



Review Article

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Dual release tablet: Clinical outcome and evaluation

C. Rubina Reichal^{*1}, N. Thirumoorthy¹ and M. Gopal Rao²

¹Department of Pharmaceutics, Cherraan's College of Pharmacy, Coimbatore, India

²Department of Pharmaceutics, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, India

ABSTRACT

The goal in designing the bilayer tablets are suitable for the sequential release of two drugs in which one layer is immediate release as loading dose and second layer as maintenance dose. The Fixed Dose Combination (FDC) of two or more drugs in single dosage form, which is more safe and effective for single or different diseases. The bimodal release of formulation is mainly used to achieve rapid and extended release in a single dosage form. For good quality bilayer tablet, the machinery should be constructed as per GMP. The present study focuses the dual release tablets on different types of press, technology and the therapeutic benefits of bilayer tablets.

Key words: Bilayer tablet, various technologies, clinical outcome, marketed products.

INTRODUCTION

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 profile immediate release with extended release.¹

Bilayer tablet is a unit compressed solid dosage form intended for oral application. It contains two layers in which one layer having conventional or immediate release part of single or multiple actives; another layer is sustained or controlled release part of single or multiple actives. They are also called as Bilayer tablet. For the identity of two layers, different coloring agents are used.²

Bilayer tablets are novel approach in the modern era and the combination of drugs with different modes of action will often to be used to achieve control and minimize the potential dose dependent side effects. Bilayer drug delivery systems in combination of drugs with a single unit having different release profiles improve patient compliance, prolongs the drugs action, avoid saw tooth kinetics resulting in effective therapy along with better control of plasma drug level.^{3,4}

Rationale in designing bilayer tablet:⁵

- (1) To get synergistic effect
- (2) Reduce the frequency of dosing
- (3) To modify the surface area
- (4) To separate incompatible
- (5) To prepare novel drug delivery system eg. Buccal system, HDBS (hydrodynamically balanced System)
- (6) The safety margin of high potency drug can be increased
- (7) To inhibit drug interaction
- (8) Theapeutic justification
- (9) To control the delivery rate eg. Single or two different APIs
- (10) Reduce pill burden

Merits:⁵

- (1) Flexible concept
- (2) Lower cost
- (3) Easiest & cheapest form to pack
- (4) Greatest chemical and microbial stability
- (5) Elegance to the product
- (6) Used for different ailments in the same patient, with one pill eg. Co-morbid conditions

Demerits:

- (1) Difficult to swallow for children
- (2) Capping
- (3) Hardness may occur
- (4) Layer separation may occur
- (5) Drugs owing amorphous, low density character are easiest compression

Different types of approaches in Bilayer Tablet^{8,9}**(1) Floating Drug Delivery System**

Floating Drug Delivery System designed to have a low density and thus float on the gastric contents after administration until the system either disintegrates 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 dual release of bilayer tablet is designed in such way that, one layer gives the immediate dosing of the drug, gives quick or faster onset of action, the other layer is designed as a floating layer for extended release.

(2) Polymeric Bioadhesive System

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

(3) Swelling System

These are designed to be sufficiently small on administration on so as not to make ingestion of the dosage forms difficult (eg. Less than approximately 23 mm long and less than 11mm wide for an oval or capsule shaped tablet where 10 – 12 mm in diameter for round tablets). On ingestion they rapidly swell or disintegrate or unfold to a size that precludes passage through the pylorus until after drug release has progressed to a required degree. Gradual erosion of the system or its breakdown 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 or both as controlled release layer.

Various methods of fabrication of dual release Tablet:^{5,6}**OROS Push Pull Technology:**

The OROS push pull technology consists of one or more layer are essential of the drug and other layer consists of push layer fig (1). The semipermeable membrane surrounds the tablet core and also consists of suspending agent and osmotic agent.

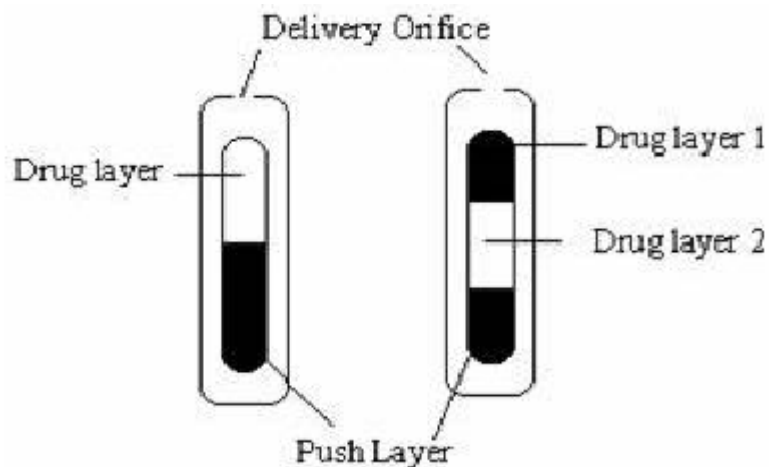


Figure 1: Bilayer / trilayer OROS push pull Technology:

L-OROS Technology:

This system used for the solubility concern Alza developed the L-OROS system Lipid soft gel product containing drug in a dissolved state is initially manufactured, then coated with a barrier membrane, next osmotic push layer, after that a semipermeable membrane which drilled with an exit orifice.

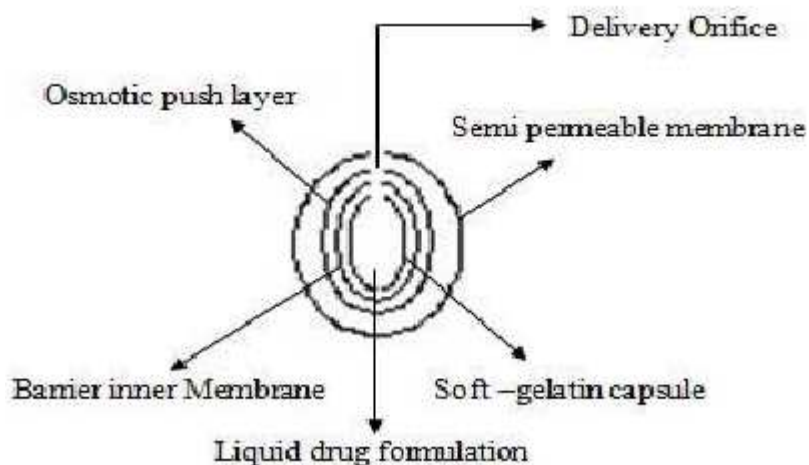


Figure 2: L-OROS TM Technology

DUROS Technology:⁷

DUROS Technology based on implant technology, which provides an alternative for the delivery of a wide range of therapeutic compounds, mostly peptides, proteins and other bioactive macromolecules. The system consists from an outer cylindrical titanium alloy reservoir (fig 3). The DUROS technology is the miniature drug dispensing system that opposes like a miniature syringe and religious minute quantity of concentrated form in continves and consistent form over months or year.

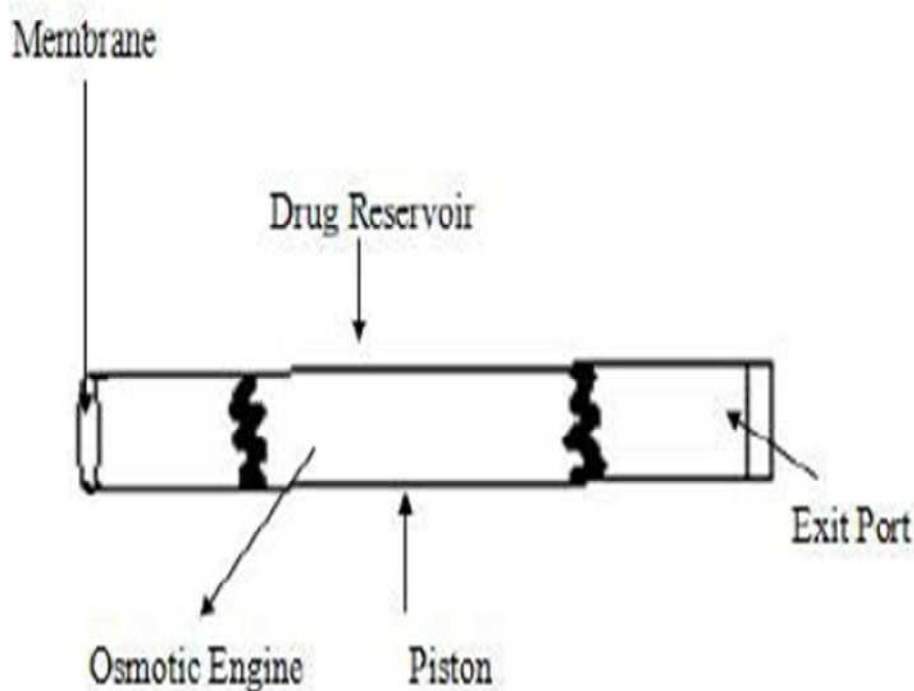


Figure 3: DUROS Technology

DUREDAS TECHNOLOGY

Duredas technology can provide immediate or sustained release of two drugs or different release tablets of the same drug in one dosage form.

The tableting process can provide an immediate release and a modified release hydrophilic matrix complex as separate layers within one tablet. The modified release properties of the dosage form are proceeding by combination of hydrophilic polymers.

Steps of compression in dual release tablets

Filling of first layer

Compression of first layer

Ejection of upper punch

Filling of second layer

Compression of both layer together

Ejection of dual release tablets

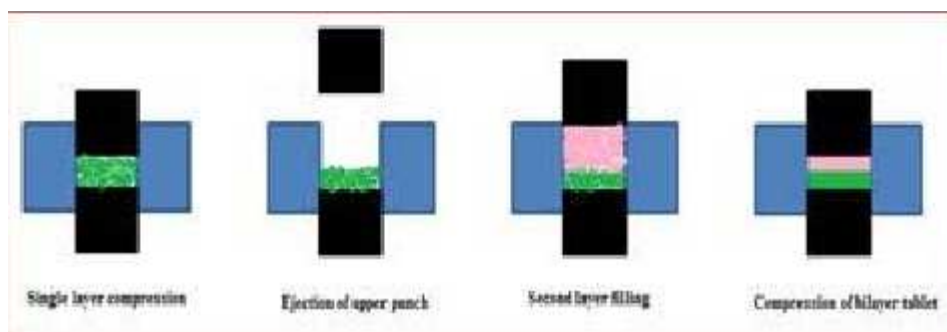


Figure 4: Bilayer tablet compression cycle

Problems occur in developing bilayer tablets:

- (1) Layer separation
- (2) Order of layer sequence
- (3) Layer weight ratio
- (4) Elastic mismatch of the adjacent layers
- (5) Cross contamination between layer

GMP & Quality of Bilayer Tablets⁵

To prepare a quality bilayer tablet, in a validated and GMP way. It is important to select a bilayer tablet press capable of:

- (1) Prevent layer separation
- (2) Maximum yield
- (3) Prevent capping
- (4) Provide sufficient tablet hardness for disintegration and dissolution specification
- (5) Produce a clear visual separation between two layers
- (6) Prevent cross contamination between two layers

Types of bilayer tablet press:

(1) Single sided tablet press⁵

It is simple with both chambers of the double feeder separation from each other. The each chamber is fed with different drug powder, to form the two individual layers. When the tablet passes under the feeder, the first layer provides powder (drug), followed by the second layer powder (drug). After compression, the bilayer is produced in one or two steps.

Single sided press has certain limit

- Weight control of each layer not monitored
- Distinct visual separation of two layers visualised
- Difficult first layer tablet sampling and sample transport in quality control, (weight and recalibration)



Figure 5: Single Sided Bilayer Press

(2) Double sided tablet press

Precompression and main compression for each layer is offered in double sided tablet press it will go for four compression stages before ejection. It has more advantages than single side press.

- * Weight control for accurate and control independent of the individual layers
- * Low compression force showed on first layer to avoid capping & layer separation
- * Maximum yield and prevention of cross contamination of two layers.



Figure 6: ADEPT Double Sided Tablet Press

(3) Bilayer press with displacement monitoring⁵

Weight control of tablet using 'displacement' is on constant force and is measure that precompression. Separation of the two individual layers is the consequence of insufficient bonding between the two layers during final compression. The basic problem, inherent to the compression force monitoring is overcome by using different weight monitoring system based upon 'displacement' and is shown in Fig.4.

The Courtoy R292F Tablet Press

The double sided tablet press mainly developed for the production of quality dual release tablets and provides

- Displacement weight monitoring / control for accurate and independent weight control of the two individual layers
- To avoid tapping and layer separation low compression force extended on first layer
- Pre compression of increased dwell time on both first and second layer provide sufficient hardness
- High prevention of cross contamination
- High yield



Figure 7: Bilayer tablet press with displacement

Clinical outcome of Bilayer Tablet:¹⁰

- (1) Drugs may produce additive / synergistic effect eg.: Anti Asthmatic Drugs
- (2) Drugs may have opposite action (reduce the side effect of each) eg.: Antacids + NSAIDS
- (3) Incompatible drugs
- (4) Drugs may have low biological half life (for modified release)
- (5) Drugs may be unstable at intestinal pH (Gastro retentive bilayer floating Drug Delivery System)

The various combinations and marketed available bilayer tablets are given in table 1&2

Table 1: Combination of drugs and clinical outcome of bilayer tablets ^{11,12}

Drug(s)	clinical outcome
Glimepride, Metformin HCl	Improve oral therapeutic efficacy with optimal control of plasma drug level
Ranitidine, Ranitidine	Improve patient compliance and provide additional effect
Valsartan, Metformin HCL	Improve patient compliance and synergistic effect
Glibenclamide, Metformin HCL	Reduce frequency of administration and improve patient compliance
Losartan Potassium, Metformin HCL	Enhance patient compliance and better disease management
Gliclazide, Metformin HCL	Prolong release upto 12hrs and improve patient compliance
Diclofenac, Cyclobenzaprine	To produce Synergistic effect in pain
Metformin HCL, atorvastatin Calcium	To develop polytherapy for the treatment of diabetes and hyperlipidemia
Cefixime Trihydrate Dicloxacillin Sodium	To produce synergistic effect in bacterial infections
Piracetam, Vinpocetin	To produce synergistic effect in alzheimer disease
Metformin HCL, Pioglitazone	To produce synergistic effect in diabetes mellitus
Atenolol	To overcome bioavailability problem and reduce the frequency of administration and side effect
Cefuroxime Axetil Potassium Clavulanate	To produce synergistic effect against microbial infections and minimize dose dependent side effects
Amlodipine Besilate Metoprolol Succinate	To produce synergistic effect in hypertension
Diclofenac Sodium, Paracetamol	To produce synergistic effect in pain
Ibuprofen, Methocarbamol	To produce synergistic effect in backpain
Losartan	To produce dual release profile
Guaifenesin	Biphasic release profile
Tramadol, Acetaminophen	To produce synergistic effect in pain
Montelukast, Levocetirizine	To improve the stability of drugs in combination and improve the patient compliance
Salbutamol, Theophylline	To produce synergistic effect in asthma
Glipzide, Metformin HCL	To avoid interaction between incompatible drugs and produce synergistic effect in diabetes
Amlodipine, Atenolol	To produce synergistic effect in hypertension
Rifampicin, Isoniazid	To improve the patient compliance
Misorostol, Diclofenac	To minimize contact between drugs
Aspirin, Isosorbide 5-mono nitrate	Use in the treatment of pain fever and inflammatory conditions and improve the patient compliance
Granisetron HCL	To overcome bioavailability problems and reducing side effects

Table 2: Marketed Bilayer Tablet in India ^{5,8}

Brand Name	Name of the Drug	Manufacturer
Clarinox – D	Desloratadine / Pseudoephedrine Sulphate	Merck & Co.
Ditropan XL	Oxybutynin Chloride	Alza Corporation
Augmentin	Amoxicillin / Clavulanate	Janssen Pharmaceuticals
Zyrtec – D	Cetirizine HCL / Pseudoephedrine HCL	Dr. Reddy's Labs
Cipro	Ciprofloxacin	Pfizer Laboratories
Istamet	Sitagliptin, Metformin Hydrochloride	Ranbaxy Laboratories Ltd.
Volise – M	Voglibose, Metformin Hydrochloride	Ranbaxy Laboratories Ltd.
Gluconorm	Glimepride, Metformin Hydrochloride	Lupin Pharmaceuticals
Pioglu	Pioglitazone, Metformin Hydrochloride	Emcure Pharmaceutical Ltd.
Alprax Plus	Sertraline, Alprazolam	Torrent Pharmaceuticals Ltd.
Diamicon XRMEX500	Gliclazide, Metformin hydrochloride	Sedia Pharmaceuticals (India) Pvt. Ltd.

Characterization in Manufacturing Process

Manufacturing process of tablet such as wet granulation and roller compaction and presence of binders increases the level of complexing in understanding the critical factors governing compression and tablet breaking force. During manufacture and storage, tablet breaking force should be observed. The critical material attributes of individual components final blend and the tablet press has large effect on manufacturing of tablets. The tablet precompression force, velocity of punch, dwell time, consolidation time relaxation time etc. effect quality of tablet, but tailored release profile of active pharmaceutical in gradient bilayer tablet have increasing interest.

In manufacturing aspects

Skipping first layer compression:

Number of compression manufacturing of multilayered or bilayered tablet is equal to the number of layers. If first layer is not compress adequate, it will lead to mixing of granulate of both layer migration of granules to periphery of die which may lead to cross contamination. A clear demarcation between the two layer is desirable since it is not only visual appealing but also assures that there is no cross contamination.

Tablet breaking force

According to the current USP, tablet breaking force is the force required to cause the tablets to break in a specific plane. The tablets are generally placed between two platens, one of which moves to apply sufficient force to the tablet to cause fracture. For conventional, round (circular cross section) tablets, loading occurs across their diameter (sometimes referred to as diametrical loading), and fracture occurs in that plane. Tensile strength provides a more fundamental measure of the mechanical strength of the tablet and it considers geometry of the tablet. Tensile strength is calculated by the following. $Tensile\ strength = \frac{2F}{\pi Dh}$ where, F is the load required to break the tablet diametrically (as opposed to delaminating or capping), "D" and "h" are tablet diameter and thickness, respectively. Thus, tensile strength estimates force per unit area of the tablet at breakage. This equation is applicable only for the tablets that have flat surface. For tablets that do not have flat surface, curvature needs to be considered while calculating the surface area. It is well documented that the mechanical strength of a tablet can be generally characterized by measuring the tensile strength using the compression test introduced by Fell and Newton (1970). In case of a matrix tablet, the impact of components properties, such as particle size and shape, effective contact surface area and tablet porosity on the tensile strength is well documented. To simplify the process, alternate approaches of determining adhesion strength as a measure of binary tablet performance have been developed and reported in the literature. An apparatus to measure the shear forces needed to separate the layers in the radial direction and relate these forces as a measure of adhesion strength was reported. Although measurement of tensile strength is appropriate for assessing the tablet strength; pharmaceutical firms tend to measure the tablet breaking force, which is essentially the load to break the tablet. Another measure for mechanical strength is the crushing strength-friability ratio (CSFR). Regardless of how the tablet is evaluated for its strength, a measure to assess this critical attribute must be fully evaluated and the choice of the test method must be supported by the formulation and the manufacturing process. The integrity of the tablet needs to be assessed during the stability studies to confirm that aging and environment have not negatively influenced the adhesion of the layers.

Effect of Lubrication

First layer is mostly uniform smooth and less rough lubricant affects the interfacial interaction between the first layer and the second layer. The tablet surface smoothness increases the concentration of lubricant like magnesium stearate. In order to achieve a better interfacial interaction between the layers, relatively low lubricant concentration and low compression forces are required. Adding lubricant punches and dies helps in manufacturing quality tablets.

Coating

Often multilayer tablets are coated to increase elegance, protect core tablet and to control drug release. For avoiding layer separation during the coating process it is important to know co-efficients of thermal expansion so if layer separation occurs it is recommended that layer is reformulated in such a way having same thermal coefficient of expansion.

Stability

The stability studies are performed after and during manufacturing process to check integrity of tablet throughout shelf life of formulation. This study must be performed under conditions as per ICH guidelines. It is also recommended to perform drug-drug, drug-excipients drug-polymer interaction, humidity and effect of heat on bilayer tablet.

***In vitro* Dissolution Performance**

The *in vitro* dissolution testing requirement of the bilayer tablets will vary based on the intended dosage design and the physico-chemical characteristics of the drug in each layer. This variability poses special challenges in the development of a meaningful dissolution procedure for bilayer drug product, especially if drugs with different water solubility are incorporated in the bilayer tablets. In general, attributes such as rate of swelling and rate of water uptake need to be assessed for the bilayer tablets. For example, if the goal of bilayer immediate tablet is to deliver two incompatible API, then the separation of these layers in the dissolution media may be of no significance as this would not have any impact on the product performance (in vivo). However, if the bilayer tablet is a modified release product, with the design feature to control the release rate of the API layer by compacting with placebo layer, the integrity of the layers in the dissolution media is critical to the performance of the drug product (in vivo). In the case of bilayer drug products, a biorelevant dissolution test conditions would be more meaningful in evaluating product quality and product performance. For example, *in vitro* dissolution testing of bilayer tablet made with water insoluble APIs need extensive use of simulated fluids on both fresh tablets and the long-term stability samples. Having a sensitive, reliable and discriminating *in vitro* dissolution procedure to determine the product quality and to predict bioavailability is of primary interest to the agency. It is recommended that all studies done for the development of the dissolution method must be included in the filing to support the final method that will be used for release and stability of the drug product. In general, development of a meaningful dissolution procedure for APIs with limited water solubility is more challenging than for the drug product with a high water solubility API. Having both classes of drugs in the same unit presents additional challenges to both the pharmaceutical industry and the regulatory agency. To measure the *in vitro* drug release performance of the bilayer drug product, well established techniques can be used to achieve adequate dissolution by understanding the solubility difference of the APIs (where applicable), use of relevant and appropriate amount of surfactants, composition and volume of dissolution test medium, pH, type of apparatus and rate of agitation.

Challenges involved in manufacturing of Bilayer tablets**Delamination**

Both layers do not adhere adequately with each other, may be due to increase concentration of lubricant. The two granulations should adhere when compressed.

Cross Contamination

Cross contamination occurs, when the granulation of the first layer intermingles with second layer or vice versa. For the prevention of cross contamination proper dust collection is important.

Product Yield

Losses occur by collection of dust. Due to this, bilayer tablets have lower yields than single layer tablets.

Cost and Time Consumption

Bilayer tablet press is costly, and the press runs more slowly. More time spent on formulation development, validation and process development.

Evaluation of Bilayer Tablet**Particle size distribution**⁶

Particle size distribution will be measured by using Sieving Method

Angle of Repose:

The angle of repose of API powder will be carried out by funnel method. Accurately weighed powder blend is taken in a funnel. Height of the funnel is adjusted in such ways that tip of the funnel just touches the apex of the powder

blend. The powder blend is allowed to flow through the funnel freely onto the surface. The diameter of the powder cone is measured and angle of repose will be calculated using the following equation;

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

where, θ - is the angle of repose; h - height of the powder cone; r - radius of the powder cone

Bulk Density

Accurately weigh 20 gm of the powder, which is previously passed through 20# sieve and transferred in 100ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume. Calculate the apparent bulk density in gm/ml by the following formula.

$$\text{Bulk Density} = \text{Weight of powder} / \text{Bulk volume}$$

Tapped bulk density

Accurately weigh 20 gm of the drug, which is previously passed through 20# sieve and transferred in 100 ml graduated cylinder. Initial volume is observed. The cylinder will be tapped initially 100 times and measure the tapped volume to the nearest graduated units. The tapping can be repeated additional 750 times. Again the tap volume is measured to the nearest graduated unit.

Calculate the tapped bulk density in gm/ml by the following formula:

$$\text{Tapped density} = \text{weight of the powder} / \text{Tapped volume}$$

Compressibility index and Hausner's ratio

The Compressibility Index of the powder blend is determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material.

$$\text{Carr's Index (\%)} = [(TBD - LBD) \times 100] / TBD$$

$$\text{Hausner's ratio} = TD / BD$$

where, TD – Tapped Density; BD – Bulk Density

Moisture Sorption Capacity

Disintegrates may have capacity to absorb moisture, which affects the ... moisture sensitive drugs.

The Moisture Sorption Capacity test was performed by (1 g of disintegrate uniformly distributed in petri-dish) stability chamber at $37 \pm 1^\circ \text{C}$ and 100% R^H for 2 days and measure the amount of moisture uptake.

General appearance^{5,6,13}

The general appearance of tablets is visual identity and overall elegance is essential for consumer acceptance for the production process.

Size and Shape

The shape and dimensions of compressed tablets are determined by the type of tooling during the compression process.

Thickness and Diameter

The diameter of the tablets is determined with a Vernier Caliper (or) Screw Gauge

Weight Variation Test

For Weight Variation Test, twenty tablets are selected randomly and the average weight is calculated thereafter the weight variation is calculated and weight variation is compared with IP standard.

Friability

Friability will be measured by taking randomly 10 tablets which is weighed and placed in a Friabulator (Roche Friabilator) and rotated at 25rpm for a period of 4 minutes. After resolution, the tablets can be dusted and weighed.

Friability is calculated by the following formula.

$$\text{Friability} = \frac{W_1 - W_2}{W_1} \times 100$$

where W_1 = Weight of the tablets before test, W_2 = Weight of the tablet after test

Hardness

The hardness of the tablet will be carved out using Monsanto type hardness tester. The hardness of the tablet Kg/Cm² is measured.

Assay

The assay can be evaluated using validated analytical techniques to ensure the quality of the formulation.

In-vitro Dissolution Studies

The bilayer formulations 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. The *in-vitro* drug release studies are carried out using USP dissolution apparatus type-II at specified rpm (or) the procedure mentioned in official monograph.

Stability Studies¹

Stability study of the bilayer tablet can be evaluated as per ICH guidelines Q1C.

Table 3: Recommended Long Term and Accelerated Storage Conditions

Study	Storage Condition	Minimum Time Period
Long term	25°C±2°C / 60% RH ± 5% RH	12 months
	30°C±2°C / 65% RH ± 5% RH	
Intermediate	30°C±2°C / 65% RH ± 5% RH	6 months
Accelerated	40°C±2°C / 75% RH ± 5% RH	6 months

Drug Release Kinetics¹⁴

The bilayer tablet formulation, drug release profile to be assessed for release kinetics Zero order, First order, Higuchi, Korsmeyer, etc and is used to obtain drug release mechanism. All the release kinetics is carried out by appropriate statistical analysis.

Zero Order

Cumulative amount of drug released Vs time

First Order

Log cumulative percentage of drug remaining Vs time

Higuchi's

Cumulative percentage of drug released Vs Square root of time

Korsmeyer's

Log cumulative percentage of drug released Vs log time

CONCLUSION

This article explains the novel approach of dual release of bilayer tablet and technology which gives more clinical outcomes than conventional tablets. It concludes that, the Fixed Dose Combination Therapy is important in the modern era for various disease and disorders such as hypertension, diabetes, inflammatory and asthmatics. Bilayer tablet has been done with different or various combination, which is useful for different ailments. Thus bilayer formulation is safe, convenience dosage form and greater advantages to both patient and clinician that it may be administered as a single tablet in once a day. Bilayer tablet is quality and GMP requirements can vary widely.

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