International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 8S, 2025
https://www.theaspd.com/ijes.php

Bilayer Tablets: An Innovative Approach for Potential Drug Delivery System

Unnati Rajput[1], N. G. Raghavendra Rao[2]*, Anuj Pathak[3], Ridhima Sharma[4] and Pratibha[5]

[1,4,5]PG Research Scholar, KIET School of Pharmacy, KIET Group of Institutions, Delhi-NCR, Muradnagar, Ghaziabad-201206, U.P., India.
[2,3]Department of Pharmaceutics, KIET School of Pharmacy, KIET Group of Institutions, Delhi-NCR, Muradnagar, Ghaziabad-201206, U.P., India.

*Corresponding author: Dr. N. G. Raghavendra Rao, Professor, KIET School of Pharmacy, KIET Group of Institutions, Delhi-NCR, Ghaziabad; Email: raghavendra.rao@kiet.edu and drngraghu@gmail.com

Abstract: *Over the past three decades, focus is increased in field of sustained, controlled or delayed release drug delivery system because of their advantages over the conventional drug delivery system. The controlled release mechanism has entered a new era with the bilayer tablet. Bilayer tablet technology, which has a controlled release layer for maintenance doses and an immediate release layer for loading doses, aids in the separation of two incompatible substances. To release the medication at an interval other than just after delivery, a delayed-release dosage form is used. These tablets are used as advanced technique to subdue the problem of conventional single-layered tablet because they improved bioavailability of drug and fewer doses are needed. Bilayer tablets is an innovative formulation, which allow the controlled drug release, targeted delivery and combination therapies. They are mainly used to manage the chronic diseases, such as diabetes and hypertension. Many times, people with hypertension find it difficult or impossible to manage their blood pressure with just one medication or a drug. It has been shown that mono-therapy is very useful in treatment of patients with type 1 hypertension but it did not shown the desired therapeutic effects in some patients or with the type 2 hypertension patients, therefore combination of an antihypertensive drugs is required to achieve a desired therapeutics effects and the different drugs are combined to formulate a bilayer tablet for treating a hypertension. A combination of two or more antihypertensive drugs is significantly more successful or effective at lowering blood pressure than either one would be alone. This is due to the complementary types of action of the drugs. The introduction of techniques, advantages of the bilayer tablet, its components, and its benefits were the main topics of this review article. It also provided an explanation of the product quality.*

Keywords: *Bilayer tablets, techniques, tablet press, controlled drug release, delayed release, enteric-coated.*

1. BILAYER TABLET INTRODUCTION

In the preceding decade, a great deal of attention being paid to the commercialization of novel drug molecules which accelerated the emergence of sustained or controlled drug delivery system, these new therapeutic compounds have been combined and grown to combat a variety of diseases that call for varying dosing schedules (1,2). Many developed and underdeveloped nations are now considering combination therapy, to treat conditions like diabetes, cardiovascular disease, and hypertension that call for long-term treatments (3). Over 90% of contemporary formulations are intended for oral ingestion. This demonstrates how popular this formulation type is worldwide, which is why the majority of scholars or researchers decide to addresses this. Its objective is to decrease frequency of doses (4). A bilayer tablet is introduced and one of its layers aims for a quick increase in serum concentration and is made to ensure the drug's instant extraction. A hydrophilic matrix with regulated release makes up its second layer, which provide an efficient plasma level for a long time (5).

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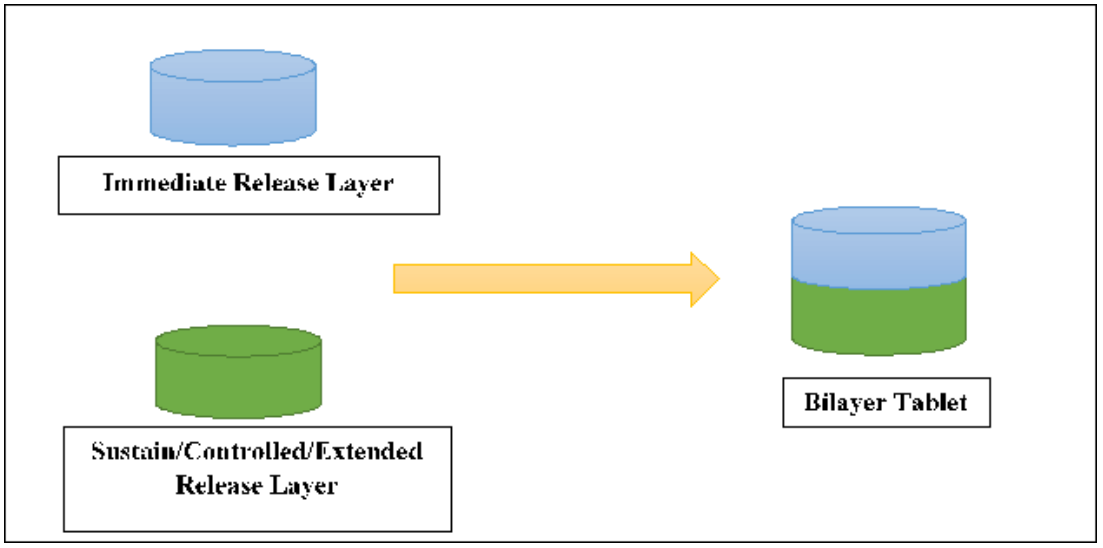

Fig 1: Bilayer Tablet

1.1 TYPES OF BILAYER TABLETS

HOMOGENEOUS BILAYER TABLETS

- It contain same medication in two layers, although their release profiles differ.

HETEROGENEOUS BILAYER TABLETS

- It can be used to constantly release two drugs together or to separate two incompatible substances (6).

1.2 NEED OF BILAYER TABLET

- In order to provide fixed dosage combinations of various APIs with dual release.
- For the development of innovative methods, such as gastro-retentive and buccal/muco-adhesive delivery systems. It helps to control how quickly one or two drugs delivers.
- To create a swell able/erodible barrier for modified release, one or two active layers should be positioned between bi-layer tablets so that the active ingredient layer get more surface area.
- By using the property of another layer, this facilitates controlled release of an API from a single layer, allowing two incompatible APIs to be combined in a single dosage (7, 8).

1.3 OPTIMAL CHARACTERISCTICS OF BILAYER TABLET

- During production, transportation, dispensing and packaging, a bilayer tablet should be strong enough to withstand mechanical force.
- Free from chips, cracks, discolorations, and contaminants.
- Elegant appearance.
- It ought to possess the physical as well as chemical stability so that the API doesn't change and physical properties should be maintained throughout life.
- It should releases reliably and consistently its drug components. (9, 10).

1.4 ADVANTAGES AND DISADVANTAGES OF BILAYER TABLET

ADVANTAGES	DISADVANTAGES
• By physically separating APIs, it helps prevent chemical interaction. • Inexpensive in comparison to alternative dose forms. • The highest level of microbiological and chemical stability when compared to other oral dosing methods. • Coating technology can cover up offensive tastes and smells. • Bilayer tablets eliminate the need for repetitive dosing that comes with traditional dosage forms. • Provide the least amount of content uniformity and the highest level of precision. • Simple to swallow, with few hang-up issues. • Smaller, lighter, and less expensive to carry and remove (11, 12). • It maximize the effectiveness of a combination of two medications by preventing direct contact between them. • The potential application of feed granules for a single entity. • Better patient compliance results in more effective medication regimens. • Compared to a typical delivery system, fewer daily doses are needed, which improves patient compliance. • Keep things stable chemically and physically. • It is simple to identify the product (11, 13).	• Difficult for kids and unconscious or paralyzed individuals to chew and swallow. • A number of drugs are amorphous and low density, making them difficult to condense into dense compacts. • Drug that is sensitive to the surroundings, has a bad smell, or is a bitter testing medication may need to be encapsulated or coated. • Inaccurate weight management for individual layers. • Inter-layer cross-contamination (14).

1.5 PROCEDURES USED IN THE PRODUCTION OF BILAYER TABLETS

The bilayer tablet is made up with a two layer of drugs or APIs, the API can be same or can be different in both the layers, first layer of tablet releases drug instantly, while the other layer releases later, as an extended-release version. Technique of making tablets with two incompatible APIs is to compress the inert layer between the two incompatible drugs layers so that the contact between the layers will be lessen (15).

1.5.1 Compaction:

Some specifications, like the mechanical strength and drug release profile, are necessary for creation of a bilayer tablet, however formulators find it difficult to achieve these requirements.

The materials compaction is influenced by consolidation and compression:

- **Compression**: It is a process of eliminating voids by applying mechanical force to materials to bring particles closer together to reduce bulk volume is known as compression. Procedures for Compressing Bilayer Tablets:

i. Compaction and die filling of the first layer.

ii. The major stress transmission characteristic is indicated by the initial layer compaction.

iii. Initial layer density profile prior to final layer die filling.

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iv. Compaction and die filling for the final layer.

v. Compaction of last layer displaying main profile of stress transmission.

vi. The bi-layer tablet's density profile prior to ejection.

vii. A bilayer tablet is ejected (16, 17).

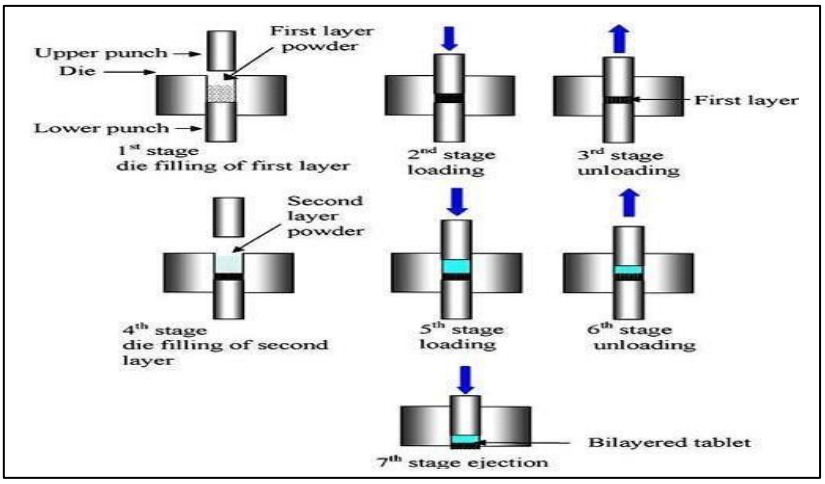

Fig 2: Preparation of bilayer tablet compaction

- **Consolidation:** It is the characteristic of the substance whereby its mechanical strength is enhanced because of inter interaction of particles. In bilayer tablet compression force was a significant element which affect the delamination of tablet, the first layer compression force need to be monitored to prevent from delamination (18, 19).

1.5.2 The importance of GMP and quality: According to Good Manufacturing Practices, to manufacture a bi-layer tablet of an excellent or high quality, the chosen tablet press must be able to:

- Creating a distinct visible division between the two layers of drugs.
- Offer a high yield.
- Provide adequate tablet hardness.
- Distinct and precisely regulate the both layers weight.
- Prevention from the capping and separation.
- Preventing the two layers of drugs from becoming contaminated (20).

1.6 OBSTACLES IN THE BILAYER TABLET MANUFACTURING PROCESS

However, despite the previously mentioned benefits offered by the bi-layer technology, several problems related to compression and manufacturing processes are stated in the literature of past years.

The main hindrances include:

1) In accurate weight control for individual layers (21).
2) Cross-contamination among layers (22-26).
3) Inconsistency in the elasticity modulus of layers that are adjacent (27).
4) A lower manufacturing yield and a propensity for successive compacted layers to delaminate (separate different layers) at the non-planer interface (28).
5) A low dosage paired with an uneven layer weight distribution (29).

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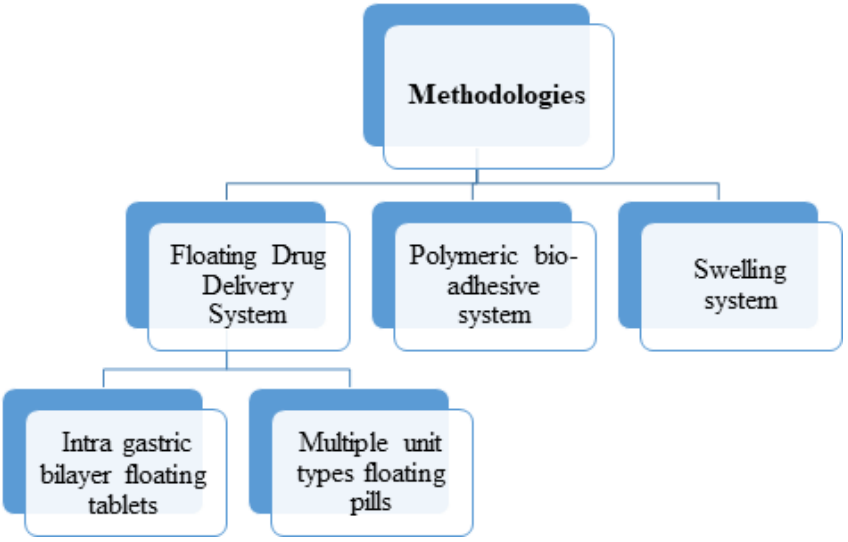
6) Inadequate hardness (30).
7) Long-term chemical and physical stability over the course of the shelf life.
8) Large pill size, which may affect how easily the unit dose is swallowed.
9) The effect of humidity or temperature on adherence of layers while being stored (31).

To overcome the above obstacles or hindrances, a concentrated effort must be made to address the following areas pertaining to:

1) Parameters for bilayer processing and material properties.
2) The first layer compression force is optimized.
3) Figuring out each layer's mechanical characteristics.
4) Measuring and comprehending the elements that lead to delamination.
5) Maximizing the layers' interfacial adhesion.
6) Evaluation of the effects of the layer weight ratio and layer sequence.
7) Choosing suitable tablet press for bilayer tablet with reliable weight-control delivery systems (30, 32, 33).

2. DIVERSE METHODOLOGIES FOR BILAYER TABLETS



2.1 Floating Drug Delivery System (FDDS)

FDDS is designed be buoyant above the contents of stomach due to their decreased density. When this type of system is given, they will continue to do so until the fluid is absorbed by the device, lowering its buoyancy and density so that it can easily exit the stomach and causes the stomach to empty. One layer is intended to deliver an immediate dosage of the medication, which ensures a quicker onset of action, and a floating layer (second layer), on the other hand floats inside the stomach (3, 13,).

Example: Indomethacin, Furosemide, Cefuroxime axetil, Atenolol, Lovastatin (34).

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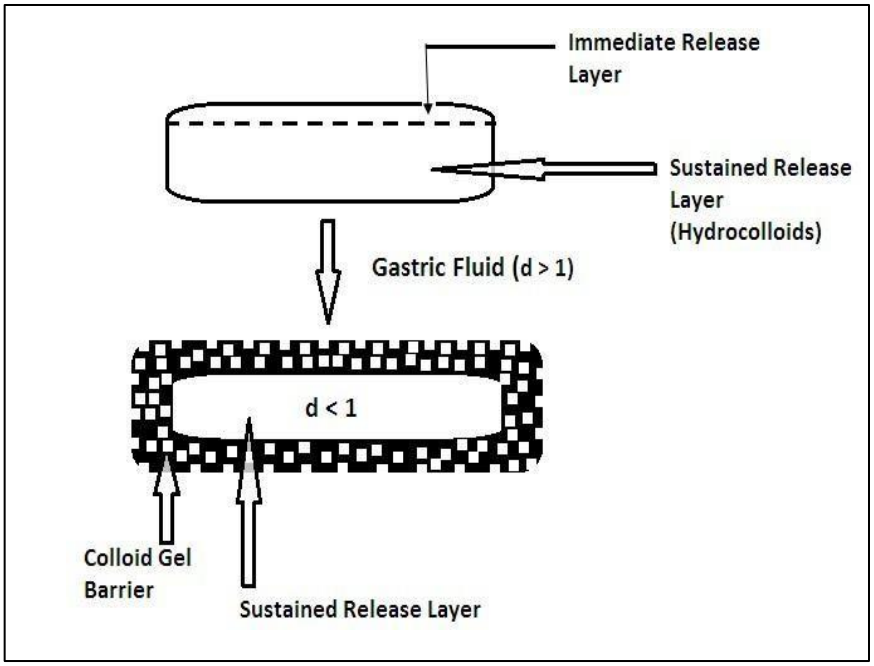

Fig 3: Floating drug delivery system

Advantages and Disadvantages

Advantages	Disadvantages
✓ Increased bioavailability ✓ Sustained delivery of medication ✓ Decreased frequency of dose ✓ Targeted treatment for upper gastrointestinal tract conditions ✓ Less variation in drug concentration ✓ Enhanced receptor activation selectivity (18, 35).	✓ Use of high dose of water soluble drugs is not possible or recommended. ✓ They may not regulate density loss. ✓ Alignment may also affect how well a floating formulation works. Therefore, it is reasonable to assume that the applications of floating dosage forms will be restricted.

Types of FDDS:

2.1.1 Intra Gastric FDDS: The two main layers of this system are the immediate layer, which releases the first dose of medication and rapidly affects the region of interest, and the sustained release layer, that creates a barrier of gel around the surface of tablet, this barrier is made by absorbing the gastric fluid by a bilayer tablet. Since of the gel barrier, a medication floats in the stomach since it is less dense than gastric juice.

2.1.2 Multiple Unit Types FDDS: The double-layered seeds that creates this system have an enlarged or sustained release. Effervescent agents make up the inner layer chemically, whereas the swellable membrane layer makes up the outer layer. Such tablets initially sink in a solution at normal temperature, but because of their low density, they expand up like a balloon and float on the surface (35).

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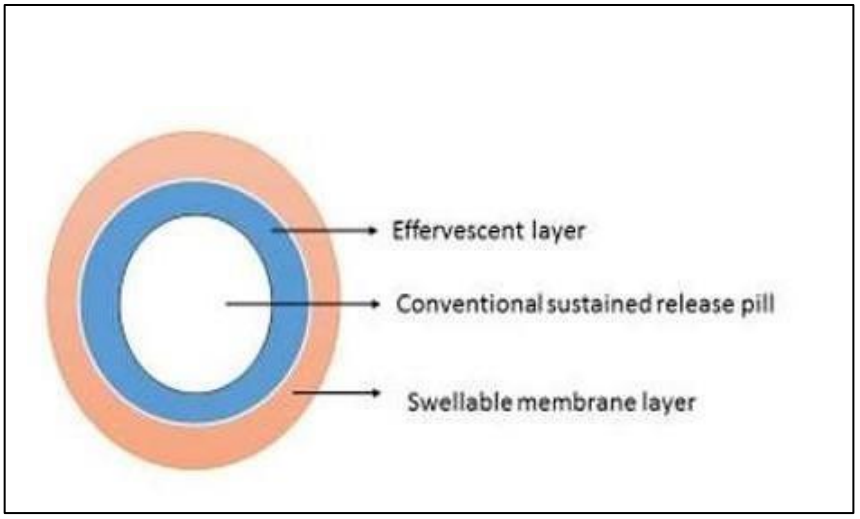

Fig 4: Oral FDDS in several units

2.2 Polymeric Bio-adhesive System

This system absorb the liquid once it is delivered. After then, the outer layer thickens and sticks or adhere to mucus membrane of stomach. In order to tilt the adhesiveness, this promotes stomach preservation. These have two layers: one for instant dosage and the other with bio-adhesive qualities (36).

Example: Propranolol HCL, Famotidine (34).

Disadvantages:

- ✓ Human mucous membranes can easily shed and carry drugs with them.
- ✓ The device sticks to mucous rather than mucosa (37, 38).

2.3 Swelling System

A formulation in a swelling system swells as it comes into touch with bodily fluids, like gastrointestinal fluids. These are intended to be much smaller. Soon after ingestion, they break apart, swell and stops it passing from pylorus till release of drug is increased to proper level. After proper release of drug start, the system eventually breaks down in small fragments and escape the stomach. While the other layer system swells and releases the leftover drug over time, guaranteeing extended action, the first layer can provide fast release (39, 40).

3. VARIOUS BILAYER TABLET TECHNIQUES

3.1 OROS ® Push-Pull Technology

This technique usually has a number of layers, first layer contain the APIs, followed by two three others and the push layer at the bottom. The drug layer is prepared by APIs and a small number of excipients and are constituted of a weakly soluble substance. Additionally, an osmotic and suspending agent might be included. Tablet core and surrounds are kept apart by a semipermeable layer (41-46).

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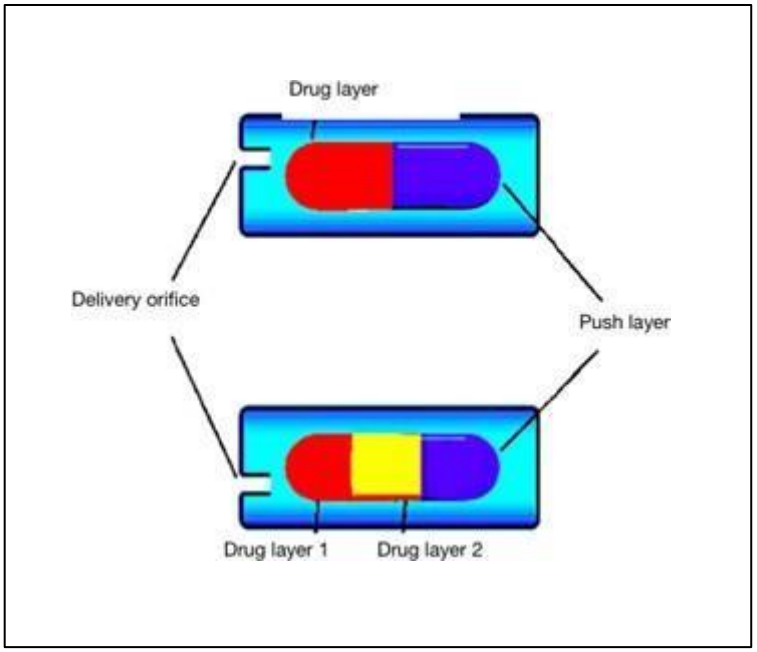

Fig 5: Osmotic-Controlled Release Oral Delivery System

3.2 L-OROS Tm Technology

Delivering insoluble medications and macromolecules is especially well suited for a liquid formulation and this technology solve the solubility problem. ALZA is the maker of this technology. Prior to the semipermeable membrane being pierced to form an exit canal, the drug was first covered with a barrier membrane, then push layer made up of osmotic agent. Continuous distribution of liquid drug formulation and enhanced drug bioavailability were the goals of the L-OROS system's design (47-50).

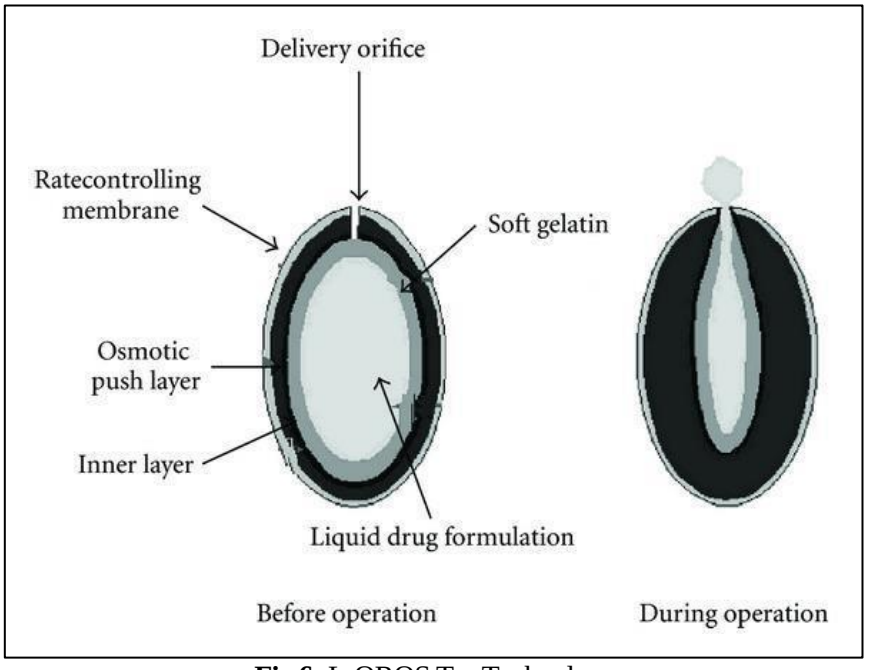

Fig 6: L-OROS Tm Technology

3.3 DUROS Technology (Miniature drug dispensing technology)

The distribution of many therapeutic components, such as proteins, peptides, and other biochemical substances, can be replaced by this implant-based technology. It functions in the same way of a tiny needle which dispenses drug steadily and continuously in a concentrated form gradually and

continuously for a lengthy duration. DUROS made up of an exterior reservoir made of titanium alloy that is cylindrical. With its great impact strength, this reservoir shields molecules of drug from the enzymes and make them resistant. With this device, a semipermeable membrane allows water to enter one end of the cylinder, while a port at the other end delivers the medicine at a regulated rate suitable for the particular therapeutic agent (51, 52, 53, 15).

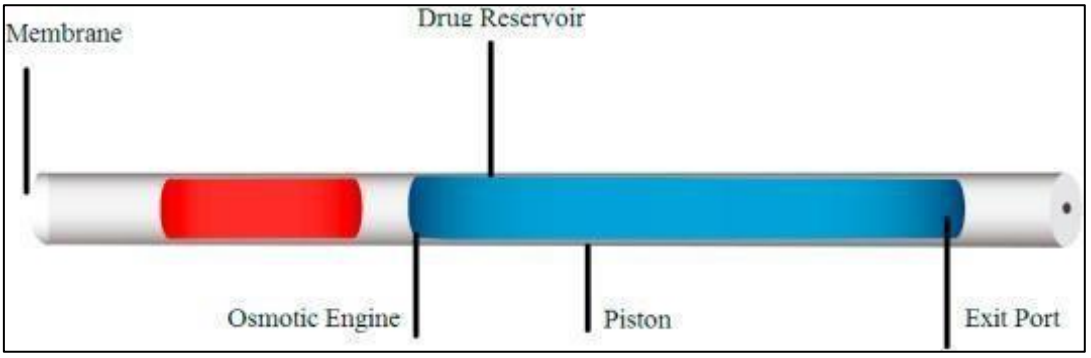

Fig 7: DUROS Technology

3.4 DUREDAS Technology (Dual release drug delivery system)

With these techniques, the two layers were combined into a sole tablet through two separate direct compression stages. It provides a release of two or more drugs in combined form or either unique release of one drug. DUREDAS TM Technology accomplishes it different release patterns by combining hydrophilic polymers to manufacture the bilayer tablet. The development of OTC release anesthetics was the initial application of this technology (3, 16, 54, 55, 56).

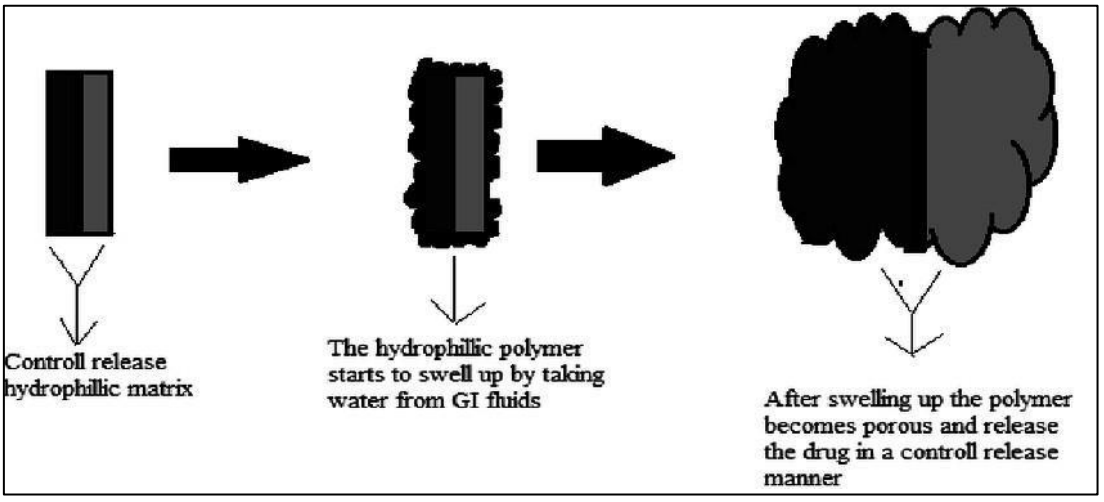

Fig 8: Schematic diagram of DUREDAS

3.5 EN SO TROL Technology

Solubility can be improved with help of this technology. Using a combined approach for the drug delivery system, the Shire laboratory efficiently finds and adds the solubility enhancer or agent to achieve the best dosage form in the controlled release drug delivery system (57).

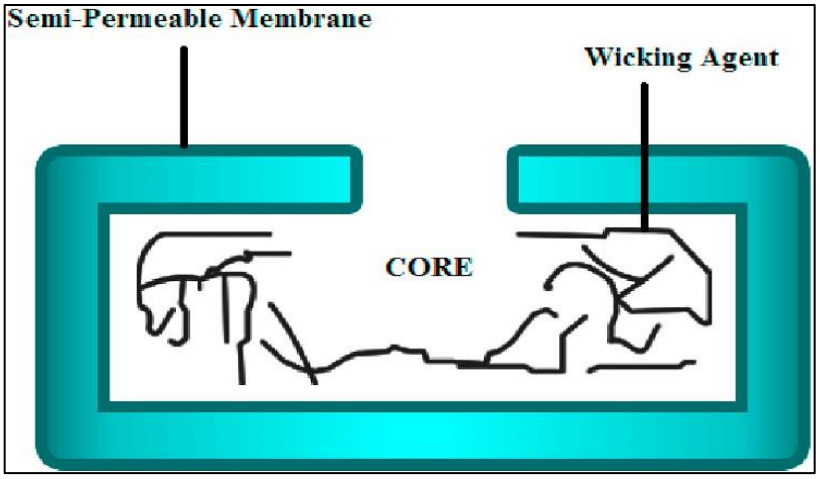

Fig 9: EN SO TROL Technology

3.6 Geminex Technology

This method significantly improves the therapeutic efficacy of drugs while reducing adverse effects. With a single dose, it release the drugs combination at different rates. Penwest, a pharmaceutical company which uses it widely for many diseases. The foundation of this technique is a bi-layer tablet that uses a TIMERx matrix in the controlled release layers (58).

3.7 PRODAS Technology

It is a multi-particulate drug technology, in this technology a single formulation or tablet contains a combination of various mini-tablets that give desired release rate such as immediate, sustain, controlled, or delayed release and it is also referred as "Programmable oral drug absorption system" . The method combines the advantages of hydrophilic matrix tablets and multi-particle tablets to deliver the combined effects of both medications in a single dosage. Sometimes, Minitab is integrated with different APIs to create products with expected release schedules. PRODAS technology helps deliver drugs to the GIT in a targeted manner (59, 60).

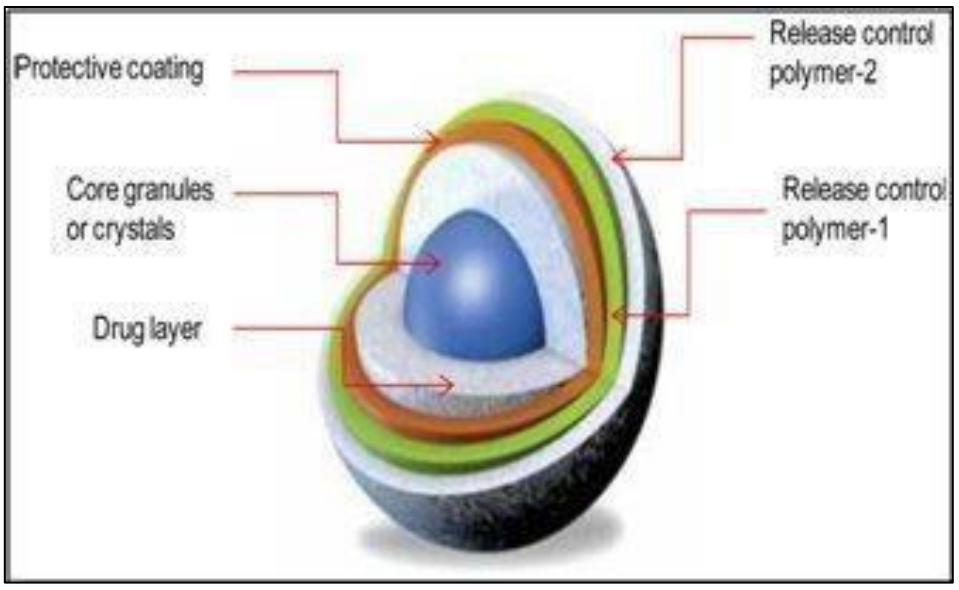

Fig 10: PRODAS Technology

3.8 Erodible Molded Multilayer Tablet

It has a coat and matrix and is manufactured using ordinary plastic injection molding and pattern of release is determined by engineering and design of the matrix and coat. It has biodegradable coat which possesses least permeability to water. This method helps distribute the drug in a zero-order release

pattern without affecting gastrointestinal disorders. For drugs that have stability issues when subjected to water, such as chemical as well as physical stability issues, this technique is particularly beneficial. Additionally, it production cost is cheap and offers correctness and reproducibility (31, 61, 62, 63).

4. BILAYER TABLET PRESS TYPES

4.1 Single Sided Rotary Tablet Press

With its independent doublet feeder chambers, the single-sided press is thought to be most fundamental type model. The powder has passed beneath the feeder, it is first put into the die for the first layer and then again for the second layer to create a two separate layers of tablet and then the separate layers are connected by a few steps at their interface, to strengthening the bond between them and decreasing the possibility of separation (64-67).

4.1.1 Constraints of the one-sided press

- The layers don't appear to be distinct from one another.
- The initial layer's short dwell time because of the tiny compression roller could lead to less capping, hardness, and de-aeration (16, 67).
- Insufficient control and weight measurement for the two separate layers (16, 68, 69).

4.1.2 Dwell time

It denotes the time interval taken by the force of compression to exceeds 90% of its maximum value. Extended period of dwell are a feature of high-quality tablets, particularly when a complex composition is compacted (7, 70, 71).

4.1.3 Compression force

Since the bonding between first and second layer may weaken if the compression force above 100 daN is applied to first layer, so to preserve the ability of layers to link with one another, compression force on initial film is likely <100 daN. Inadequate layer bonding reduces the tablet's hardness (2, 72, 73).

4.2 Double Sided Rotary Tablet Press

The tablet weight is managed, tracked, and adjusted using the compression force (10, 74). Each tablet effective peak compression force is determined by the control system compression on main layer. When required, control system adjusts die's filling depth and rejects tablets that are not within tolerance using this force of compression as a signal (75, 76).

4.2.1 Merits of double sided tablet press

- Better weight monitoring and independent mass management
- Avoid capping, by using minimal compression on the initial layer.
- Their dwell time has been extended to ensure adequate hardness (77, 78).

4.2.2 Constraints of the double-sided press

- Minimal compression given to first layer, which could lead to weak bindings or interaction between the layers.
- Sometime compression force is Insufficient, and it can contribute to the restricted accuracy of weight monitoring (79, 80).

4.3 Bilayer Tablet Press With Displacement

It operates differently; during displacement measurement, the control system's responsiveness depends on delivered pre-compression force (81). Pre-compression force decreases to enhance, the connection among the initial and subsequent layers. The bilayer tablet press consists of two compressors: the top and bottom pre-compression rollers. While the latter, that controls height of compression, hangs on the yoke and former is attached to an air piston (8, 71, 82, 83).

4.3.1 Merits of press with displacement

- This type of press provides precise weight monitoring and independent weight adjustment for each layer.
- It also provides sufficient strength at maximum wheel speed.
- By employing a modest pre-compression force, it also avoids capping and the breakage of the two-layer connection.
- By eliminating the visual contrast among layers, it maximizes profit.
- Prevent layers from becoming contaminated with one another (1, 13).

5. BILAYER TABLET CHARACTERIZATION

5.1 Physical Appearance

When it comes to customer acceptability of a tablet, there are a number of variables that are vital to consider. These factors include the general look, visual identity, and style of the tablet. The sizes, forms, colors, flavors, surface textures, physical defects, scents (or not), consistency, and distinguishing markings of tablets vary widely (84, 85, 86).

5.2 Thickness of Bilayer Tablets

Uniform tablet thickness is used by some filling machinery to count. For tablet size consistency, tablet thickness and diameter were crucial. A micrometer device for ten tablets or an standard vernier caliper are utilised to gauge the thickness of tablets. To guarantee consistency and uniformity in bilayer pills, the thickness must be uniform within the statistical limit (13, 86, 87).

5.3 Weight Variation

The official books provide standard techniques to be followed for the evaluation of weight variance. An approximate level of content consistency is ensured by the study's appropriate outcome. In the weight variation test, selection of twenty tablets at random is done, than determine their average weight, and compare it with regular procedures that are followed are described in full in the official books (88, 89).

5.4 Distribution of Particle Sizes

The sieving method was used to measure the distribution of particle sizes (90).

5.5 Angle of Repose

Diameter and angle of repose of the powder cone were estimated using the following formula:

$\tan ø = h/r$

Where, h = Height,

r = Radius of the powder cone.

The flow properties of powder mixtures are found using the following formulas:

Hausner ratio = Tapped density/Bulk density

Carr′s index = (Tapped density− Bulk density)/ Tapped density

5.6 Moisture sorption capacity

Every disintegrant has the ability to take in moisture from the air, that has an impact on the drugs that are sensitive to moisture. One gram of disintegration was used to test the moisture sorption capability. The one gram of disintegrant uniformly dispersed in a petri dish, maintained for two days at 37±1°C and 100% relative humidity in a stability chamber, and the amount of moisture absorbed by weight difference was examined (91, 92).

5.7 Hardness of Bilayer Tablet

The crushing strength is another term for the hardness. An extremely delicate tablet is unable to withstand abrasion on subsequent processes, whereas an excessively rigid tablet might fail shatter when necessary to meet the dissolution criteria. Optimal tablet crushing requires a minimum breaking force of 4 kg, and the power needed to break them is expressed in kilograms (kg) (93). A tablet's density and porosity, among many other characteristics, are largely related to its hardness. It largely depends on tablet attributes such as size, dimensions, excipients, composition, and compression force and differs throughout tablet types. In the 1930s, Monsanto created a compact, portable testing device that is currently referred to as the Monsanto or Stokes hardness tester. Later, the Schleuniger and Pfizer Strong-Cobb device was also introduced (94).

5.8 Friability of Bilayer Tablet

The friability test is focuses on the tablet's hardness, assesses how well a tablet can tolerate stress and friction during handling, packaging, and shipping. A percentage is used to measure the friability value. Tablets that show a weight loss of no more than 1% are collected, while broken tablets are left uncollected (95). Typically, friability is determined using the Roche Friabilator, in which already weighs a set number of tablets were places in the device, rolls them repeatedly, gives them shocks, and causes them to fall 6 inches with each turn. The tablets are weighed once more after almost four minutes have passed, and the difference between their current weight and the initial weight is determined as the tablet's friability (96).

$$\text{Friability} = (W_o - W_f) \times 100 / W_o$$

Where, W_o is the initial weight of tablets,

W_f is the final weight of tablets.

5.9 Buoyancy Determination

The gastro-retentive bilayer tablets are used for this test. The 900 ml of 0.1N HCl is used as the dissolution medium, one tablet is placed inside it, and then suitable rotation per minute (rpm) is established, and the temperature is then kept at 37±2°C. The two key parameters that define it are "Total Floating Time" and "Floating Lag Time." TFT measures how long a tablet stays afloat on medium, whereas FLT measures how long it takes a tablet to float on medium; both times will be tracked and recorded (97).

5.10 Swelling Index

After being carefully weighed, each tablet would be kept in fifty milliliters of water. Shortly after an hour, the tablets would require being carefully removed, dried using filter paper to get rid of any last bits of water, and then weighed exactly. The following formula would be used to get the percentage of swelling: (98)

Swelling study = Wet weight - Dry weight x 100/ Dry weight

5.11 Drug Content

After the dissolving process is finished, a sample of the solvent used for the dissolution study can be taken in order to ascertain the drug content of compounds present in various layers. To make up for sampling loss during the dissolution investigation, the right amount is calculated. At least three duplicates of the study are conducted, and the standard deviation is used to express the results (67).

5.12 Dissolution Studies

The tablets need to go through an in-vitro drug release test to see if they could offer the desired controlled drugs delivery. Under controlled circumstances, dissolution tests calculate the length of time require by drug to break apart from a tablet into a solution. A site of dissolution can influence the

choice of dissolution medium. Researchers use the United States Pharmacopeia (USP) dissolution apparatus to perform in vitro drug release experiments. The percentage of a drug that dissolves in a solvent system under conditions outlined in the drug's official monograph is known as dissolution. One or more pharmacological substances may be present in the two layers of bilayer tablets (86, 99).

5.13 Stability Studies

Following appropriate packaging, the bilayer tablets are stored under ideal circumstances for the amount of period recommended by the ICH (International Council for Harmonization of Technical *Requirements* for Pharmaceuticals for Human Use) guidelines. After fifteen days, these tablets are removed and their chemical and physical properties such as their durability, visual defects, pharmaceutical ingredients, dissolution, and friability are assessed. The kinetics of deterioration are ascertained by fitting the gathered data into the deregulations. The Arrhenius equation is used to plot the accelerated stability data in order to determine the tablets' shelf life at room temperature, or 25 °C (100, 101).

5.14 Transmission Raman Spectroscopy (TRS)

Transfer Raman Spectroscopy (TRS) is a technology that is being used more and more in pharmaceutical tablet analysis for quality control, formulation, and process understanding. Because of its intricate construction, the bilayer tablet poses an exceptionally difficult scenario. Predicting the API content of stacked tablets was the goal of our quantitative analysis methodology (102, 103).

5.15 Scanning Electron Microscopy

The shape and structure of tablets can be seen using the SEM. The tablets are cut using a scalpel, attached with adhesive tape to a brass stub, covered by thin coating of gold (about 150 Å) for a short while under vacuum, and then examined under a microscope (104).

5.16 Differential Scanning Calorimeter

Using DSC, thermal analysis is done. When exposed to nitrogen (N2) gas, pure pharmaceutical components, excipients, and bilayer tablets should be tightly packed in aluminum pans and provided with temperatures ranging from 20 to 300 °C at a linear heating rate of 10 °C min–1. Each component of a drug has a unique peak. Drug material is molecularly distributed throughout the tablet matrix system if this peak is absent from the DSC thermo-gram (105).

5.17 X-Ray powder diffraction (XRPD)

XRPD is employed for evaluating the active components crystallinity. XRPD tests utilizing a Cu anode and a graphite mono-chromator were carried out at a room temperature with an input voltage of 35 kV and the current-voltage of 20 mA. The process parameters were adjusted to a scan step-time of 25s and a scan-size of 0.02 ° (2θ). The 2θ diffraction angle is used to evaluate bilayer tablets at a range of 5 to 50 °. Potential alterations in the pharmacological compounds' distinctive peaks suggest that they are changing from crystalline to amorphous forms (106).

6. APPLICATIONS OF BILAYER TABLETS

6.1 Hypertension

Due to its complicated nature, a mono therapy strategy to high blood pressure treatment is typically unproductive. To achieve their ideal blood pressure, most people need to take multiple drugs from different classes (107). Bilayer technology offers a number of benefits over alternative therapies, such as a more straightforward dosage schedule, better patient adherence, fewer adverse effects, a slower emergence of antibiotic resistance, and possibly cheaper costs associated with production, handling, packing, and shipping. The goal of developing sustained delivery systems is to guarantee uniform drug distribution, enhance therapeutic effectiveness, or reduce the frequency of doses (108).

International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 8S, 2025
https://www.theaspd.com/ijes.php

Table 1: Some marketed anti-hypertensive bilayer tablets (109)

S. No.	Class	Name of Drugs
1.	Combinations of Diuretics	Amiloride and hydrochlorothiazide
		Spironolactone and hydrochlorothiazide
		Triamterene and hydrochlorothiazide
2.	ACE inhibitors and diuretics	Benazepril and hydrochlorothiazide
		Captopril and hydrochlorothiazide
		Enalapril and hydrochlorothiazide
		Lisinopril and hydrochlorothiazide
		Moexipril and hydrochlorothiazide
3.	Angiotensin-II receptor antagonists and diuretics	Losartan and hydrochlorothiazide
		Valsartan and hydrochlorothiazide
4.	Calcium channel blockers and ACE inhibitors	Amlodipine and benazepril
		Diltiazem and enalapril
		Felodipine and enalapril
		Verapamil and trandolapril
5.	Beta blockers and diuretics	Atenolol and chlorthalidone
		Bisoprolol and hydrochlorothiazide
		Metoprolol and hydrochlorothiazide
		Nadolol and bendroflumethazide
		Propranolol and hydrochlorothiazide
		Propranolol ER and hydrochlorothiazide
		Timolol and hydrochlorothiazide
6.	Miscellaneous combinations	Clonidine and chlorthalidone
		Hydralazine and hydrochlorothiazide
		Methyldopa and hydrochlorothiazide
		Prazosin and polythiazide

6.2 Diabetes

Combination therapy is advised to patients when mono therapy is unable to regulate their glycemic parameters. This will help them establish glycemic control and postpone the degradation of their β-cells. Two or three drugs may be used in combination therapy. Oral hypo-glycemic are occasionally used in conjunction with insulin therapy (110,111).

Table 2: Some antidiabetic bilayer tablets available in market (112)

S. No.	Drug's name	Manufacturer
1.	Sitagliptin (DPP-4 inhibitor) and Metformin (extended-release).	Merck.
2.	Empagliflozin (inhibit SGLT2), Linagliptin (inhibit DPP-4), and Metformin (extended-release).	Boehringer Ingelheim and Eli Lilly.
3.	Dapagliflozin (SGLT2 inhibitor) and Metformin (extended-release).	AstraZeneca.
4.	Empagliflozin (SGLT2 inhibitor) and Linagliptin (DPP-4 inhibitor)	Boehringer Ingelheim
5.	Empagliflozin (SGLT2 inhibitor) and Metformin (extended-release).	Boehringer Ingelheim and Eli Lilly.
6.	Alogliptin (DPP-4 inhibitor) and Metformin.	Takeda.
7.	Alogliptin (DPP-4 inhibitor) and Pioglitazone (thiazolidinedione).	Takeda

8.	Pioglitazone (thiazolidinedione) and Metformin (extended-release).	Takeda
9.	Ertugliflozin (SGLT2 inhibitor) and Metformin (extended-release).	Merck and Pfizer.
10.	Linagliptin (DPP-4 inhibitor) and Metformin (extended-release).	Boehringer Ingelheim and Eli Lilly.

6.3 Nocturnal Asthma

One prevalent condition with a greater circadian disparity is asthma. Treatment for Nocturnal Asthma (NA), which is characterized by an increase in warning signs at night and a loss in lung functions, is necessary. It is an intermittent exacerbation of asthma. These symptoms are referred to as circadian events and are associated with sleep. Since bilayer tablets are made in accordance with the body's circadian cycle, they have attained a notable level of responsiveness. Two layers are combined to create a bilayer tablet: a sustained release layer that releases drug gradually for prolonged period, maintaining therapeutic levels of drug during night and a fast release layer that distributes the medication quickly, relieving asthma symptoms quickly after ingestion. This helps prevent nocturnal asthma attacks and ensures uninterrupted sleep (113).

- **Some examples of bi layer tablets are:**

✓ Fexofenadine and Montelukast (114),

✓ Montelukast sodium (115) and

✓ Terbutaline sulphate (116).

6.4 Sexually Transmitted Diseases

Another name for (STDs) is venereal diseases. STDs are a major health issue. Gonorrhea, trichomoniasis, chancroid, syphilis, bacterial vaginosis, and genital candidiasis are among the common sexually transmitted diseases. Unwanted toxicity has been found to result from the large range of fluctuations in plasma drug concentration that the conventional form of the drugs causes. Controlled drug delivery systems are necessary due to a number of issues, including recurrent drug dosage and irregular absorption. The current approach of treating STIs (STDs) is fraught with challenges, including drug resistance. Patients who are allergic or pregnant have limited medication options. The bi-layered tablet is a new technology that is widely used today to provide a controlled medication release mechanism that delivers drugs efficiently. When two incompatible medications need to be separated, bi-layer tablet technology is the best option for their continuous release (117). Currently, there are no commercially available bilayer tablets specifically intended for the management STDs. However, research has been conducted to develop such formulations.

- **Research include:**

✓ Cefixime trihydrate and Ofloxacin (118)

✓ Disulfiram and 5-Fluorouracil (119)

6.5 Psychosis and Other Mental Health Disorders

Customized drug regimens are frequently necessary for psychosis and other mental health conditions such bipolar disorder, schizophrenia, and depression. Bilayer tablets can be made to simplify regimens, improve drug absorption, and combination of two drugs.

- **Some marketed formulations are:**

✓ Olanzapine and Samidorphan (120, 121)

✓ Flupentixol/Melitracen Combination

✓ Olanzapine/Fluoxetine Combination

7. BILAYER TABLET EXAMPLES

S. No.	Name of Drugs	Purpose	References
1.	Statin, Aspirin	To reduce drug-drug interactions and aspirin adverse effects	40
2.	Metformin, Glipizide	Diabetes synergistic impact	122
3.	Telmisartan, Simvastatin	To reduce the interaction between telmisartan and simvastatin	123
4.	Propranolol HCl	Bimodal drug release	124
5.	Misorostol, Diclofenac	To reduce drug-to-drug contact	125
6.	Amlodipine, Atenolol	To increase the stability of the combination drug	126
7.	Telmisartan, Hydrochlorthiazide	To reduce the amount of hydrochlorothiazide that comes into touch with the essential elements of telmisartan	127
8.	Glipizide, Metformin HCl	To prevent drug interactions when mismatched	128
9.	Salbutamol, Theophylline	combined impact on asthma	54
10.	Montelukast, Levocetirizine	To increase the stability of the combination medicine	129
11.	Pioglitazone HCl, Gliclazide	Treatment for Type II Diabetes	130
12.	Losartan potassium	Treatment of hypertension	131, 132
13.	Trimetazidine HCl, Clopidogrel bisulphate	Platelet inhibitors and cytoprotective anti-ischemic drugs for acute coronary crises	133
14.	Diclofenac, Cyclobenzaprine	combined impact on pain	134
15.	Metformin HCl	Diabetes synergistic impact	135
16.	Diclofenac, Cyclobenzaprine	combined impact on pain	88
17.	Metformin HCl, Atorvastatin Calcium	For creating polytherapy NIDDS and treating hyperlipidemia	136
18.	Cefixime Trihydrate, Dicloxacilline Sodium	combined impact on bacterial infections	137
19.	Piracetam, Vinpocetin	The combined impact of Alzheimer's	138
20.	Metformin HCl, Pioglitazone	A combined impact on diabetic mellitus	139
21.	Cefuroxime Axetil, Potassium Clavulanate	synergistic action against microbial diseases and to reduce the dose's adverse effects	140
22.	Amlodipine Besilate Metoprolol Succinate	synergistic impact on high blood pressure	141, 142
23.	Diclofenac Sodium, Paracetamol	combined impact on pain	143
24.	Ibuprofen,	Back pain synergistic impact	144
25.	Paracetamol, diclofenac	combined impact on pain	145

26.	Metformin HCl, Pioglitazone	A combined impact on diabetic mellitus	86
27.	Tramadol,	combined impact on pain	146
28.	Atorvastatin, Atenolol	Treatment of hypertension and hypercholesterolemia	147, 148
29.	Nifedipine	Treatment of hypertension and angina	149
30.	Aspirin, Isosorbide 5-mono-nitrate	Treatment of pain, fever, and other inflammatory conditions	150, 137
31.	Granisetron HCl	For resolving the problems with bioavailability and minimizing adverse effects	71
32.	Indomethacin	Drug release in two phases	151
33.	Atenolol	Reducing adverse effects, frequency of administration, and bioavailability problems	152
34.	Atorvastatin, Calcium	Reducing adverse effects, frequency of administration, and bioavailability problems	144
35.	Atenolol, Lovastatin	Biphasic release profile and hypertension: a synergistic impact	153
36.	Cefuroxime, Axetil	Bimodal drug release	154, 155
37.	Furosemide	For enhancing bioavailability	156

8. CONCLUSION

In summary, by joining many APIs and excipients, bilayer tablets formulation offer a modern type of therapy that efficiently heals medical conditions. These formulation are prepared correctly while taking into account all GMP guidelines to preserve its quality over time and they have a lesser amount of adverse effects. Different approaches and presses are utilized to achieve these requirements in order to maximize effectiveness and reduce negative effects. To guarantee its efficacy and stability over the course of its shelf life, the produced tablet is assessed chemically and physically. These days, in order to maintain a long-lasting effective plasma level, the similar drug is used in place of a loading or initial dose and a maintenance or extended dose, or multiple bilayer tablets are created with different APIs for combination therapy.

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