



BILAYER TABLET: AN DUAL RELEASE DRUG DELIVERY SYSTEM

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ABSTRACT:

These days various developed and developing countries go towards a combination therapy for prevention of various diseases and disorders requiring long term therapy such as hypertension, diabetes and cardiovascular diseases. About 90% of the preparations, formulated today are ingested orally. It shows that bilayer tablet is popular worldwide and major attention of researchers is towards this direction. Bilayer tablet is a novel technique for the successful development of controlled release of formulation as well as various characteristics to provide a way of successful drug delivery system. Bilayer tablet can be a better option to reduce chemical incompatibilities taking place between active pharmaceutical ingredient and to enable the development of various drug release profiles. Bilayer tablets are appropriate for the sequential release of two drugs to be given combined. It separates the two mismatching drugs. The sustained release tablets whose one layer provides instant drug release as an initial loading dose while the second layer contains the sustained dose. Bilayered tablet is an improved beneficial technology to overcome the shortcoming of single layered tablet. Bilayer tablet prepared by using different techniques such as OROS push pulls technology, L OROS technology, EN SO TROL technology. This systemic review explains about various techniques of bilayer tablet, ideal characteristics of bilayer tablet, various types of bilayer tablet, and the method of preparation of bilayer tablets, challenges in manufacturing of bilayer tablets, and the evaluation of bilayer tablets. There are various applications of bilayer tablets which consist of monolithic partially coated or multilayered matrices.

KEYWORDS: Bilayer tablets, OROS technology, Fixed dose combination, Sustained release, Immediate release layer.

INTRODUCTION:

There are different ways to administer drugs into the body like oral (via swallowing), sub mucosal (via buccal and sublingual mucosa), parenteral (via injection), transdermal (via skin), pulmonary (via inhalation) etc. Tablets (pharmaceutical powder compact) are common, convenient, and existing administration method for the systemic delivery of drugs. It has several advantages such as ease of dose administration, patient compliance and flexibility in formulations. The oral drug delivery practice depends upon factors like gastric emptying process, gastrointestinal transit time of dosage forms, drug release from the dosage form and site of absorption of drugs.¹⁶

Conventional dosage forms are not suitable to target drugs at specific sites, but the novel drug delivery systems (NDDS) are much systematic to maintain drug concentration to the site of action for an extended period of activity. Conventional dosage form produces wide range of fluctuation in drug concentration in blood stream and tissue with undesirable toxicity and poor efficiency. Repetitive dosing and erratic absorption led to concept of controlled drug delivery system. The main aim of developing sustained or controlled drug delivery is to decrease dose frequency and by localization at site of action and provide uniform drug delivery¹⁹. One of the most important is

that combination therapy has various advantages over monotherapy. Combination therapy plays an most important role in clinical role because it is more effective and less side effects.¹

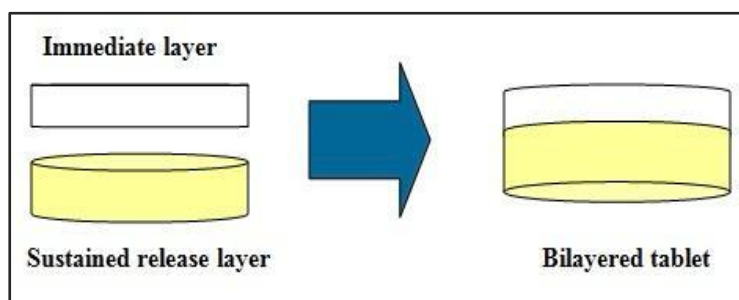


Fig: Bilayer Tablet

In the last decade, there is increase in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bilayer tablet) in the pharmaceutical industry, promote patient convenience and compliance.² The concept of bilayer tablet is utilized by Skye Pharma PLC in their Geomatrix tablets, which is made up of different layers. The system allows the combination of more than one drug into dosage form.¹⁸ Bilayer tablets, sometimes called as double layer tablets and are newer technology for the development of controlled release formulations. a bilayer tablet is a fixed-dose combination (FDC) intended for oral administration. The product has two layers i.e. one is immediate release layer and second is the sustained release layer. The immediate release layer acts as a loading dose and the sustained release layer maintains the therapeutic plasma concentration for an extended period.³ for the identification of two drugs different colors are used. The immediate release layer contains super disintegrates, which promote drug release rate and gives onset of action quickly and the sustained release layer (maintainance dose) release the drug in sustained manner for prolonged period of time by use of various polymers as release retardants.⁵ Bilayer tablets are suitable to avoid chemical incompatibilities between APIs by physical separation and enabling the development of dual drug release profiles.⁴ In addition, bilayer tablet have enabled the development of controlled delivery of active pharmaceutical ingredient with pre-determined release profile by combining layer with various release pattern.³ The preparation of tablets in multilayer form is use to provide system for administration of drugs, they are incompatible and to provide controlled release tablet formulation by providing multi swelling layers.¹⁸

The biphasic system is used mostly when maximum relief required to achieved quickly and it is followed by sustained release phase. It also prevented from repeated administration of drug. The agents like coronary vasodilators, antihypertensive, antihistamines, analgesics, antipyretics and antiallergenic are mainly suitable for this type of drug delivery. Some bilayer tablets have both the layers as the sustained release layers e.g. certain antidiabetic agents.²⁰

ADVANTAGES OF BILAYER TABLET:

1. They are unit dosage form and give the greatest capabilities of all other dosage form for greatest dose precision and least content variability
2. The cost is lower as compared to all other oral dosage forms
3. They have greatest chemical and physical stability over all oral dosage forms
4. Patient convenience is improved because of lesser daily dose is required as compared to traditional drug delivery
5. Separation of incompatible components
6. Suitable for large scale production
7. It is easy to swallow with a minimal hang up
8. Due to synergistic action, the active ingredients efficacy is increased
9. Flexible concept

DISADVANTAGES OF BILAYER TABLETS:

1. Adds complexity and bilayer rotary presses are inexpensive
2. The drugs with bitter taste, objectionable odour as well as sensitive to oxygen may require encapsulation or coating
3. Slow breakdown and dissolution may cause bioavailability issue
4. Adds complexity, bilayer tablet presses are expensive
5. Difficult to swallow in case of children and unconscious patient
6. There should be compatibility between the two active ingredients.

IDEAL CHARACTERISTICS OF BILAYER TABLET:

1. A bilayer tablet should have free of defects like cracks, chips, contamination and discolouration
2. It should have the chemical and physical stability to maintain its physical attributes over time
3. It should have sufficient strength to withstand mechanical shock during its production, packaging, shipping and dispensing
4. The tablet must release the drug in a reproducible manner.

TYPES OF BILAYER TABLET: Bilayer tablet is a combination of two or more active pharmaceutical ingredients in a single dosage form. The bilayer tablets, may be either the same (homogeneous) or different (heterogeneous)¹

Homogeneous type: These are recommended when the drug shows dual release profile. They are formulated in a way that immediate release layer acts as a loading dose and sustained release layer acts as a maintenance layer. i.e. the same drug with different release pattern.⁴

Heterogeneous type: These are preferred when two incompatible substances are combine in a single dosage form separated from each other. i.e. similar drugs with same or different release pattern.⁴

METHOD OF PREPARATION:

Bilayer tablet is prepared with one layer of drug for immediate release and the second layer for to release drug later i.e. in extended-release form. The method of preparation of tablet consists of following types:

1. Compaction
2. Compression
3. Consolidation

1. Compaction: for the formulation or production of tablet certain requirement are necessary such as the mechanical strength and the desired drug release profile. Compaction is defined as the process by which the porosity of a given powder is decreased, as a result of its grains being compress together by the weight of mechanical means. In bilayer tablet formulation, it is tough to maintain those conditions when the double compression technique is used, because of poor flow and compatibility characteristics of the drug which will results in capping or lamination. The compaction of a material involves compressibility as well as consolidation.^[4,7,8]

2. Compression: it is defined as the reduction in bulk volume by eliminating voids and bringing particles into closer contact.¹⁰

3. Consolidation: it is the property of material in which the increase in the mechanical strength due to inter particular interaction. The compression force on layer 1 was found to be major factor influencing factor tablet delamination.⁸

CHALLENGES IN BILAYER MANUFACTURING [4,5,15]:

Bilayer tablet is the combination of two or more active pharmaceutical ingredient (API) in a single dosage form. Also, bilayer tablets have some manufacturing challenges⁵

Delamination: when two layers of tablet do not bond completely tablet descend. During compression, granules of both layers should have adhered.⁴

Cross contamination: when the granulation of two layers intermixes or vice versa, cross contamination occurs.⁵ genuine dust collection is a best technique for the prevention of cross contamination.¹⁵

Production yield: to stop the cross contamination, dust collection is necessary which can cause the losses. Hence, bilayer tablets have low yield than single layer tablets.¹⁵

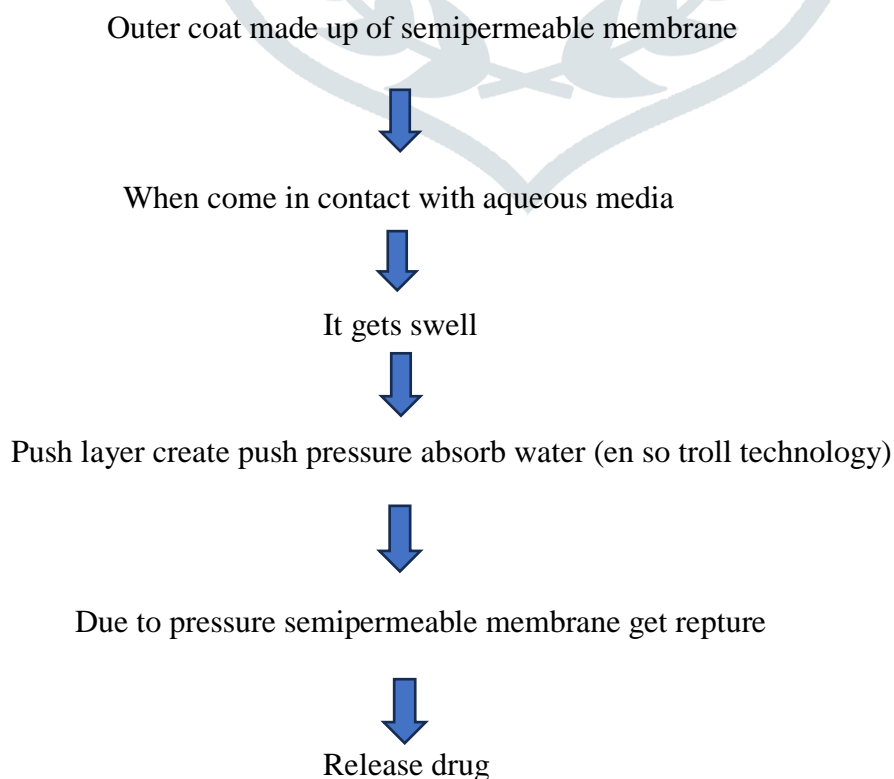
Cost: in comparison with the single layer tablets, bilayer tablets are expensive. It has several parameters it as follows:

- The cost of tablet press is expensive
- In bilayer tablet, the tablet press generally runs more slowly
- The evolution of two compatible granulation is necessary, i.e. more time spend on formulation development, analysis and validation.

These all parameters if not improved then it will affect the compression of bilayer tablet as well as quality aspect of tablet. Hence, it is required to design of robust products and processes.

VARIOUS TECHNIQUES FOR BILAYER TABLET:

GENERAL MECHANISM OF RELEASE OF DRUG OF ALL TECHNIQUES:



1. OROS push-pull technology
2. L-OROS technology
3. EN SO TROL Technology
4. DUROS TECHNOLOGY
5. GEMINEX TECHNOLOGY
6. DURADAS TECHNOLOGY
7. PRODAS
8. ERODIBLE MOLTED MULTILAYER TABLET

OROS push-pull technology: pharmaceutical technologies such as OROS -CT consist of push-pull units (bilayered-drug, osmotic push layer with semipermeable membrane); when it reaches to the colon, the system permits water or gastric fluid create hydrostatic pressure to deliver the active agent. The osmotic-controlled release oral delivery system is an advanced drug delivery technology that use osmotic pressure as a driving force to delivered pharmacotherapy in many therapeutic areas. The osmotic drug delivery system not only acts as a tool for control release of drugs but also avoid the repeated administration. Over the past decades, different OROS osmotic dosage forms have been studied to promote extended-release oral administration by controlling the rate of drug release, providing different release profiles.⁶

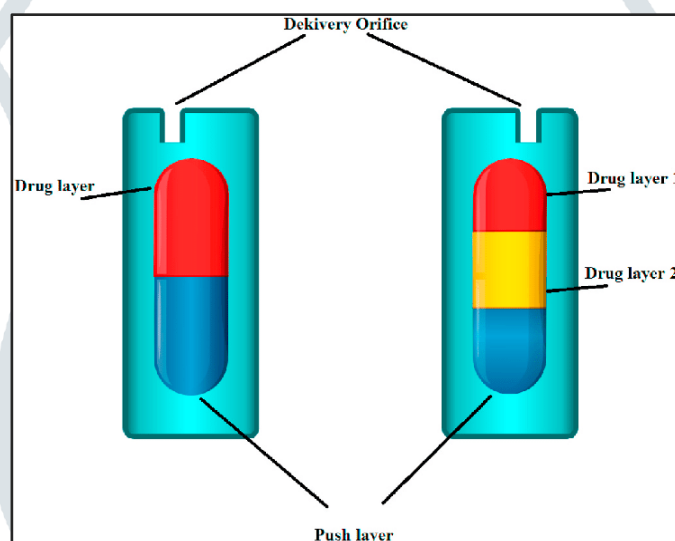


Fig: ORSO push-pull technology.

Osmotic drug delivery system consists of a compressed tablet core which is coated with a semipermeable membrane coating. The core consists of drug formulation in which it contains an osmotic agent and a water swellable polymer. This coating has one or more delivery ports via solution or suspension of drug is released over time. The osmotic pressure generated by the generated by the core component and the permeability of the membrane coating is depends on the rate at which the core absorbs water. The core absorbs water, it increases in volume, and it pushes the drug solution or suspension out of tablet via one or more delivery ports.⁹

L-OROS Technology: Alza developed the L OROS system the L OROS system is designed to provide continuous delivery of liquid drug formulation and improve bioavailability of drugs. Each of the system consist of a liquid drug layer, an osmotic engine and a coating of a semipermeable membrane. When the system comes in contact with aqueous environment water permeates over the rate controlling membrane and activates the

osmotic layer. The increase of osmotic layer results in the development of hydrostatic pressure inside the system, thereby forcing the liquid formulation to be delivered via delivery orifice.

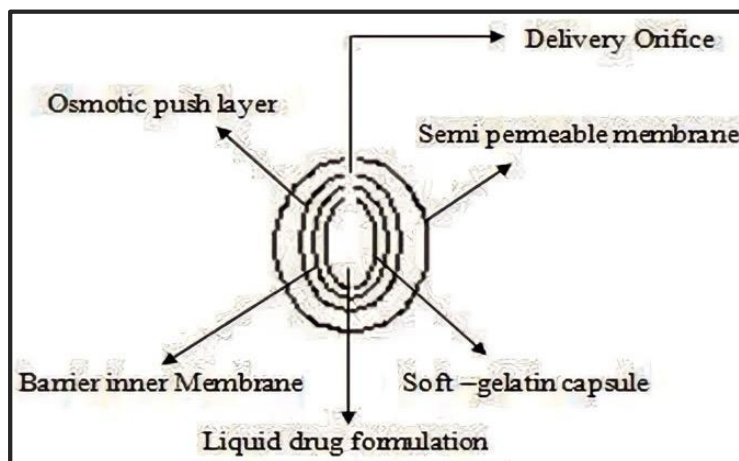


Fig: L-OROS Technology.

L OROS have three types these are:

1. L OROS hard cap: It is designed to give continuous drug delivery
2. L OROS soft cap: it is designed to give continuous drug delivery
3. Delayed liquid bolus delivery system: it delivers pulse type of drug delivery
 1. Placebo delay layer
 2. Liquid drug layer
 3. Osmotic engine. [4,7]

EN SO TROL TECHNOLOGY: enhancement of solubility of an order of magnitude or to design optimized dosage form uses an approach to drug delivery focus on identification and incorporation of identified enhancer into controlled release technology. [12,2]

DUROS TECHNOLOGY: The DUROS is based on implant technology, that provides a wide range of therapeutic compounds, i.e. peptides, proteins, and other bioactive macromolecules. the DUROS technology is the miniature drug dispensing system because it with stand like a

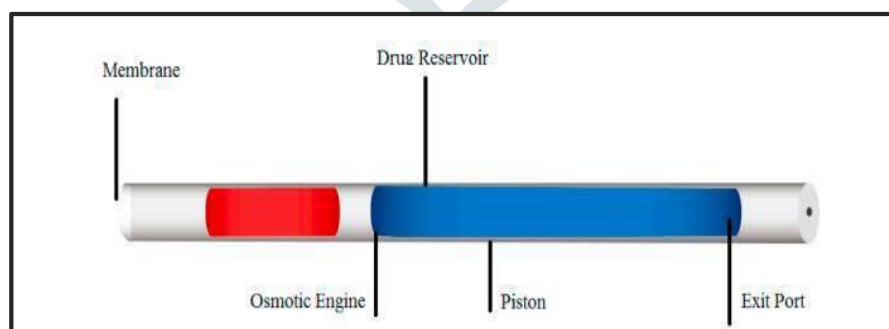


Fig: DUROS Technology.

miniature syringe and release small quantity of concentrated form in continuous and consistent from over months or years. The system includes an outer cylindrical titanium alloy reservoir. With the help of these cylindrical titanium alloy reservoir which is present outside and having high impact strength the drug molecules are protected from enzyme. [10,11,12]

GEMINEX TECHNOLOGY: GEMINEX is a dual drug delivery technology. The technology delivers one or more drug with different release rate at different times. With the help of these the therapeutic efficacy of drug will be increase and the side effects will be minimized. It is useful not only for industry but also for patients. Geminex technology is applied by pen west in – diabetes, cardiovascular system, cancer and CNS disorders. ^[10,11]

DUREDAS™ TECHNOLOGY: this system called as Elan drug technologies Dual release drug delivery system. DUREDAS™ technology is a bilayer tablet in which immediate or sustained release of two drugs or different release rate of same drug in single dosage form. The different release is due to combination of hydrophilic polymer. The technology firstly used for development of OTC controlled release profiles. ^[2,11,12]

PRODAS TECHNOLOGY: Programmable Oral Drug Absorption System is a multiparticulate drug delivery technology, is a unique and it combines the wellbeing of tableting technology inside a capsule. This delivery system is presented as a number of minitabets combined in a hard gelatin capsule and is based on the encapsulation of controlled release minitabets in range of 1.5 to 4 mm in diameter. It Is possible to incorporate many different minitabets, each one is formulated individually and programmed inside the gastro-intestinal tract for release of drugs at different site. This drug delivery system has one advantage is that the combination of multiarticulate and hydrophilic matrix tablet technologies are in one dosage form. ¹⁰

ERODIBLE MOLDED MULTILAYER TABLET: Egalet erodible molded tablets is an erosion-based platform. Egalet erodible molded multilayered tablets prepared by injection molding Egalet technology which includes a coat and a matrix. It has one benefits is that delivering zero order or delayed release with minimal impact from the gastrointestinal conditions. Drug release is controlled via gradual erosion of matrix part. The mode and rate of release are developed by altering the matrix, the coat, the geometry to achieve zero order release or delayed release. For a zero order, the drug is dissolved or dispersed via matrix. The coat has biodegradable but it has poor water permeability to prevent its penetration. The matrix tends to erode when comes in contact with available water. The erosion of matrix is caused due to the gastrointestinal fluid and promote by gut movement in the gastrointestinal tract. The drug release is mediated almost by erosion due to dosage form is developed to slow down the water diffusion into matrix. It is more advantageous for drugs with chemical as well as physical stability issues after contacting with water. Egalet delivery technology is based on standard plastic injection molding to ensure accuracy, reproducibility and low production cost. ^[10,13]

EVALUATION TEST FOR BILAYER ^{[4,14,16,17]:}

1. **General appearance**
2. **Size and shape**
3. **Weight variation**
4. **Tablet thickness**
5. **Friability**
6. **Hardness**
7. **Dissolution study**

General appearance: The general appearance of a tablet, for consumer acceptance its visual identity and all elegance is necessary. It includes tablets size, shape, color, odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

Size and shape: The size and shape of the tablets can be dimensionally described monitored and controlled.

Weight variation: Standard procedures are followed according to official books.

Tablet thickness: For uniformity of tablet size, the thickness and diameter of tablets were determined using vernier caliper.

Friability: The major forces such as friction and shock that cause tablets to chip, cap or break. The friability test is associated with tablet hardness and is meant to gauge the power of tablet to face up to abrasion in packaging, handling and shipping. The friability of tablets can be determined by using Roche friabilator.

Hardness: the resistance of tablet to shipping, capping, breakage under condition of storage, transportation and handling before usage is depends on hardness. The hardness of each tablet is measured by tester that's called Monsanto tester and was measured in kg/cm^2 . The hardness of oral pills ranges from 4 to 10 kg. hypodermic and chewable tablets are (3 kg) softer and sustained release tablets are (10-20 kg). hardness generally increases with the normal storage of tablets and it depends on the shape, chemical properties, binding agent and pressure applied during compression.

Dissolution studies: bilayer tablets were treat with in vitro drug release studies in simulated gastric and intestinal fluids to evaluate their ability in providing the desired controlled release drug delivery. Drug release studies carried out using USP dissolution test apparatus 1.....

CONCLUSION:

Conventional solid oral dosage forms are a traditional approach, but bilayer tablet is a novel approach that requires new machinery for manufacturing. Bilayer tablet is an advantageous technology to control the shortcoming of single layer tablets. Bilayer tablet is an sequential release of two drugs in combination, separate two incompatible substance and also for sustained release tablet, the one layer is immediate release layer as initial dose and second layer is maintenance dose. The process is repeatable, inexpensive, and safe. The bilayer tablet is a more advanced and practical technology that addresses the drawbacks of the monolayer tablet. This technology avoids frequent administration of dosage forms. Now a days such technology is used for co administration of two drugs. The critical parameter in designing and manufacturing the bilayer tablet and heterogeneity of adjacent layer which has significant effect on the properties of individual layer and interfacial strength. To overcome these problems, pharmaceutical technology and manufacturer are constantly evolving to develop new and improved techniques and methods.

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