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Bilayer Tablets – A Brief Review

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ABSTRACT:
Bi-layer tablets are now being developed by a number of pharmaceutical companies for a number of reasons, including patent extension, therapeutic efficacy, marketing, etc. Capital investment has been decreased by using this technology. Bilayer tablets represent a new stage in the successful development of controlled release formulation and have a number of properties that enable effective drug delivery. In order to prevent chemical incompatibilities between API by physical separation and to enable the development of various drug release profiles, such as the immediate release with extended release, bilayer tablets can be a key alternative.An alternative form of analgesic and anti-inflammatory is the bilayer pill. A bi-layer tablet is appropriate for the combined sequential release of two medications as well as for tablets with sustained release, where the first layer is for immediate release as the initial dose and the second layer is for maintenance. The disadvantage of the single-layered tablet is overcome by the bilayer tablet, a superior technology. The player tablet has a variety of uses and is made up of monolithic partially coated or multilayered matrices. Bilayer tablets represent a new stage in the successful development of controlled release formulation and have a number of properties that enable effective drug delivery.
The bilayer tablets preparing by using different techniques such as OROS® push pulls Technology, L-OROSTM Technology, EN SO TROL Technology, DUREDAS™ Technology and DUROS Technology.
Keywords: Bilayertablets, GMP requirement for bi-layer tablets, Preparation, Sustained release, Characterization.

I. INTRODUCTION:

Bilayer tablets are prescription medications that combine two of the same or different medications in a single dose to effectively treat an illness. Based on these factors, we have developed a bilayer tablet, in which the first layer is designed to achieve fast drug release, with the objective of quickly achieving a high blood concentration. A controlled release hydrophilic matrix, found in the second layer, is intended to keep an effective plasma level for an extended length of time. The pharmacokinetic benefit is based on the fact that drug release from the rapid releasing layer causes a sharp increase in blood concentration. Although the drug is released from the sustaining layer, the blood level is kept constant.To separate incompatible active pharmaceutical ingredients (APIs) from one another, to control the release of API from one layer by utilising the functional property of the other layer (such as, osmotic property), to change the total surface area available for API layer either by sandwiching with one or two inactive layers in order to a Bilayer tablets feature a number of significant advantages over.For instance, these tablets are frequently employed to prevent physical separation of formulation components from chemical incompatibilities. Bilayer tablets have also made it possible to create therapeutic combinations that can be taken as a single dose for efficient illness treatment. and offer responses to these difficultiesTo prevent the physical separation of formulation components from chemical incompatibilities, for instance, these tablets are widely used. Additionally, the development of single-dose therapeutic combinations for effective illness treatment using bilayer tablets has been made possible. and provide solutions to these problems.These tablets are frequently employed, for example, to avoid the physical separation of formulation components from chemical incompatibilities. Bilayer tablets have also enabled the development of single-dose therapeutic combinations for the efficient treatment of sickness. and offer remedies for these issues. Therefore, a bilayer matrix tablet with a single medication in both the fast release layer and the sustained release layer may be helpful for chronic diseases like asthma, migraine, diabetes, hypertension, and inflammation, which typically call for both immediate effect and maintenance therapy.

- **Need of bilayer tablets:**

I. For the fabrication of novel drug delivery systems such as chewing devices and floating

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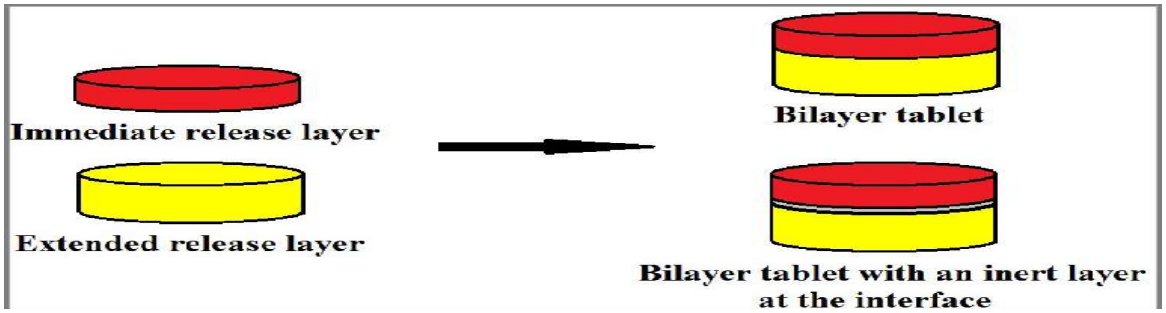
tablets for gastro-retentive drug delivery, prolong the lifecycle of drug products, fixed dose combinations of multiple APIs 13, and vocal mucoadhesive delivery systems. Controlling the delivery rate of either single or two different active API'S.

II. To create swellable (or erodible) barriers for modified release by modifying the total surface area available for the API layer by sand mixing with one or two inactive layers.

III. To isolate suitable active pharmaceutical ingredients (APIs) from one another so that you can use the functional feature of the other layer to control how much API is released from one layer.



- **Application of bilayer tablet:**
  - A bi-layer tablet is appropriate for the sequential delivery of multiple medicines. Separate two substances that are incompatible.
  - Separate two compounds that are incompatible.
  - A tablet with a sustained release formula in which the first layer is an immediate release initial dose and the second layer is a maintenance dose.
  - A bilayer tablet is an upgraded technology that addresses a drawback of a single-layered tablet.
- **5 Ideal Characteristics of Bilayer Tablet**
  - It must be strong enough to endure mechanical shock while being produced, packaged, shipped, and administered.
  - The product should be elegantly crafted and free from flaws like chips, fractures, stains, and contamination.
  - Must have a chemical stability shelf life to avoid causing the therapeutic agents to change.
  - The bilayer tablet's medication release must be predictable and repeatable.
  - It must be stable on both a physical and chemical level to sustain its physical properties throughout time.

- **Types of bilayer tablets:**

1. Single sided tablet press.
2. Double sided tablet press
3. Bilayer tablet press with displacement monitoring.
4. Multilayer compression basics.

1. Single sides press:

The simplest design is a single-sided press with the two chambers of the doublet feeder kept apart. The two discrete layers of the tablets are created by forcing or gravity-feeding a different quantity of energy into each chamber.As the die moves below the feeder, the first layer of powder and then the second layer of powder are loaded into the die. The tablet is then fully compressed in one or more steps.

- Limitations of single sided press: No weight monitoring / control of the individual layers.
- No distinct visual separation between the two layers.

2.**Double sided tablet press:**The majority of double-sided tablet press machines with automated production control use compression force to maintain and regulate tablet weight. During major compression of the layer, the control system measures the effective peak compression force that is applied to each individual tablet or layer. The control system receives a signal from this measured peak compression force, rejects out-of-tolerance die fill depths, and makes the appropriate changes.

- Limitations:Correct bonding is only accomplished when the first layer is crushed at a low compression force, allowing for this layer to still interact with the second layer.

3. **Bilayer tablet press with displacement monitoring:**The displacement pill weight control principle and the compression force concept are

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highly unlike. The sensitivity of the control system when monitoring displacement is determined by the applied precompression force rather than by the weight of the tablet.

4. Multilayer Compression: Basics Presses can be altered to accommodate multipliers, or a standard double press can be created especially for multi-layer compression. Long-term drug release formulations have been developed using the concept of a multilayer tablet.

To maintain medication release from the tablet, these tablets may include players or triple layers in addition to a fast-releasing layer.The pharmacokinetics advantage is based on the observation that, in contrast to fast-releasing granules, which induce a sudden rise in blood concentration, sustained granules cause a steady rise in blood concentration.

- **Various techniques for bilayer tablet formulation :**

1 Push pull Oral Osmotic (OROS) technology

- This structure has two or three levels. It mostly functions according to the osmotic pressure theory. One layer, referred to as the push layer, is made up of an appropriate osmogent (such as mannitol, HPMC, etc.), whereas the other layers are made up of drugs.
- A sufficient osmogent causes the push layer to swell when it comes into contact with watery liquids. Around the delivery orifice-containing tablet core is a semi-permeable membrane. The medicine is continuously administered through the delivery orifice in zero order as a result of the osmogent's ongoing swelling.

2 L-OROSTM technology:

This technique is employed for medications with solubility problems. The Alza-developed L-OROS method involves manufacturing a lipid soft gel product initially comprising medicine in a dissolved condition, coating it with a barrier membrane, surrounding it with an osmotic push layer, semipermeable membrane, and finally drilling a hole for an escape orifice. Tech. 1.3.5.3 EN SO TROL Through the use of this technique, poorly soluble drugs can have their solubility increased by an order of magnitude or have their dose forms optimised. The drug delivery strategy utilised by Shire Laboratory was an integrated one with an emphasis on the selection and inclusion of the right enhancer into dosage forms for controlled release.

- **DUROS technology:**
  - An exterior cylindrical titanium alloy reservoir with strong impact strength serves as the system's main component and often shields the drug molecules from enzyme action.
  - The DUROS technology is a tiny medication delivery mechanism. It operates like a little needle and continuously and continuously supplies small amounts of concentrated form over the course of months or years.
- **DUREDAS technology**-] Elan Corporation introduced the Dual Release Drug Absorption System (DUREDAS), which made use of bilayer tableting technology. Dual release, or two separate release rates of a medicine from a same dosage form, is a feature that has been specifically developed for it. An immediate release granulate and a controlled release hydrophilic matrix technology are combined into one tablet during two distinct direct compression stages.

- **Approaches for bilayer tablet**
- It consists of two drugs in same tablet having different layers. One layer is immediate release layer and other layer is sustained release layer.

- **Different types of bilayer tablet**
- Bilayer modified release tablet
- Bilayer floating tablet
- Bilayer buccoadhesive tablet

1. Bilayer modified release tablet : This type of bilayer tablet consists of two different types of release profile layers. One layer is immediate release layer in which drug will release 90% of concentration within 30 minutes. Other layer is sustained release layer where drug will release slowly up to 12-24 hrs. e.g. MetaclopramideHCl+ Ibuprofen

2. Bilayer floating tablet:This particular combination of medications, which is sensitive to stomach pH, is included in a bilayer tablet. In the stomach, one layer of the medication is metabolised, and in the intestine, another layer is destroyed.e.g. Rosiglitazone Maleate

3. Bilayer buccoadhesive tablet: Drugs with mucoadhesion and the ability to adhere to buccal mucosal membranes and sustain drug release are contained in this form of bilayer tablet.. e.g. PropanololHCl

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- **Prefomulation studies to be carried out before formulation of bilayer tablet**

➢ Solubility of drug

- Drugs that are going to be made into bilayer tablets should be tested for solubility in a variety of mediums, including distilled water, 0.1N HCl, 0.1N NaOH, ethanol, methanol, PBS pH 6.8, PBS pH 7.2, and others.

➢ Particle size determination

- There are two ways to determine particle size. Either a mechanical sieve shaker or the Malvern particle size analyser can be used to make the determination.
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➢ Bulk density

- To correctly weigh 25g of the medication, run it through sieve no. 20. Put it in a graduated measuring cylinder with a 100ml capacity.
- Note the initial apparent volume (Vo) of the measuring cylinder without disturbing it.

Calculate bulk density by the following formula:-

Bulk density = $Weightofdrug Bulk \div volume$

➢ Tapped density

- Precisely weigh 25g of the medicine, put it through sieve #20, and then pour it into a graduated measuring cylinder with a volume of 100ml.
- Measure the cylinder's initial volume (Vo), then tap it around 100 times. Next, calculate the final volume (V1).
- The formula to use to determine the tapped density is as follows:

Tapped density = $Weightofdrug \div tappedvolum$

➢ Carr's index

- It is ratio of tapped density and bulk density. It can be calculated by the formula:-

Hausner's ratio = $Tappeddensity \div Bulkdensit$

➢ Hausner's ratio:

- It is a measure for compressibility index developed by carr and Neumann. It can be calculated by the formula:-
- Carr's index = $Tappeddensity - BulkdensityTappeddensity \times 100$
-

➢ Angle of repose:

- Accurately weigh 10g of the medication. Get ready to assemble a tripod platform, funnel, and paper. Pour the medication freely through the funnel, then use a scale and pencil to determine the height and diameter of the resulting pile. The following formula can be used to determine angle of repose:

Angle of repose = tan-1 $h \div$r

➢ Drug excipients compatibility studies

- This test is run to determine the best conditions for solid-state medication storage. This procedure involved choosing various excipients and mixing them separately with the medicine in a proportion that is typically used for tablet manufacture.
- For measurement at various RH and temperatures, three mixtures of each set are made. Check for colour changes in each combination after one month under the same condition. FT-IR analysis or DSC are the primary determinants of this.

- **Formulation of bilayer tablet**: Bilayer tablet is formulated by mainly two methods:-
  - Wet granulation method
  - Direct compression method

I. **Wet granulation method :**Pass through sieve #100 after correctly weighing all medications and excipients. Get binder solution ready. In a pestle and mortar, the mixture and binding solution are wet massaged.Using sieve #10, filter the moist substance. Granules are dried. To create flowing powder after drying, combine with the aid of lubricants and disintegrants. Make tablets out of the mixture using a flat punch. method of direct compression All excipients and medications should be correctly weighed before passing through filter #100. Combine all the ingredients in a pestle and mortar, then directly compress them into tablets. cycle of bilayer tablet compression

II. **Direct compression method:**Weigh accurately all the excipients and drugs and pass through sieve# 100. Mix all the components in a pestle mortar and compress them in the form of tablet directly

- **Steps for compression cycle of bilayer tablet**
  - Filling of first layer.
  - Compression of first layer.
  - Ejection of upper punch.
  - Filling of second layer.
  - Compression of both the layers together.
  - Ejection of bilayer tablet.

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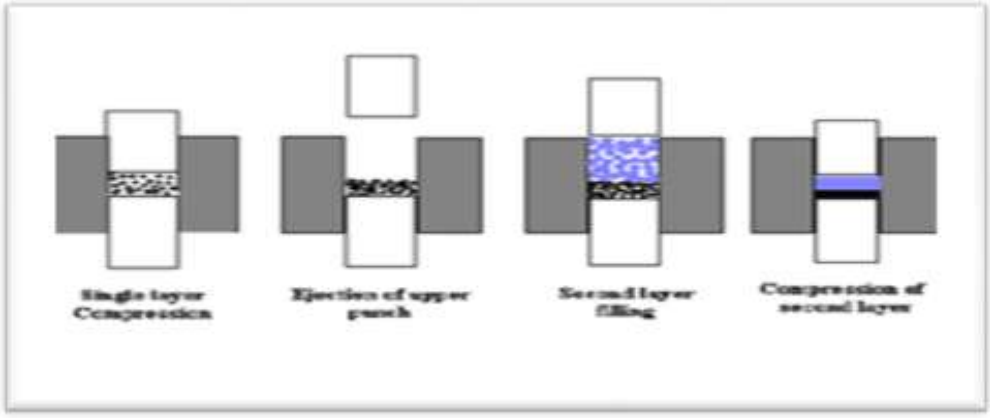

- **CHALLENGES IN BILAYER MANUFACTURING** :Conceptually, bilayer tablets can be seen as two single-layer tablets compressed into one. In Practice, there are some manufacturing challenges.
  - **Delamination:** Tablet falls apart when the two halves of the tablet do not bond completely. The two granulations should adhere when compressed.
  - **Cross-contamination**:Cross-contamination happens when the granulation of the first layer mingles with the granulation of the second layer or the other way around. It might defeat the bilayer tablet's fundamental aim. Cross contamination can be greatly reduced with proper dust collection. production output Dust collection is necessary to prevent cross contamination, yet this causes losses. As a result, single-layer tablets provide higher yields than bilayer tablets.
  - **Cost**:For a number of reasons, bilayer tableting is more expensive than single layer tableting. The tablet press is firstly more expensive. Second, in bilayer mode, the press often operates more slowly. Third, creating two compatible granulations is necessary, which requires extra effort to create, analyse, and validate the formulation.If these factors are not properly controlled or optimised, they will adversely affect the qualitative attributes of the bilayer tablets (sufficient mechanical strength to maintain its integrity and individual layer weight management), as well as the bilayer compression per se. Understanding the root causes is essential for developing a strong product and process.

- **Characterization of bilayer tablet:**

A. Appearance :

The shape, size, colour, and presence or absence of odour, taste, and surface texture of the bilayer tablet were visually identified as well as the overall look.

B. Weight variation:

Weigh 20 tablets accurately. Determine average weight of tablets. The individual weight of each tablet was compared with average tablet weight.

C. Thickness

Randomly tablet was selected and its thickness was measured by using verniercaliper scale.

D. Hardness

The hardness of tablets determines how resistant they are to shattering during storage, transportation, and handling prior to use. The Monsanto hardness tester can be used to assess the hardness of a tablet. In kg, the hardness was calculated.

E. Friability:

The strength of a tablet is gauged by its friability. The Roche friabilator can be used to determine friability. Twenty tablets are precisely weighed and put in a tumble device that rotates at 25 rpm, falling the tablets across a six-inch distance with each revolution. The tablets are weighed after 4 minutes, and the percentage of weight loss is computed.

% loss = initial weight of tablets – final weight of tablets/ initial weight * 100

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F. Disintegration time

In a disintegrating device with distilled water or another acceptable medium at 370C, 6 pills are consumed. Determine the rate at which the pill becomes soluble. It was established how long bilayer and quick release pills will take to disintegrate. Tablets intended for immediate release shouldn't take more than 15 minutes to dissolve.

G. Dissolution time

With the aid of the USP paddle equipment, the dissolution profile is assessed. The vessel is filled with 900ml of appropriate dissolving medium and kept at 370C and 75rpm. The breakup took place for almost 12 hours. At regular intervals, 5 ml of sample was removed, and 5 ml of new medium was added to the tank. For the combination medications, absorbance is recorded for each sample at particular lambda maxima.

- **Evaluation of Bilayer Tablets:**

1. General Appearance

Consumer acceptability of a tablet depends heavily on its overall design, visual identity, and overall elegance. Size, shape, colour, taste, texture of the tablet's surface, physical defects, consistency, and legibility of any identifying markings are all considered.

2. Size and Shape

Thesizeandshapeofthetabletcanbedimensionallydescribedmonitoredandcontrolled.

3. Table tthickness

Tablet thickness is a crucial element in both duplicating appearance and counting with filling machinery. The uniform thickness of the tablets is used as a counting mechanism by some filling equipment. A micrometre was used to measure the thickness of ten pills.

4. Weight variation[2]

Standard procedures are followed asdescribed inthe officialbooks.

5. Friability

The forces that frequently cause the tablets to chip, chop, or break are friction and shock. The friability test, which measures a tablet's resistance to abrasion during handling, packaging, and shipping, is closely connected to the hardness test. Usually, the Roche friabilator is used to measure it. A number of tablets are weighed and put within the device, where they are subjected to repeated shocks and rolling as they drop 6 inches with each spin. The tablets are weighed and the weight is contrasted with the original weight after this treatment has taken place for four minutes or 100 revolutions. The tablet friability is measured by the loss through abrasion. A percentage is used to represent the value.

6. Hardness

The hardness of tablets determines how resistant they are to capping, abrasion, or breakage during storage, transportation, and handling before to use.In the middle of the 1930s, Monsanto produced and presented the compact and portable hardness tester. It is currently known as the Stokes or Monsanto hardness tester. When a coil spring's force is applied diametrically to a tablet, the gadget measures the amount of force needed to shatter the tablet. The strong-Cobb Pfizer and Schleuniger instrument, which was later developed, calculates the amount of force needed to break a tablet when applied in two directions. Crushing strength—a more appropriate term for hardness—determinations are made during tablet manufacture and are used to assess whether the tablet machine's pressure needs to be adjusted. If the tablet is too soft, it might not be able to resist the handling during future processing, such as coating or packaging and shipping activities. If the tablet is too hard, it might not disintegrate in the needed amount of time to meet the dissolving standards. The crushing strength of a tablet is measured in kilogrammes, and 4Kg is typically thought to be the minimum for acceptable tablets. While chewable and hypodermic tablets are typically significantly softer (3 kg), some extended release tablets are much harder (10–20 kg), and oral pills typically range in hardness from 4 to 10 kg. Tablet density and porosity as well as hardness have been linked to other tablet characteristics. The shape, chemical characteristics, binding agent, and pressure used after compression all affect how hard a tablet will be. Hardness normally increases with the normal to range of tablets.

7 Stability Study

The ICH guideline for expedited research directs that the bilayer tablets be stored under the following conditions for a specified amount of time after being packaged in appropriate packaging.After 15 days, the tablets were taken out and examined for physical characteristics such as visual flaws, hardness, friability, and drug content.

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II. CONCLUSION

Bi-layer tablets give producers a great chance to stand apart from the competition, increase the effectiveness of their products, and safeguard against knockoffs.Bilayer layer pills, which feature two layers that are gradual release and instant release, were presented. One layer of these tablets is formulated to achieve immediate drug release, with the goal of quickly increasing serum concentration.A controlled release hydrophilic matrix, found in the second layer, is intended to maintain an effective plasma level for an extended length of time.Atorvastatin, Atenolol, Nifedipine, Aspirin, Isosorbide 5-mononitrate, Pioglitazone HCl, Gliclazide, Losartan potassium, and Trimetazidine hydrochloride, clopidogrel bisulphate are some of the bilayer pills that are made nowadays.

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