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Review On Bilayer Tablet

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Abstract-

Bi-layer tablet is a new era for the successful development of controlled 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, 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. Bi-layer tablets has been developed to achieve controlled delivery of different drugs with pre defined release profiles. In the last decade interest in developing a combination of two or more API's in a single dosage form has increased in the pharmaceutical industry, promoting patient convenience and compliance. Several pharmaceutical companies are presently developing bi-layer tablets, for a variety of reasons patent extension, therapeutic, marketing to name a few. To decrease capital investment, quite often existing but modified tablet presses are used to develop and produce such tablets. This article explains about different techniques of bi-layer tablet and why development and production of quality bi-layer tablets need to be carried out on purpose built tablet presses to conquer common bilayer problems, such as layer separation, insufficient hardness, inaccurate individual layer weight control, cross contamination between the layers, reduced yield etc. There are various applications of the bi-layer tablet consists of monolithic partially coated or multilayered matrices.

Introduction-

Over the past 30 years greater attention has been focused on development of sustained or controlled release 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 and compliance[1]

Bilayer tablet is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. 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 [2]

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 [3]

(Kumar et al., 2010). 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

(Shiyani et al., 2008). There is various application of the bi-layer tablet it consist of monolithic partially coated or multilayered matrices. In the case of bi-layered 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.

Types of bilayer tablet press[4,5,6]

1. Single sided press [7]

The most basic design is a single-sided press with both chambers of the doublet hopper isolated from one another. The two distinct layers of tablets are produced by gravity or force feeding each chamber with varied power. The first layer powder is put onto the die as it travels through the feeder, following the second layer powder. After that, in one or two steps, the entire tablet is compacted

2. Double sided tablet press [8] Compression force is used to manage and control tablet weight in the majority of doublesided tablet press machines with automated production control. During main compression of the layer, the control system measures the effective peak compression force applied on each individual tablet or layer. The control system uses this observed peak compression force as a signal to reject out-of-tolerance die fill depths and adjust them as necessary

3.Bilayer tablet press with displacement monitoring

The principle of displacement tablets weight management is significantly different from the compression force principle. The sensitivity of the control system while monitoring displacement is determined by the applied precompression force rather than the tablet weight.

Challenges related to bilayer technology

In spite of the aforementioned advantages provided by the bilayer technology, several issues associated with the mechanisms and compression of bilayer tablets have been reported in the literature in recent years. The formulators and process scientists need to overcome the challenges to deliver a robust bilayer tablet and manufacturing process. Some of the key challenges are:

• Inaccurate individual layer weight control **(Charman and Charman, 2002).**

• Cross contamination between the layers **(Hiestand et al., 1977; Karehill et al., 1990; Poon and Bhushan, 1995; Inman et al., 2007; Akseli et al., 2013).**

• Elastic modulus mismatch between the adjacent layers. High elastic modulus ratio between adjacent layers could cause insufficient layer bonding and relatively low interfacial strength (Akseli et al., 2010).

• Reduced production yield and the propensity to delaminate (distinct layers separation) at the non-planer interface between the adjacent compacted layers **(Abdul and Poddar, 2004).**

• Disproportionate layers weight ratio coupled with low drug load **(Martin et al., 2012).**

• Insufficient bilayer tablet hardness **(Abdul and Poddar, 2004).**

• Long term physical and chemical integrity throughout shelf life.

• Large tablet size, which can impact the swallowability of the unit dose.

• Impact of high temperature and humidity on layer adhesion upon storage **(Kottala et al., 2012a).**

Advantages of bilayer tablet [9,10]

1. They are utilized as an add-on to conventional technologies.
2. Maintain chemical and physical stability
3. Maintain potency and dosing precision

4. In compare to conventional delivery systems, patient compliance is improved because reduced daily doses are required.

5. Patient compliance improves, resulting in better treatment regimen efficacy.

6. A drug's blood level can be maintained at a therapeutic level for increased drug delivery, safety, accuracy and side effect reduction.

Bi-layered tablets are well-suited to repeat-action drugs, with one layer providing the initial dose and the other layer providing the maintenance dose.

Disadvantages of bilayer tablet [11]

1. Because of the amorphous nature and low density, several drugs resists compression into dense solid compacts.

2. Encapsulation or coating may be required for bitter-tasting medications, drugs with an offensive odour, or drugs that are oxygen-sensitive.

3. Difficulty in swallowing for unconscious patients and children.

4. It may be challenging to design a tablet that provides adequate or full drug bioavailability for drugs with poor wetting, slow dissolution profile, or optimum absorption high in the GIT. 5. Inaccurate weight control for individual layers.

6. There may be chances of cross contamination within the layers.

ADVANCED TECHNIQUES USED IN PREPARATION OF BILAYER TABLET:

OROS Push Pull Technology

- **L-OROS Technology**
- **EN SO TROL Technology**
- **DUROS TROL Technology**
- **Elan Drug Technology'**

Dual release Drug Delivery System OROS Push Pull Technology: This approach comprises mainly two or three layers, one or more of which must contain the drug, and the other is a push layer. Generally, it consists of a drug and two or more agents utilized in the drug layer such as suspending and osmotic agents. A semipermeable membrane surrounds the core of the tablet [12]

L-OROS Technology:

This system is used to resolve the solubility problem associated with the drug. L-OROS system contains a lipid soft gel product holding drug in a dissolved state and an osmotic push layer with semi permeable membrane and a drilled for exit orifice [12]

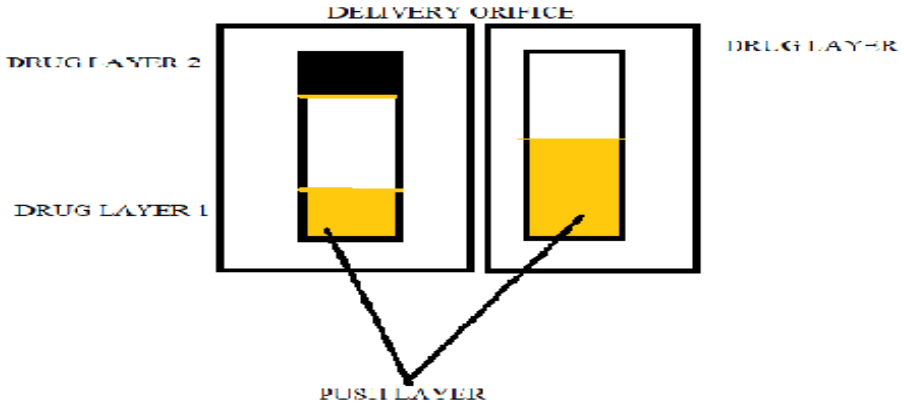

Fig. L-OROS Technology

ENSOTROL Technology:

Increased solubility by an order of magnitude or creation of an optimal dose form Shire's drug delivery laboratory takes an integrated strategy, concentrating on the identification and implementation of discovered enhancers into controlled release technologies [13]]

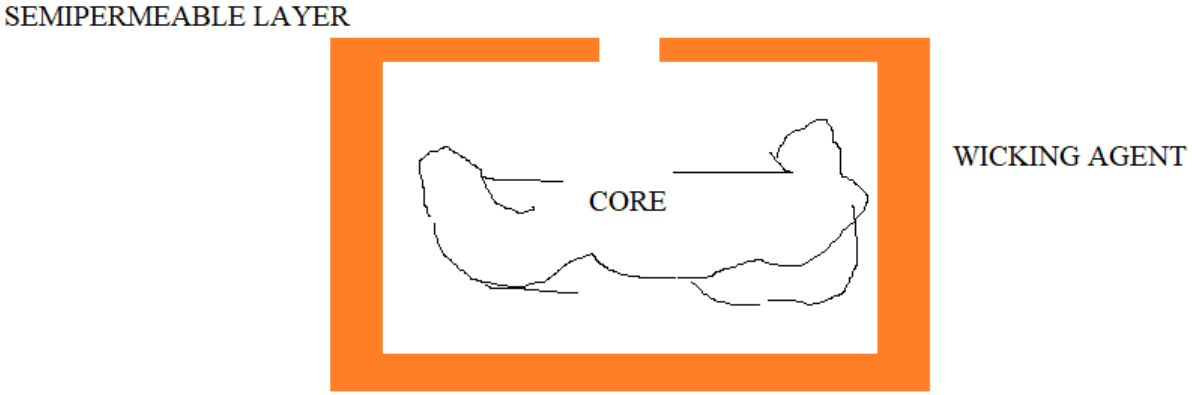

Fig. ENSOTROL Technology

DUROS Technology:

The system is comprised of an outer cylindrical titanium alloy reservoir and an inner cylindrical titanium alloy reservoir. This reservoir is extremely robust and effectively protects the drug molecules from enzymes. The DUROS technology is a small medicine delivery system that resembles a miniature syringe and continuously and consistently releases minute amounts of concentrated medication over months or years.

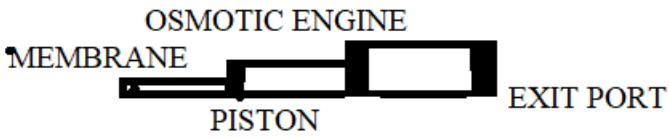

Fig. DUROS Technology

DUREDAS™ Technology:

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[14]

Need of bilayer tablets [15]

1. Controlling the delivery rate of single or two different active pharmaceutical ingredients.

2. To modify the surface area available for API by swellable/erodible barriers for modified release.

3. To separate incompatible Active pharmaceutical ingredient (APIs) from each other.

4. To control the release of API from one layer by utilizing the functional property of the other layer.

5. For the administration of fixed dose combinations of different APIs.

Preformulation studies

Pre-formulation study is the initial step in the development of a drug substance's dosage forms. The process of optimizing drug delivery by determining the physicochemical features of excipients that may affect drug performance and developing an effective, stable, and safe dosage form is known as Preformulation studies. It establishes a framework for combining drugs with pharmaceutical excipients in a dosage form.

1.Determination of λmax [16]

APIs are to be dissolved in a solvent, then diluted using the same solvent and scanned in a UV Visible spectrophotometer to determine their maximum absorbance

2. Solubility [17]

In distilled water, methanol, ethanol, acetone, chloroform, and pH 6.8 phosphate buffer, API solubility will be tested by the shake flask method.UV-Visible Spectrophotometer is used to determine absorbance. The standard graph is used to determine the drug content.

3.Melting point [18]

The melting points of the APIs are to be determined in triplicate using the capillary technique.

4. Standard Curve for API [19]

To make the initial stock solution, In 100 ml of solvent, 100 mg of APIs are to be suitably weighted and dissolved. The second stock solution was made by diluting 10 mL of the previously described solution to 100 mL with the same solvent. The final solution is to be diluted from the aliquot quantity of IInd stock solution to yield 5, 10, 15, 20, 25, and 30 g of drugs per ml. A UV spectrophotometer was then used to quantify the absorption

5.Compatibility studies :

FT-IR spectroscopy is used to study the drug's compatibility with polymers.

6. FT-IR Spectroscopy [20]

To ensure that the drugs and excipients are compatible, FT-IR spectroscopy was used. A thermal Nicolet FTIR is used to do infrared spectroscopy. The spectrum is captured in the 4000 to 400 MHz cm-1range. Using a hydraulic press at a pressure of 5 tones for 5 minutes, the sample (drug and drug-excipient combination in 1:1 ratio) is compressed into discs in KBr (200-400mg).

IR-spectral investigations seek for any shift in drug peaks in the spectrum of a physical combination of drug and excipients to explore the interaction between drug and excipients.

7. DSC Analysis for formulation [21]

The thermal characteristics of the pure medicine and the physical combination of API and excipients are examined using a Differential Scanning Calorimeter. The samples are heated in thermically enclosed aluminum pans. The heat runs for each sample are set between 25 and 350 degrees Celsius, with a heating rate of 10 degrees Celsius per minute and nitrogen as a blanket gas.

Preformulation evaluation parameters

1. Angle of repose [22]

The funnel method is use to calculate the granules' angle of repose. A funnel is use to collect the precisely weighed granules. The height of the funnel was adjusted such that the tip of the funnel just touched the granules heap's peak. The granules are allowed to flow freely onto the surface as they pass through the funnel. The diameter of the powder cone was measured, and the angle of repose was calculated using equation.

tanϴ

Where = angle of repose,

h = height of the heap of the powder,

r = radius of the heap of the powder

Table 1: Angle of repose.

Sr. No.	Angle of repose	Types of flow
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Very poor

2.Determination of bulk Density and Tapped density [23]

In a 25 ml measuring cylinder, 2 gram of each formula's powder (W) was added. After the first volume measurement, the cylinder was permitted to fall at 2 second intervals from a height of 2.5 cm onto a hard surface under its own weight. The tapping was continued until there was no more volume fluctuation. The following formulas were used to get the bulk and tapped densities.

The following formulae were used to determine LBD and TDB:Bulk Density= wt. of powder/Bulk volume

Tapped density= Mass of powder/Tapped volume of the powder

3. Carr's Index / Compressibility Index [24]

The compressibility index (CI) is a measure of a powder's compressibility. As a result, it's a measurement for the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are less significant, and the bulk and tapped densities approach each other in value.

Carr's Index/ %Compressibility Index: Tapped Density-Bulk Density/Tapped Density× 100

Table no. 2: Range of Compressibility Index and Hausner's ratio.

Flow character	Compressibility Index (%)	Hausner's Ratio
Excellent	< 10	1.00 – 1.11
Good	11 – 15	1.12 – 1.18
Passable	16 – 20	1.19-1.25
Fair	21-25	1.26-1.34
Poor	26-31	1.35-1.45
Poor	32-37	1.46- 1.59
Extremely poor	> 38	> 1.60

Evaluations of bi-layer tablet [24]

In the preparation of the tablets, the following parameters were evaluated:

- **Weight variation**
- **Hardness**
- **Friability**
- **Drug content**
- **In-vitro Dissolution Studies**

1.Weight variation test

To determine weight fluctuation, twenty tablets of each formulation are weighed using an electronic balance, and the test is to be carried out according to the standard technique.

Table no. 3: Range of weight variation test

Average weight	Percent difference
Less than 130	10
More than 130 but less than 324	7.5
More than	324

2.Tablet thickness

The thickness of the tablet has a considerable impact on the consistency of tablet size. Vernier Calipers were used to measure thickness. It was established by measuring the thickness of ten different formulations of tablets. In the Vernier caliper, both metric and imperial scales are included. The primary matric scale is read first, then the "hundredths of mm" on the imperial scale (Count how many divisions there are until the lines match the main metric scale.). The number on the imperial scale is multiplied by 0.02. The final measurement is obtained by multiplying the number acquired from the imperial scale by the primary metric scale.

3.Hardness

Tablet hardness influences how resistant they are to fracture or during shipment, storage, transportation, and handling before use. The hardness of each batch of tablets was determined using a Monsanto hardness tester. The hardness was measured in kilograms per square centimetre. Five tablets were chosen at random for their hardness. Five different readings were used to get the average hardness.

4.Friability

The weight loss of tablets in containers due to particles removal from the tablet surface is referred to as friability. A lack of cohesion amongst tablet ingredients is usually the source of friability. The weight of 10 tablets was measured before they were placed in a Roche friabilator and spun for 100 rotations at a speed of 25 rpm. The tablets are then removed from the friabilator, dusted, and weighed again, with the weight recorded.

The % friability was calculated using the formula.

% Fribility= Initial weight – final weight x 100 /Initial weight

2. In vitro drug release studies

The USP dissolving test apparatus was used to conduct in vitro drug release experiments (Type 1). Using a pH progression strategy, the dissolution tests were carried out in 900ml of dissolution medium agitated at 50 rpm at 37.5°C. i.e. pH 1.2 for the first 2 hours, pH 6.8 for the next 24 hours. Aliquots were taken out and replaced with fresh medium on a regular basis.

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