# Tablet in Tablet Technique for Oral Drug Delivery

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## Abstract

The innovation of controlled release formulations with multiple functions to ensure successful drug administration has entered a new era with the multilayer tablet. Bilayer tablets can help to prevent chemical disparities between pharmaceutically active substances (APIs) and promote the development of diverse profiles by separating them physically. The multilayer tablet is suited for the sequential release of two medications in combination, as well as for the continuous release of tablets, with one layer serving as a loading dosage and the other serving as a maintenance dose. As a result, the usage of bilayer tablets for antihypertensive, diabetic, anti-inflammatory, and analgesic medications, where combination therapy is frequently utilised, is a very different aspect. Bilayer tablets are being developed by many pharmaceutical companies for a number of reasons, including patent extension, therapeutics, and marketing, to mention a few. Although the basic principles of tablet manufacture remain the same, much more must be considered because the creation of multilayer tablets necessitates the use of several incompatible components, additional equipment, and numerous formulation and operating issues. The purpose of today's essay is to present an overview of bilayer tablet technology, the problems of multilayer tablet production, the numerous tablet presses utilised, quality criteria and GMP for their manufacture, as well as current advances in bilayer tablet technology.

**Key Words :** Multi-layer tablet, Loading dose, Maintenance dose, Bi-layer technology

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## Introduction

Oral medication delivery is the most prevalent method of administering drugs among the numerous drug delivery techniques. Pharmaceutical studies have recently shifted its focus to controlled drug delivery, which has distinct advantages over the standard release formulation of the same medicine.[1] Controlled delivery systems with zero-order medication distribution offer the potential to improve efficiency while reducing dose frequency and toxicity. By providing additional release region over time to compensate for the reduced release rate, the multilayer matrix system overcomes the inherent problems of non - linearities encountered with diffusion-controlled matrix devices. [2]This technology also exhibits a high degree of adaptability for a variety of applications. The functioning of these systems relies heavily on polymeric materials. In the production of matrix-type controlled delivery systems, hydrophilic polymers are frequently employed.[3] Bilayer tablets are being developed by many pharmaceutical companies for a number of reasons, including patent extension, therapeutics, and marketing, to name a few. Existing but modified tablet presses are always utilised to design and manufacture such tablets in order to reduce capital investment. As a result, using customised tablet presses to make a high-quality bilayer tablet under GMP conditions is not practicable, particularly when production demands are high.[4] The costs and challenges of bringing new pharmacological devices to market have escalated over the last 30 years, and greater focus hasbeen dedicated to the development of drug delivery systems. The dual-layer tablet represents a new age of successful development that offers regulated versions with a variety of features that enable drug delivery. [5]The prescription control of multilayer drug control versions, the mechanism of drug promotion, system design, and numerous parameters and process factors are all covered in this review.

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The multilayer tablet represents a new age of successful development in terms of offering regulated versions with diverse functionalities in order to provide a successful medication delivery system. The typical dosage form generates substantial changes in the drug's concentration in the blood and tissues, resulting in unfavourable and low yields. [6] As a result, issues like frequent dosage and absorption might make the design of controlled drug delivery systems uncertain. By changing the work area, reducing dosing frequency, or diminishing uniform administration, robust or controlled delivery systems can reduce dosing frequency or boost therapeutic efficiency. The main purpose is to maintain a consistent version, assure patient safety, and improve therapeutic efficacy and adaption. [7] The bilayer tablet can be used to serialise two groups and separate dissimilar materials, including for solid pills, with one layer serving as the major dose and the other as the continuity layer. The bilayer pills are developed to achieve various pharmacological administrations with specific return characteristics. The pharmaceutical industry, patient progress and adaption, and the development of a mixture of active pharmaceutical ingredients (APIs) in the form of a single dose have all piqued attention in recent years (bilayer tablets).[8]

## Problems Related with Conventional Drug Delivery System

Drug insufficiency or overdose can occur as a result of unavoidable changes in drug concentration.[9]
Overdosing on a medicine with a narrow therapeutic index can cause certain side effects due to fluctuations in drug concentration.[10]
Poor treatment adherence.
The peak plasma concentration is used to generate a sampling period profile, making it challenging to maintain a steady state.[11]
Patient compliance is likely to be poor when patients are forced to take their medication three to four times a day on a regular basis. As a result, controlled release dosage forms have been introduced to address these shortcomings.
A short half-life that necessitates repeat administration lowers the chance of missing a dosage.

## Basic Terminology

## Sustained Release Dosage Form

By releasing the drug for a longer period of time, the drug delivery system is aimed to create a long-term therapeutic impact. [12]

## Advantages of Multi-layered Tablet

Patient compliance can be improved.
It is a scale-up technology for pilot plants is feasible.
It's a solitary dosage form with the best chance of achieving maximum dose accuracy and minimum content change of any oral dosage form.
It is less expensive than other forms of oral medication.
The coating process can disguise unpleasant smell and bitter tastes.
Concept that is adaptable.

## Disadvantage of Multi-layered Tablet

Drugs with low hydration, delayed dissolution, and high optimum absorption from the gastrointestinal system might be challenging to synthesise or manufacture as tablets while maintaining appropriate or total bioavailability.
Medicines that are bitter, have a strong odour, or are oxygen-sensitive may need to be packed.
Because of their amorphous form and low density qualities, some medications are resistive to compression in dense compression processes.
Other difficulties encountered throughout development include establishing a layering hierarchy, determining the thickness of the first layer, and preventing cross-contamination between layers.

## Objective of Preparing Multilayer Tablets

To combine compatible or incompatible medications with differing release characteristics in the same dosage form while improving the dosage form's stability relative to its previous dosage form.
To treat serious disease conditions in which a single active is unable to provide complete therapeutic activity and must be maintained for at least 12 hours.[13]
To overcome constraints in the event that a single medicine is unable to treat or prevent undesirable drug effects.
To obtain a dual release profile in order to decrease dose frequency and hence improve patient



compliance.14

## Types of Multilayer Tablets

The Multilayer Tablet are classified into different types as [7,8]
Bilayer Tablet
Triple Layer Tablet
Surrounding coated Core tablet

## Bilayer Tablet

Bi-layer tablets have the ability to send two distinct APIs serially and at the same time. The first layer is an immediate release, while the second layer is a continual release that acts as a maintenance dose. The bilayer tablet can administer two medications at the same time without causing pharmacological or pharmacodynamic disruption.

**Fig 1: Bilayer Tablet**

## Triple Layer Tablet/Trilayered tablet

The triple layer pill has three layers, the first of which is for quick release and the second of which is for long-term release. The middle septum layer separates these two layers. This is better for delivering two medications that overlap. Figure 3 depicts triple-layer tablets.



**Fig 2: Trilayered Tablet**

## Surrounding Coated Cora Tablet

## Multilayer Tablet and Controlled Release

The multilayer tablet has the capacity to prevent drug resistance by combining drug layers with various release rates. For one or more medications, it provides a kinetic index for numerous releases in a drug delivery system. It is created as a control system because of the quick and prolonged release of the drug. The fast dissolving layer with a disintegrating monolithic matrix is meant to reach the initial peak, and the following component is a stable release layer with a homogenous matrix for erosive drug delivery to sustain the drug's plasma concentration. Figure 4 depicts the medication release mechanism from multilayer tablets.

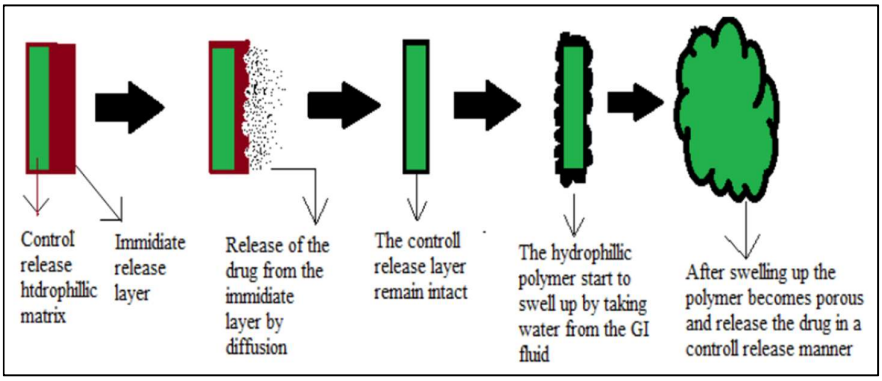
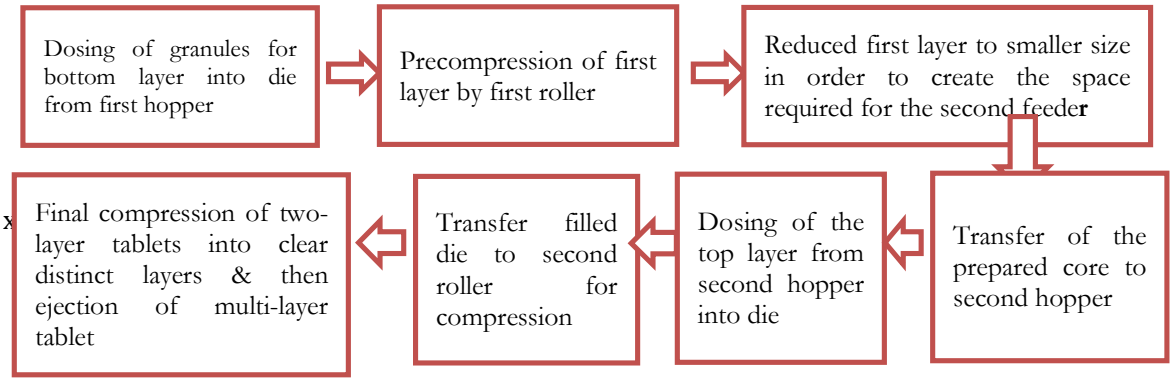



**Fig 3: Multi-layered Tablet and Controlled Release.**

## Steps Involved in Formation of Multilayer Tablet

Various steps involved in preparation of multi-layered tablet are as follows[11]

Bilayer Tablet



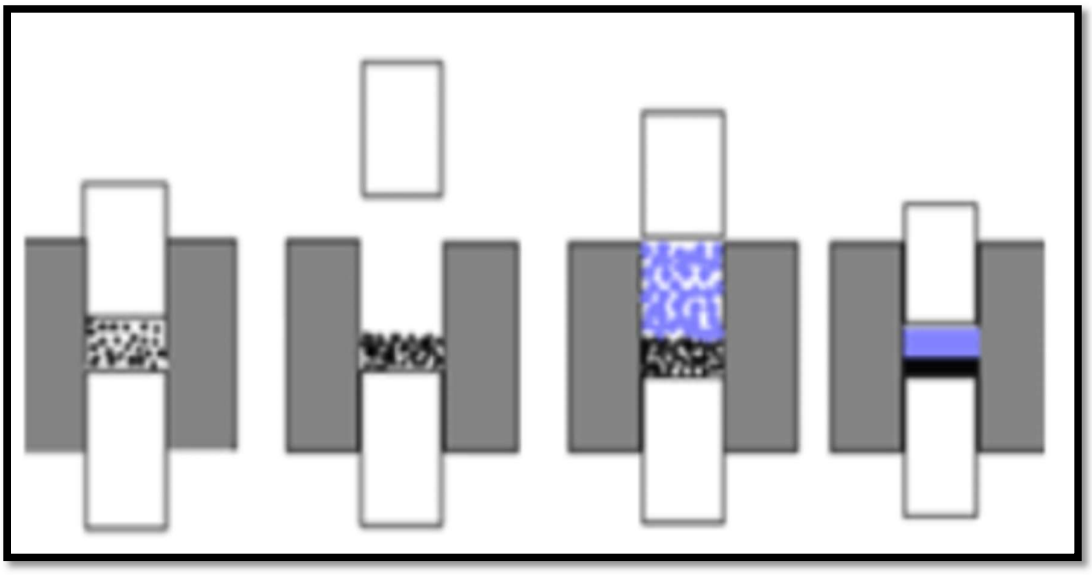



**Fig 4: Compression process of bilayer tablet**

## 2. Trilayered tablet

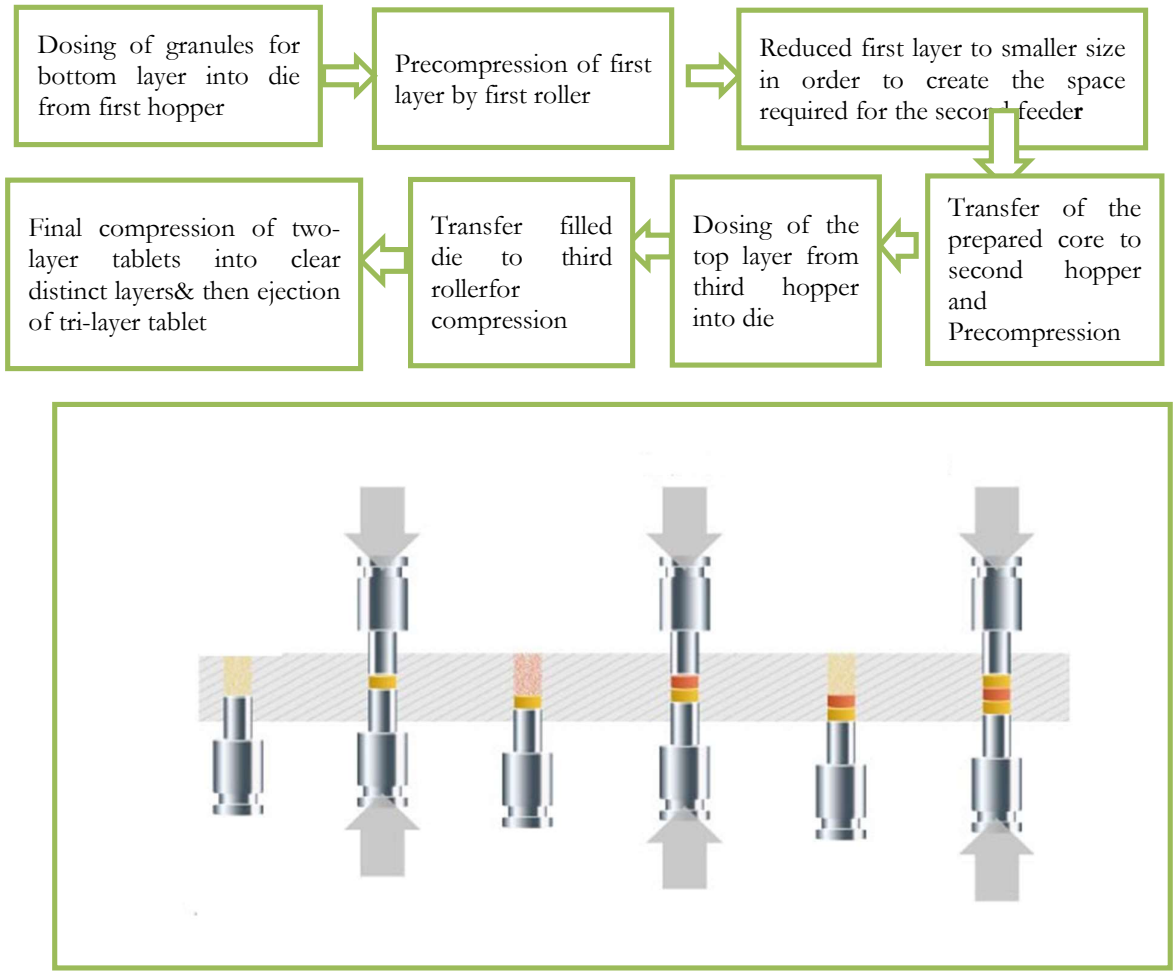



**Fig 5: Steps in formation of tri-layered tablet**



## Various Kinetic Models in Development of Multi-layered Tablets

Multi-layer design permits alternative designs of production tablets with particular release characteristics to achieve varied nebulization modes such as pulsatile, two-dimensional, delayed, and multi-modal release by modifying the geometry of the hardware or modulation layers. Below are a few schemes that will be discussed[14,15,16]

Zero order sustained release.
Quick / slow delivery system
Time programmed delivery system
Bimodal release profile.

## Zero Order Sustained Release

A hydrophilic or hydrophobic polymer is used in the system's formulation as a matrix or barrier layer to control drug release. One side of the matrix is covered in polymer on both sides, but the other side is left open to the dissolving medium to sustain drug release.11

## Quick / Slow Delivery System

A quick/slow release method with an initial fast release followed by an extended/extended drug release to generate an instant therapeutic effect while maintaining a steady drug release to keep plasma concentrations stable. When the single-release dosing schedule fails to match the requirements, this concept is used.

## Time Programmed Delivery System

When timed delivery of a medicine in the gut is required, rather than constant drug delivery in a circadian rhythm, a scheduled timed delivery

method delivers rapid drug delivery followed by a timed release. The system is made up of a core that is surrounded by multiple polymer barriers. The drug is released from the base plate after the hydrophobic or hydrophilic coating barrier swells or erodes, which suggests a pulsed release of the drug.

## Bimodal Release Profile

A sigmoid release profile, which is a two-dimensional release profile, shows an initial rapid release phase, then a moderate release period, and finally another rapid release phase. With the help of programmed pulse releases that work better at the action site, this technology adapts for sluggish absorption in the stomach and small intestine and executes periodic changes.

## Therapeutic Advantages

## Multiple Release Profiles

Multiple release kinetics for the same drug or distinct pharmaceuticals with the same or different physical and chemical properties can be provided by two or more layers in tablets, and each layer can be formulated to distribute the dose of medication with different release control mechanisms. e.g. Naproxen.[17]

## Decrease Burst Effect and Fast Initial Release Rate

A substantial initial dosage of medicine is released immediately the release rate preceding approaches a stable profile when a formulation with controlled release is placed in a release or dissolving medium (stable matrix formation). Burst release is a typical term for this phenomena, which can be controlled with multilayer tablets.

## Reduction In Dosing

Frequency Provides a definite layer as an instant-release dissolving film that offers the rapid initial necessary release to reach peak plasma concentrations then continues to take the same medication for more than 12 hours., decreasing the need for multiple dosing and hence the scaled medicine. The customizable delivery system minimizes dosing frequency by delivering the same or varied activity with a single dosage.

## Delayed Release

The second batch of medications can be delivered to the last part of the gastrointestinal tract using a rapid and delayed erodible monolith. .

## Better Execution of Release Profile

One of the most promising alternatives to conventional matrix tablets for avoiding the spread of the initial outbreak and achieving a zero-order release profile that extends drug availability for at least 12 hours was layering on the tablet, which fared substantially better in the diffusion profile. e.g. Venlafaxine hydrochloride[18]

## Controlled Release

Simultaneous swelling happens when the medication is constantly delivered into the gastrointestinal system due to an inflammatory erosion mechanism.

## Patient Compliance

To increase treatment adherence with reduced pill consumption, 'layers' on the tablets are exhibited in two completely different hues, resulting in a product that is more attractive than a typical white 'pill.' Few protective materials have two layers but appear to be made of one material. This results in smaller doses and lower peak plasma concentrations, resulting in better patient adherence. Controlled release systems are multilayer systems that contain bilayers, trilayers, tetramers, and other components. Figure 5 shows a step-by-step diagrammatic preparation of several tablets.



## Characterization Of Multilayer Tablets

Micrometrics Properties:[7,9]
Particle Size Distribution: To determine the particle size distribution, sieving is performed..
Photo-Microscope Study: A photomicroscope is used to obtain an image of TGG and GG (at X450 magnifications).
Angle of Repose: Following equation is used to calculate the angle of repose by taking diameter of the powder cone.

$$\tan = h/r,$$

where h =height of powder cone
r = radius of powder cone

## Moisture Absorption Capacity

Moisture-sensitive medications are affected by all disintegrates' ability to soak up moisture from the environment. Weighing 1 g of material evenly

dispersed in a Petri dish and monitoring it for 48 hours at 37 °C and 100 % relative humidity allows us to calculate the quantity of moisture uptake.

## Density

The tapped bulk density (TBD) and loose bulk density (LBD) were measured and verified.

## Dwell Time

When the punch head meets the compression roller that point is known as Dwell time. The defects like pores, aeration, capping, and hardness related arise if the first layer dwell time is minimized. These problems can be resolved by reducing the turret rotation or increasing the dwell time.

## Cohesiveness

The binding between layers is tightly regulated when the first layer is squeezed at a very high compression force. To protect the capacity of the first layer to connect with the second layer, some bi-layer formulations require a first layer compression force of NMT 3 Kpor 30 N. As a result, increased manufacturing rate raises the risk of separating and capping, which can be reduced by regulating proper dwell time at all compression stages.

## Risk of Separation and Capping

Making the proper connections acquired by constructing the initial layer of low compressive strength is required to reduce hazards of loosening and sealing. During the final tablet compression, the first layer be able to indeed connect with the second layer.

## Cross-contamination

Suction nozzles or dust extractors are used in multilayer tablet machines to eliminate small powder or granules, preventing cross-contamination between layers and ensuring a good separation. It is critical to take out residual powder from the mould for this action, a specific scraper plate is used prior and after every mould filling to take away remaining powder dust from the mould table, which houses the high-efficiency suction nozzles.

## Desertion

Powder movement and grain rearranging in the mould increase as shelf life increases. As a result of these two elements, the hardness of the pills is substantially increased, and possible cap difficulties are avoided.

## Final Compression Force

The compressive power applied to the last bi-layer tablet has all the time been higher than the compressive strength applied to the first layer, resulting in strong adhesion between the two layers.

## Weight Variation

Weight fluctuations will occur for some time due to uneven granule flow, incomplete mould filling, and reduced spiral winding due to the presence of too small particles in the final combination. As a result, when inserting the pill, these characteristics should be carefully evaluated[19]

## First Layer Weight Layer Measurement

This stage is difficult to complete when creating multiple layer tablets for a variety of causes, including the difficulty of sampling the first layer for weight checks at the creation and end of the compression cycle. Because the first layer rigidity is often low and complex to handle, the first weight layer is crushed at a high hardness to allow for sample, easy separation, and weighing. Reduce pressure by 20 to 30 N once the first layer has reached its target weight. Many customized tablet presses have a push button that, owing to pressure differences, automatically separates layered tablets.



## Weight Adjustment

The first layer's pressure can be used to calculate the weight of the second layer. Many operators utilise this method to acquire the desired weight rather than using a weight adjustment knob, which is entirely dependent on the operator's knowledge with double rotation pressure.

## Layer Weight Ratio

For the formulation of such tablets, layer weight ratios of 50:50, 60:40, and 25:75 are commonly utilized, assuming that the granules have excellent binding properties.

## Segregation

Because granules might separate after they exit most machines, it's essential to mix them before reusing them in the hopper. This will reduce

content uniformity in the final product

## Multilayer Tablet Presses

The machines having both D,B,or both types of tooling are useful for manufacturing of multilayer tablets.Leading companies in pharmamachineary like Cadmach, Karnavati, Elizabeth-Hata, KG pharma, Fette, GEA Process Engineering, Korsch, and other firms provides such machines for formulation of multilayer tablets. These machines have the ability to manufacture in a variety of sizes and shapes with maximum production using modern equipment.

## Tablet Thickness and Size

For tablet size homogeneity, the diameter and thickness of the tablets were critical. The thickness and diameter was measured by using vernier caliper.

## Tablet Hardness

The resistance of tablets to shipping or breakage during handling, transportation, and storage before to use depends on their hardness. The tablet hardness of each formulation was assessed using a Monsanto hardness tester. The level of toughness was determined to be 1 kg/cm2[20]

## Friability

The strength of a tablet is measured by its friability. The following approach has been used to test the friability. Twenty pills were precisely weighed and positioned in the tumble equipment, which rotates at 25 rpm and drops the tablets six inches with each revolution. After 4 minutes, the weight of the tablets was measured to determine how much it had decreased.

[(Initial wt. of tablets – Final wt. of tablets)/ Initial wt. of tablets] = percent loss ×100 Tablets with a friability of less than 1% are regarded acceptable.

## Uniformity of Weight

Twenty tablets were randomly selected, and the average weight was then determined. We estimated weight variation and compared it to IP and USP standards[21]

## Content Uniformity

The Content Uniformity test evaluates whether the amount of a specific medication substance(s) in a variety of different dosage units falls within predetermined ranges. The purpose of the content uniformity test was to validate that the active pharmaceutical components were constant within a narrow range of dosage units surrounding the label claim. When the active component makes up less than 2% of the total weight of the tablet or when the amount of active ingredient is less than 2 mg, this test is necessary. In this study 30 tablets are randomly selected using the USP technique, and by using procedure given in specific monograph10 tablets from these are analysed independently. The standard for content uniformity is met if the amount of active ingredient in 9 of 10 tablets is within the range of 85% to 115% of the label claim, unless otherwise stated in the monograph. The 10th cannot have less than 75% of the listed medication content or more than 125% of it. The remaining 20 tablets are tested individually, and none must fall outside the 85% to 115% range for the batch to be approved if one or more dosage units fail to meet these requirements.

## Dissolution Studies

In vitro drug release tests in simulated stomach and intestinal fluids were used to evaluate the potential of bi-layer tablets to offer the required controlled medication delivery. Drug release tests were carried out using USP Dissolution Test Apparatus I at 100 rpm, 37° 0.5°C, and pH 1.2 buffer (900 ml) (i.e. 0.1 N HCl) for 2 hours because the typical gastric emptying duration is about that long. After replacing the dissolution media with 900 mL of pH 6.8 phosphate buffer, the test was continued for an additional 10 hours. At different times, 5ml of the samples were taken out and reconstituted with 5ml of drug-free dissolving media. With a UV spectrophotometer operating in multi component mode, the removed samples were inspected. [5,6]



## FT-IR Compatibility Study

For structural analysis, FT-IR spectroscopy can be used. Both the core and the coated core may be evaluated using the potassium bromide sample disc method by capturing their IR spectra in the wave number range 4000 - 400 cm-1; the characteristic peaks seen are then matched with reference peaks. FT-IR analysis of the sample can also corroborate the identification of the drug and drug additives, as well as the physical composition, revealing that there is no interaction between the drug and other additives.[11]

## Stability Study

Stability tests is performed as per to ICH requirements by storing the manufactured multi-layered tablet at different temperatures for one to three months, including room temperature (25°C + -2°C) and increased temperature (40°C +-2°C). The drug content and variance in dissolving data were checked on a regular basis.

## Various Techniques For Multilayer Tablet: [17,18,19]

EN SO TROL Technology
DUROS Technology
L-OROSTM Technology
Elan Drug Technologies's Dual Release Drug Delivery System
OROS® Push Pulls Technology

## EN SO TROL Technology

Shire Laboratory uses an integrated approach to drug delivery that focuses on the identification and incorporation of the found enhancer into controlled release technologies to either provide the best dosage forms or improve solubility by an order of magnitude.

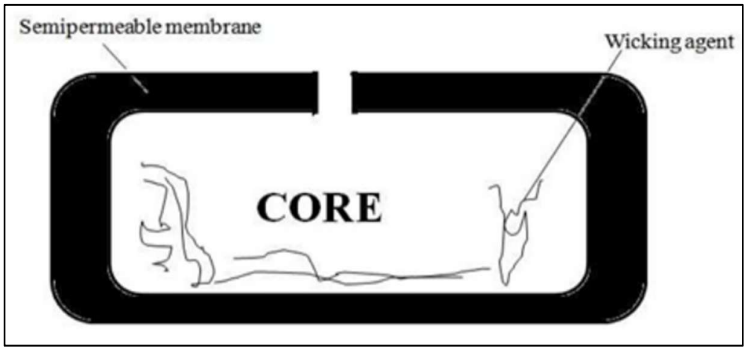



**Fig. 6: EN SO TROL Technology diagram**



## DUROS Technology

The system is composed of an external cylindrical titanium alloy reservoir. The tremendous strength and stiffness of this reservoir shields the medication particles from enzymes. The DUROS technology is a tiny medication dispensing system that functions similarly to a tiny syringe and administers a small amount of concentrated form on a consistent basis over the course of months or years. Figure 9 depicts the technological operation of DUROS.

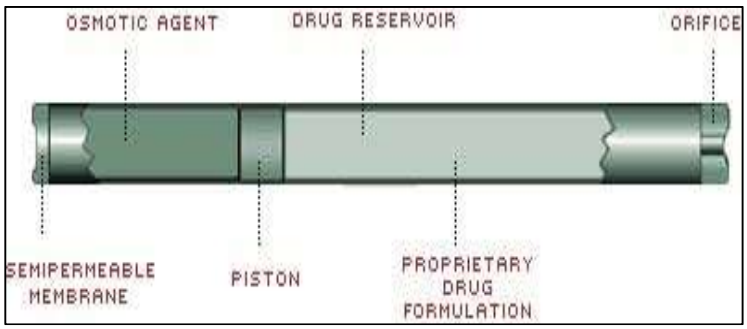



**Fig.7: DUROS technology**

## L-OROSTM Technology

Alza created the L-OROS system to address the solubility issue, in which the manufacturing process for a lipid soft gel product having medicine in a dissolved state includes coating the product with a barrier membrane, an osmotic push layer, and subsequently a semi-permeable membrane with an exit orifice. Figure 7 depicts the L-OROSTM technical presentation.

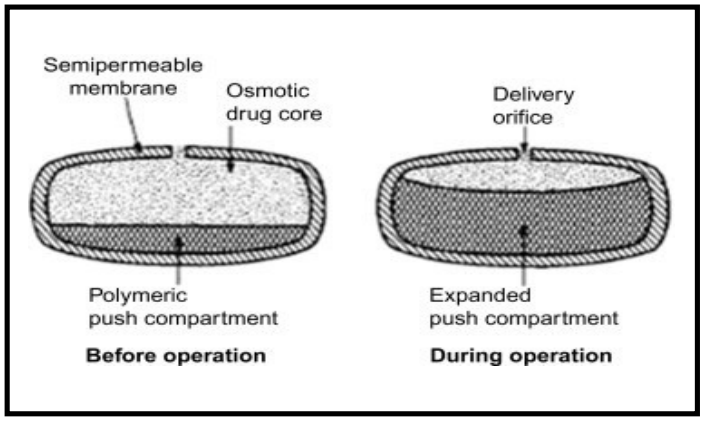



**Fig. 8: OROS® push pulls technology diagram**

## Elan Drug Technologies's Dual Release Drug Delivery System

((DUREDAS Technology) is a bilayer tablet that can give varied release rates of the same drug or rapid or extended release of two treatments in one dosing form. The tab letting process can create two distinct layers within a single tablet: an instant release granulate and a modified-release hydrophilic matrix substance. The modified-release properties of the dosage form are provided by a combination of hydrophilic polymers. Benefits offered by the DUREDAS™ technology include-

Bilayer tableting is a type of tableting that consists of two layers.

Two medication components have a customised release rate.

Combination of two separate CR formulations' capability.

In one tablet, the ability for immediate release and adjusted release components.

Presentation of the unit dose as a tablet.

The DUREDAS technology may be simply adjusted to allow the bi-layer to contain two sustained release formulations. From either side, two distinct release rates can be achieved. This allows for a longer period of sustained release to be attained. Typically, a controlled release component is squeezed first onto the original tablet, and then an instant release granulates. The final dose form has the typical bi-layer effect as a result of this. Another use of the DUREDAS technology is the development of controlled release combination dosage forms, in which two distinct drugs are combined into various layers and the drug release of each is controlled to improve the therapeutic impact of the mixture. The two medications can be used in both rapid and controlled release combinations.

This technology method has been used to analyse a variety of combination products. The DUREDAS technology was first used to develop a number of over-the-counter controlled-release analgesics. In this scenario, a fast beginning of therapeutic impact necessitates a rapid release of analgesia. As a result, one layer of the tablets is granulate for instant release. The second layer of the tablet, on the other hand, uses hydrophilic polymers to release the medicine in a regulated manner. Diffusion and erosion through the hydrophilic polymer matrix are responsible for the regulated release.



## Conclusion

The bi-layer tablet is a beneficial technology that has been enhanced to fix the problems with the single-layer tablet. A bi-layer disc made up of partly coated or multi-layered homogeneous matrices can be used in a variety of ways. The bi-layer tablet can be used for the progressive release of two active ingredients in combination, the separation of two incompatible substances, and the excretory tablet, wherein one layer releases a dose initially and a second layer releases a dose subsequently. By offering surrounding or numerous projecting layers, multilayer tablet formulations are employed to provide solutions for the distribution of incompatible medications as well as controlled release formulations. Bilayer tablet quality and GMP criteria can differ significantly. This explains why a variety of presses—from straightforward single-sided presses to incredibly complex devices like the Courtoy-R292F—have been developed and utilised to make bi-layer tablets. The best method

appears to be "air compensator" in conjunction with displacement control for producing high-quality bi-layer tablets quickly.

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