

**REVIEW ON - BILAYER TABLET**

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ABSTRACT

Over the past 30 years as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery system. In the last decade interest in developing a combination of two or more active pharmaceutical ingredient (API) in a single dosage form (bilayer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance. Several pharmaceutical companies are currently

developing bilayer tablet 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 such tablets. 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 maintained dose. Bilayer tablet is improved beneficial technology to overcome short coming of single layer tablet.

Keywords: Bilayer tablet, Approaches, Bilayer tablet presses, GMP requirement for Bilayer Tablets.

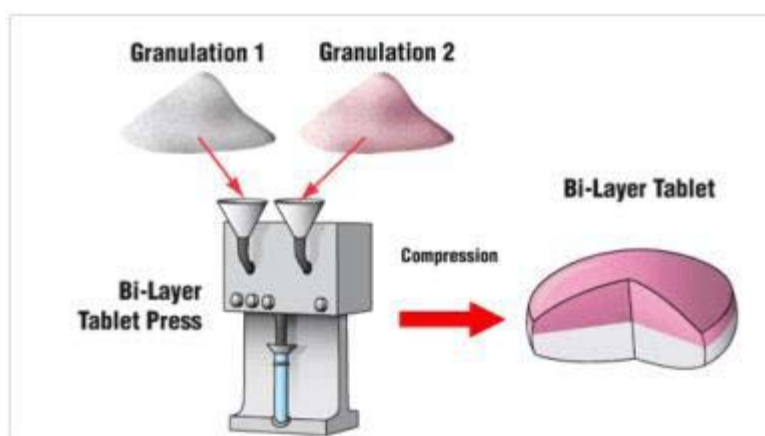
INTRODUCTION

Now a day's various developed and developing countries are moving towards combination therapy for treatment of various diseases and disorders requiring long term therapy such as hypertension, Diabetes and Rheumatoid arthritis. The problem of dose dependent side effects is minimized by combination therapies and is advantageous over monotherapy. From

last few years, interest in developing a combination of two or more active pharmaceutical ingredients in a single dosage form has increased in pharmaceutical industry.

Bi-layer tablets can be a primary option to avoid incompatibilities between APIs by physical separation. Bi-layer tablets are suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablets in which one layer is immediate release as initial dose and second layer is sustained release. There are various applications of the bi-layer tablet as it consists of monolithic partially coated or multilayered matrices.

Bi-layer tablets are tablets made by compressing two different granulations fed into a die in succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet press can be set up for two layers. More layers are possible but the design becomes very special. Bi-layer tablets are composed of two layers of granulation compressed together. They have the appearance of a sandwich because the edges of each layer are exposed. General concept of bi-layer tablet is shown in figure 1. (Shila V et al., 2013).



Generally conventional dosage forms produce wide ranging fluctuation in drug concentration in the blood stream and tissues with undesirable toxicity and poor efficiency. This factor repetitive dosing and unpredictable absorption led to concept of controlled drug delivery system.

The goal in designing sustained or controlled delivery systems is to reduce frequency of dosing or to increase effectiveness of the drug by localization at the site of action reducing the dose required or providing informed drug delivery. Primary objective of sustained release delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance.

(Divya A et al.,2011)

ADVANTAGES OF THE BILAYER TABLETS

- Bi-layer execution with single-layer conversion kit.
- Cost is lower compared to all other oral dosage form.
- Greatest chemical and microbial stability over all oral dosage form.
- Objectionable odour and bitter taste can be masked by coating technique.
- 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
- Easy to swallowing with least tendency for hang up.
- Suitable for large scale production. (GopinathC et al.,2013)

DISADVANTAGES OF BI-LAYER TABLETS

- Bi-layer rotary presses are expensive.
- Insufficient hardness, layer separation, reduced yield.
- In accurate individual layer weight control.
- Cross contamination between the layers.
- Some drugs resist compression into dense compacts, due to amorphous nature, low density nature.(Sowmya.C et al 2012)

TYPES OF BILAYER TABLETS

The term bilayered tablets containing subunits that may be either the same (homogeneous) or different(heterogeneous).

Homogenous type

Bilayer tablets are preferred when the release profiles of the drugs are different from one another. Bilayer tablets allows for designing and modulating the dissolution and release characteristics .Bilayer tablets are prepared with one layer of drug for immediate release while second designed to release drug, later, either as second dose or in an extended release manner.

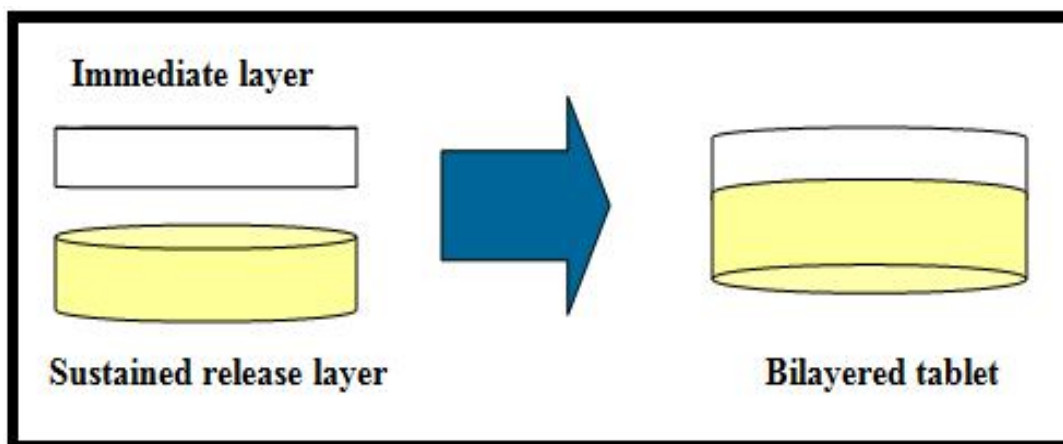


Fig.2. Bilayered tablets (same drug with different release pattern-homogenous)

Heterogenous type

Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances.

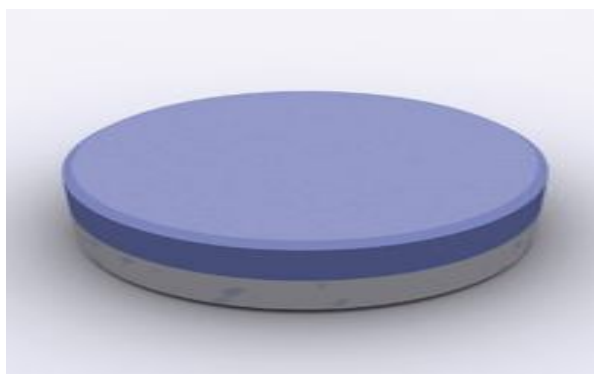


Fig3: Bilayer tablet with different drugs

Advantages

They are used as an extension of a conventional technology

- Ability to combine different release rate. IR and SR in the same tablet for chronic condition requiring repeated dosing.
- Promoting patient convenience and compliance because fewer daily doses are required compared to traditional delivery system.
- Two different drugs in the same dosage form.
- Separation of incompatible components thus minimizes physical and chemical incompatibilities.
- Solve degradation problem.
- Reduce pill burden to patient.
- Retain potency and ensure dose accuracy. (Pradeep R et al., 2013)

NEED OF BILAYER TABLETS

- For the administration of fixed dose combinations of different active pharmaceutical ingredient, prolong the drug product life cycle, buccal/mucoadhesive delivery system, fabricate novel drug delivery system such as chewing device and floating tablet for gastro-retentive drug delivery.
- Controlling the delivery rate of either single or two different active pharmaceutical ingredients.
- To modify the total surface area available for active pharmaceutical ingredient layer either by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release.
- 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) (Balaji G et al., 2013)

ADVANTAGES OF BILAYER TABLET OVER THE OTHER CONVENTIONAL TABLET

- This formulation can be used to separate two incompatible substances.
- When the two different layers of the tablet contain two different drugs, then the tablet can be easily used in combination therapy.
- It makes possible extended-release preparations with the immediate-release quantity in one and the slow-release portion in the second layer.
- In case of drugs having a low half-life, each of the two layers of the tablet respectively contain a loading dose and maintenance dose of the same and thus increase the bioavailability of the drug.
- Analytical work may be simplified by separating of the layer prior to assay.
- Two-layer tablet require less material than compression coated tablets, weight less, and may be thinner.
- The weight of each layer can be accurately controlled, in the contrast to putting one drug of a combination product in a sugar coating.
- Frequency of the dose administration is reduced which ultimately improved the patient compliance.
- For chronic condition requiring repeated dosing.
- Product identification is easy and rapid, requiring no additional step when employing an embossed and/or monogrammed punch face.

GENERAL PROPERTIES OF BI-LAYER TABLET DOSAGE FORMS

- Bi-layer tablet should have elegant product identity while free of defect like chips, cracks, discoloration, and contamination.
- Should have sufficient strength to withstand mechanical shock during its production, packaging, shipping and dispensing.
- Should have the chemical and physical stability to maintain its physical attributes over time.
- The bi-layer tablet must be able to release the medicinal agents in a predictable and reproducible manner. (Priyal N et al., 2013)

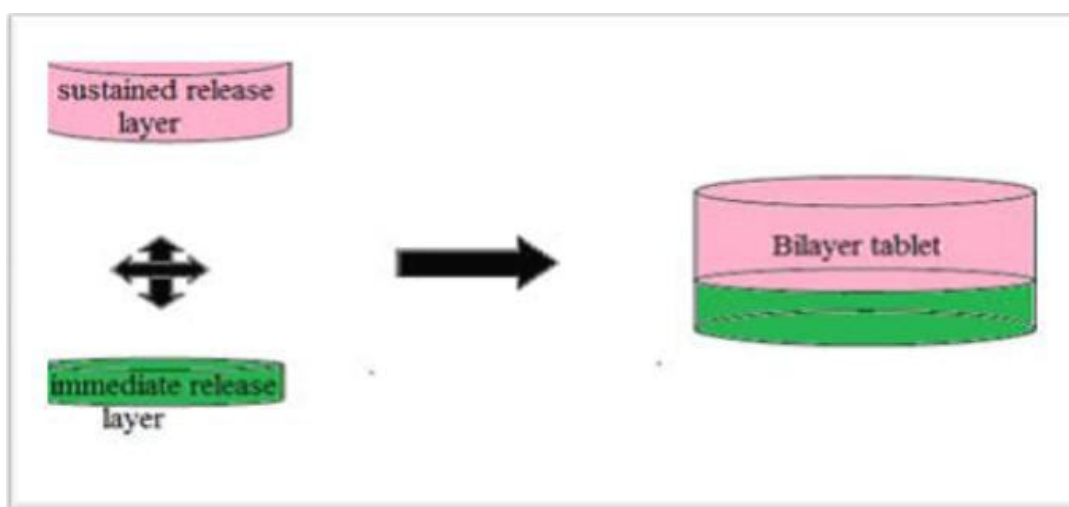


Fig 4: Bilayer tablet

VARIOUS APPROACHES USED IN THE BILAYER TABLET

➤ Floating Drug Delivery System

Floating Drug Delivery System designed to have a low density and thus float on gastric contents after administration until the system either disintegrate or the device absorbs fluid to the point where its density is such that it loses buoyancy and can pass more easily from the stomach with a wave of motility responsible for gastric emptying. The bilayer tablet is designed in such a manner that one layer gives the immediate dosing of the drug which gives faster onset of action while other layer is designed as a floating layer which floats in the stomach.

Disadvantages: It may not have the controlled loss of density alternatively required for it to eventually exit from the stomach. Floating tablets are not applicable to higher dose level of highly water soluble drugs where large amounts of polymer are needed to retard drug

release, as in case of water soluble drugs. The performance of floating formulation may also be posture dependent. A patient sitting upright may ensure prolonged gastric residence of a buoyant dosage form, whereas a supine patient might allow ready presentation of the floating dosage form to the Pylorus and thus allow rapid exit of the dosage form from stomach. Hence, floating dosage form might be expected to only have limited application.

➤ **Polymeric Bioadhesive System**

Polymeric Bioadhesive System designed to imbibe fluid following administration such that the outer layer becomes a viscous, tacky material that adheres to the gastric mucosa/mucous layer. This should encourage gastric retention until the adhesive force is weakened. These are prepared as one layer with immediate dosing and other layer with bioadhesive property.

Disadvantages

The success seen in animal models with such system has not been translated to human objects due to differences in mucous amounts, consistency between animals and humans. The system adheres to mucous not mucosa. The mucous layer in humans would appear to slough off readily, carrying any dosage form with it. Therefore, bioadhesive dosage form would appear to offer a solution for extended delivery of drug over a period of more than a few hours.

➤ **Swelling System**

Swelling System designed to be small on administration so as not to make ingestion of the dosage form difficult (e.g., 10-12 mm in diameter for round tablets, whereas less than 23 mm long and also less than 11 mm wide for an oval or capsule-shaped tablet).

On ingestion they will rapidly swell or disintegrate or unfold to a size that precludes passage through the pylorus until after release has progressed to a required degree. Gradual erosion of the system or its break down into smaller particles enables it to leave stomach. The simple bilayer tablet may contain an immediate release layer with the other layer as extended release or conventional release. (Arun D et al., 2012)

Compression steps of bi-layer tablet

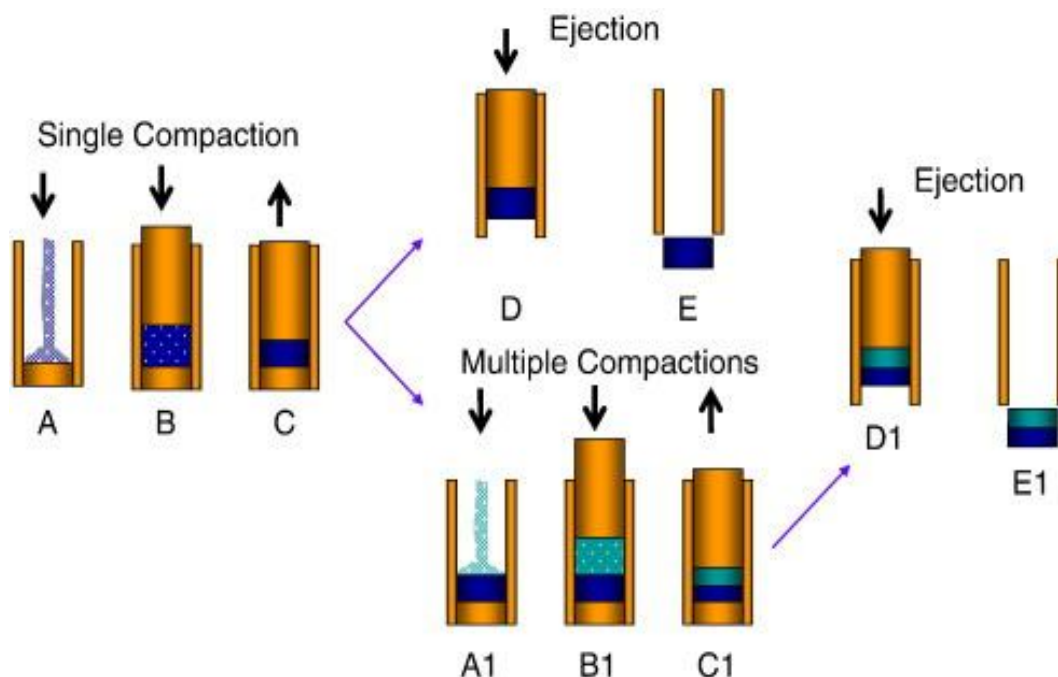


Figure-5 : Compression cycle of bilayer tablet

Various steps of bi-layer tablet formulation are as follow

- Filling of first layer.
- Compression of first layer.
- Ejection of upper punch.
- Filling of second layer.(Soham S et al.,2013)

BI-LAYER TABLET PRESS

The XM 12 Bi-layer tablet press features a retractable second layer feeder that permits automated first layer sampling at production speed. The first layer sampling capability also offers a hardening features,in which the main compression station will automatically compress the first layer tablet for in-process measurement.The two feeders are zero clearance and are configured with an integrated dust extraction manifold which cleans the die tablet and completely eliminates any potential for cross contamination. Wipcon solution available which is potent for small scale bilayer application.

The KORSCH XM 12 Bi-layer tablet press is a small-scale press which is ideal for product development, clinical trials and midrange production,The bi-layer execution, single layer single layer conversion kit and exchangeable turret offer unprecedented flexibility. The XM 12 Bi-layer tablet press offers a new standard in GMP with extreme a accessibility to the

compression zone and a combination of quick disconnects and smooth surfaces that permit fast cleaning and changeover.

The machine features a 80 KN main compression station, 5 KN tamping station, 40 KN precompression station, and a unique structural design that eliminates vibration to the head piece and base frame. Finally result is extreme reduction in the operating noise level.

(Namrata M et al., 2013)

TYPES OF BILAYER TABLET PRESS

- A. Single sided tablet press
- B. Double sided tablet press
- C. Bilayer tablet press with displacement monitoring.

A) Single-sided press

- The simplest design is a single-sided press with both chamber of the double feeder separated from each other.
- Two individual layers of the tablet produced as each chamber have gravity or forced fed with a different powder.
- When the die passes under the feeder, it is at first loaded with the first-layer powder followed by the second-layer powder.
- Then the entire tablet is compressed in one or two (pre and main-compression) steps.
- 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.



Figure 6: Single sided tablet press

Limitations of single-sided press are

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

Dwell time

Dwell time is defined as the time during which compression force is above 90% of its peak value. Longer dwell times are major factor in producing a quality tablet, especially when we compressing a difficult formulation.

B) Double sided tablet press

- A double-sided press have an individual fill station, pre-compression and main-compression for each layer.
- Most of the 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 that layer.
- Measured peak compression force (under constant thickness) is the signal used by the control system to reject out-of-tolerance tablet and correct the die fills depth when required.



Fig 7: Double sided tablet press

Limitations of compression force controlled system

- A compression force-controlled system requires a minimal compression force of several hundreds of daN.
- However, many bilayer formulations require less than 100 daN to compress first layer in order to retain the ability to bond with the second layer.
- Above 100 daN, this ability may be lost, bonding between both layers may not be sufficient, resulting in low hardness of the bilayer tablet and separation of the two layers.
- At higher production speed, the risk of separation and capping increases but can be reduced by sufficient dwell time at compression stages.

THE COURTOY R292F: “BILAYER” TABLET PRESS WITH ‘DISPLACEMENT MONITORING’

- This double-sided tablet press has been specifically designed and developed for the production of quality bi-layer tablets and provides:
- ‘Displacement’ weight monitoring/control for accurate and independent weight control of the individual layers
- Low compression force exerted on the first layer to avoid capping and separation of the two individual layers
- Increased dwell time at pre-compression of both first and second layer to provide sufficient hardness at maximum turret speed
- Maximum prevention of cross-contamination between the two layers
- A clear visual separation between the two layers
- Maximised yield.

The Courtoy-R292F: additional important features

- The R292F can be used for both single-layer double output production and bi-layer single-output tableting.
- The press is equipped with ‘air compensation’ on both pre-compression stations for ‘displacement’-based tablet weight control as described above.
- However, the R292F has several extra features specifically designed for the production of bi-layer tablets:
- The R292F has a pneumatically driven ejection cam, allowing the sampling of first-layer tablets for in-line process control and automatic weight recalibration.

- The required time to sample is extremely short to minimise powder loss.
- The time delay between sampling and re-calibration is also very short to minimise the length of the control loop.
- One powder is always re-circulated around the die table using a standard feeder with recuperation of re-circulated powder, while the other feeder is a closed type feeder.
- This closed type feeder is provided with a suitable wear plate to maximise its life expectancy.
- The R292F is equipped with several blow and suction nozzles, located at carefully determined points around the die table.
- The combined action of blowing and extracting air allows for very specific powder removal, which is vital to the elimination of cross-contamination. At the same time, powder loss is reduced to a minimum. (Jan Voegelé)

C) Bilayer tablet press with displacement monitoring

The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied pre-compression force.

This double-sided tablet press has been specifically designed and developed for the production of quality bilayer tablets and provides:



Fig 8: Bilayer tablet press with displacement (Swati A et al., 2013)

- 'Displacement' weight monitoring/control for accurate and independent weight control of the individual layers.
- Low compression force exerted on the first layer to avoid capping and separation of the two individual layers.
- Increased dwell time at pre-compression of both first and second layer to provide sufficient hardness at maximum turret speed.
- Maximum prevention of cross-contamination between the two layers - a clear visual separation between the two layers - maximized yield.

QUALITY AND GMP REQUIREMENTS

- To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the selected press is capable of:
 - Preventing capping and separation of the two individual layers that constitute the bi-layer tablet
 - Providing sufficient tablet hardness
 - Preventing cross-contamination between the two layers
 - Producing a clear visual separation between the two layers
 - High yield.
- Accurate and individual weight control of the two layers is not so easily accomplished as this article aims to demonstrate.

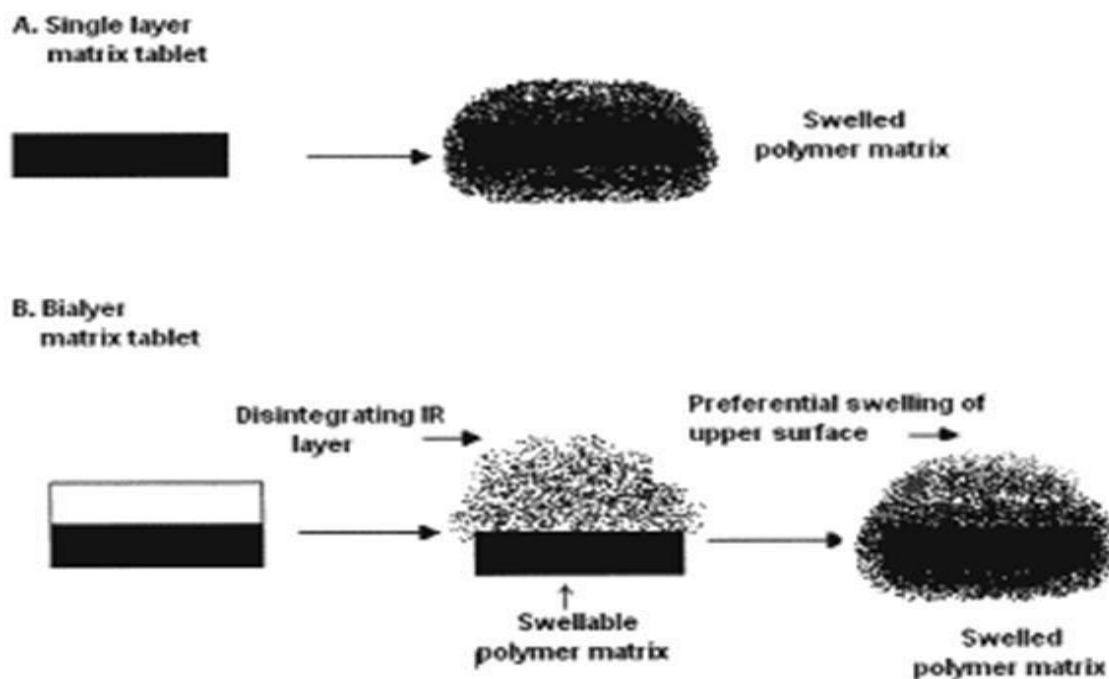


Fig 9: Drug release mechanism forms a bilayered tablet comprising an immediate release & a sustained release layer(Shweta P et al., 2013)

CHARACTERIZATION OF BILAYER TABLET

➤ Particle size distribution

The particle size distribution was measured using sieving method

➤ Photo-microscope Study

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

➤ Angle of Repose

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

$$\tan \theta = h/r$$

where h and r are the height and radius of the powder cone.

➤ Moisture Sorption Capacity

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

➤ Density

The loose bulk density (LBD) and tapped bulk density (TBD) were determined and calculated using the following formulas.

$$\text{LBD} = \frac{\text{weight of the powder}}{\text{volume of the packing}}$$

$$\text{TBD} = \frac{\text{weight of the powder}}{\text{tapped volume of the packing}}$$

➤ Compressibility

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

$$C (\%) = \frac{(\text{TD} - \text{BD})}{\text{TD}} \times 100. (\text{Sachin K et al 2011})$$

EVALUATION OF BILAYER TABLET

➤ Tablet Thickness and Size

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter was measured using vernier caliper.

➤ Tablet Hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each

formulation was measured by Monsanto hardness tester. The hardness was measured In kg/cm^2 . Other tester used to check table hardness are strong-cubb tester, Pfizer tester the Erweka tester and Schleuniger tester. (Lachman L et al., 1987)

➤ Friability

Friability is the measure of tablet strength. Electrolab EF- 2 friabilator (USP) was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed and the percentage loss in tablet weight was determined. $\% \text{ loss} = [(\text{Initial wt. of tablets} - \text{Final wt. of tablets}) / \text{Initial wt. of tablets}] \times 100$

➤ Uniformity of Weight

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

➤ Dissolution Studies

Bilayer tablets were 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 were carried 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 (900 ml) 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 were analyzed by UV spectrophotometer using multi component mode of analysis. (Arvind M et al 2013)

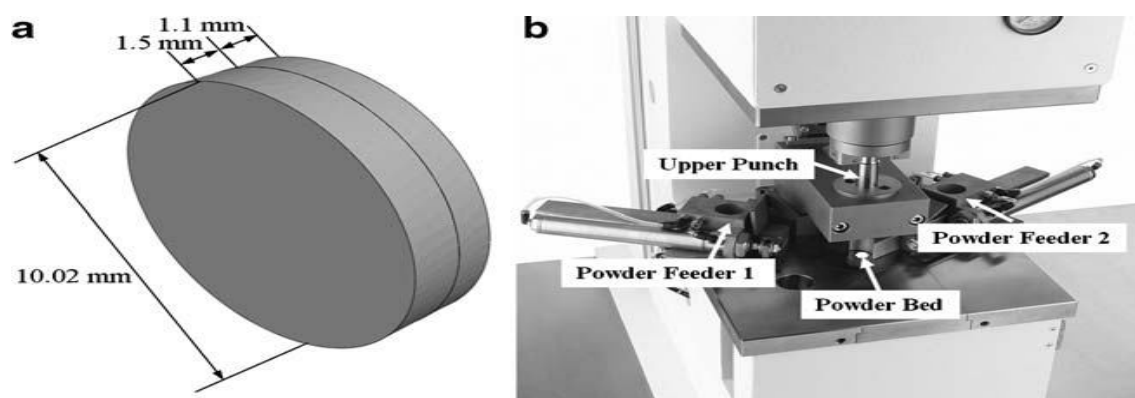


Fig.10:(a) The configuration and dimensions of a sample bilayer tablet, b the automated single-station tablet press used for compaction of the BL-tablets. (Ilgaz Akseli et al., 2011)

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