No weight monitoring / control of the individual layers.
- No distinct visual separation between the two layers.
- Very difficult first-layer tablet sampling and sample transport to a test unit for in-line quality control and weight recalibration.

(2) Double sided tablet press or "compression force" controlled tablet presses [12,15]

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 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.

Limitations [16,17]

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. Bonding is too restricted if first layer is compressed at a high compression force. The low compression force required when compressing the first layer unfortunately reduces the accuracy of the weight monitoring/control of the first layer in the case of tablet presses with "compression force measurement". Most of the double sided tablet presses with automated production control use compression force to monitor and control tablet weight.

Compression force control system is always based on measurement of compression force at main compression but not at pre-compression.

(3) Bilayer tablet press with displacement [18,19]

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 operation point, but depends on the applied precompression 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. 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 are 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 precompression 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 torrent is spinning.

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.
- 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.

Table No.1: Type of tablets & class of tablets[20]

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

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:1 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 .

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) .
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.
4. 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

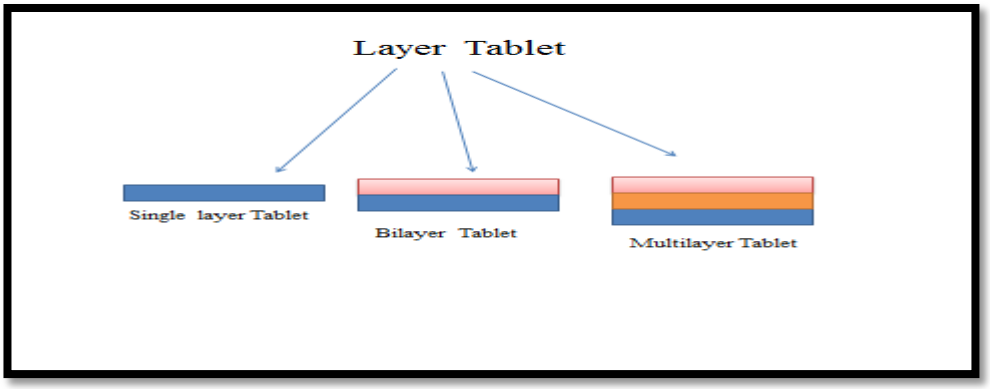

Figure 1. Layer Tablet (Single Layer, Bilayer , Multilayer Tablet.)

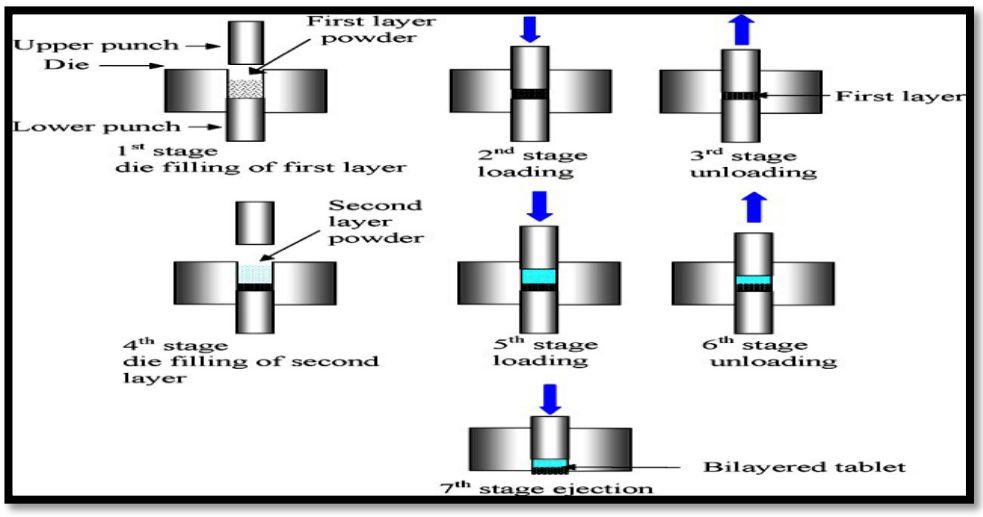

Fig 2: Preparation of bilayer tablet Compaction.

Characterization of Blend [21]

Prior to compression, the blend was evaluated for their characteristics parameters such as Bulk Density, Tapped Density, Carr's Index and Hausner's ratio, angle of repose.

1. Bulk Density [22]

Blend was poured gently through a glass funnel into a graduated cylinder exactly to 10ml mark. The weight of the cylinder along with granules required for filling the cylinder volume is calculated. The cylinder was then tapped from a height of 2 cm until the time when there is no more decrease in the volume (Tap density tester USP, Campbell Electronics). Bulk Density (gm/ml) and Tapped Density (gm/ml) are calculated using the following equation:

Bulk Density (gm/ml) **Db = M / Vb**
Where,
M=Weight of Blend taken and Vb= Bulk Volume
Tapped Density (gm/ml) **Dt = M / Vt**
Where,
M =Weight of Blend taken and Vt=Tapped Volume

2. Angle of Repose

The angle of repose of granules is determined by the funnel method. The accurately weighed granules are taken in a funnel. The height of the funnel is adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules are allowed to flow through the funnel freely onto the surface. The diameter of the powder cone is measured and angle of repose is calculated using the followingequation:

Angle of Repose **θ = tan-1 (h/r)**

Where, h = Height of the powder cone.

Table No. 2: Angle of Repose and corresponding Type of Flow.

Angle of Repose	Type of Flow
<25	Excellent
25-30	Good
30-40	Passable(may improve with glidants)
>40	Very Poor

3. Compressibility Index(Carr's Index)

The compressibility index of the granules is determined by Carr's compressibility index: Carr's index (%) **CI = {(Dt – Db) X 100}/Dt**

Where,

CI= Compressibility Index,Dt= Tapped Density,Db= Bulk Density

Table No.3: Relationship between flowability and carr's index.

Carr's Index(% Compressibility)	Type of Flow
5-15	Excellent (free flowing granule)
12-16	Good (free flowing powdered granules)
18-21	Fair (Powdered granules)
23-28	Poor (very Fluid powder)
28-35	Poor (fluid cohesive powders)
35-38	Very Poor(fluid cohesive powders)
>40	Extremely Poor(cohesive Powders)

4. Hausner's ratio [23]

Hausner's ratio indicates the flow property of powder Hausner's ratio is calculated by following equation

Hausner's ratio

HR = Dt / Db
Where, Dt = Tapped Density
Db = Bulk Density

Table No.4 : Relationship between Hausner ratio and Carr's index

Hausner ratio	Type of flow	Equivalent Carr's index(%)
<1.25	Good	20
>1.25	Poor	30

5. Particle size distribution

The particle size distribution is measured using sieving method.

Evaluation of Bilayer Tablet

1. General Appearance [24]

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

2. Thickness [24]

The thickness of the tablet is measured by vernier calipers scale. Thickness of the tablet related to the tablethardness and can be used an initial control parameter.

3. Hardness [25]

The hardness test is performed to provide a measure of tablet strength. The resistance of tablet from shipping orbreakage, under conditions of storage, transportation and handling before usage depends on its

hardness. AMonsanto tablet hardness tester is employed to determine the hardness of the tablets. For each batch three tablets are tested and the hardness is measured in kg/cm2.

4. Friability [26]

Friability is determined using a Friabilator and it is expressed in terms of weight loss and is calculated in percentage. Twenty tablets are randomly selected, dusted and weighed accurately and placed in the plastic chamber and subjected to its tumbling action at 25 rpm for 4 mins, dropping the tablets through a distance of six inches with each evaluation. After 100 revolutions the tablets are once again dusted and reweighed to determine the percentage loss of weight. The weight loss should not be more than 1%.

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

5. Uniformity of Weight [27]

Twenty tablets are randomly selected and weighed individually. The average weight is determined then percentage deviation from the average weight is calculated.

Table 5: Average weight of tablets with % deviation

Average Weight of tablet as per I.P.	% Deviation	Average Weight of tablet as per U.S.P.
80 mg	+10	<130mg
>80 mg but <250mg	+7.5	>130mg but <324 mg
>250mg	+5	>324 mg

6. Disintegration time [28,29]

The disintegration time is recorded using an USP disintegration test apparatus with distilled water at 37±0.5°C. The disintegration time is taken to be the time when no granules of any tablets are left on the mesh of the apparatus. The time reported to obtain complete disintegration of six tablets is recorded and mean value is reported.

Table No. 6: Limits for disintegration test for tablets.

Types of tablet	Medium	Temperature	Limit
Uncoated	Water	37± 2°C	15 minutes or as indicated in monograph
Coated	Water	37±12°C	60 minutes or as indicated in monograph
Film coated	Water	37± 2°C	30 minutes or as indicated in monograph
Enteric coated	0.1 M Hcl	37± 2°C	Should not disintegrate at the end of 2 hours
Hard capsules	Water	37± 2°C	30 minutes
Soft Capsules	Water	37± 2°C	60 minutes
Dispersible/soluble	Water	24 to 26°C	<3 minutes

7. Dissolution Studies [29]

Bilayer tablets are 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 are 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 is replaced with pH 6.8

phosphate buffer (900ml) 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 are analyzed by UV spectrophotometer using multi component mode of analysis.

8. Stability studies [30,31]

In order to determine the change on storage, stability study is carried out a 25°C / 60% RH and 40°C / 75% RH in a stability chamber. Samples are withdrawn at regular intervals. Formulation is evaluated for changes in Hardness, Thickness, Disintegration time and in vitro release studies

Conclusion

Bi-layer tablet is improved beneficial technology to overcome the limitation of the single layered tablet. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substancesand 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.

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