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Review Article

Bilayer Tablet a Dual Released, an Emerging Trend for Novel Drug Delivery System

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Abstract:

Bilayer tablets are a kind of medication that effectively treats illness by combining two pharmaceuticals, either the same or different ones, in a single dosage. Physically separating active pharmaceutical ingredients (API) may prevent chemical incompatibilities, and bilayer tablets can pave the way for the creation of various drug release profiles, such as immediate and prolonged release. Analgesic and anti-inflammatory bilayer tablets are significantly different. Two medications may be sequentially released from a bi-layer tablet, making it ideal for sustained-release tablets. One layer can be immediate-release for the first dosage, while the other can be a maintenance dose. The purpose of this review is to identify problems with bilayer tablet preparation and to suggest ways to fix them. To further aid comprehension, the article goes on to list the many kinds of bilayer tablets, including single-side presses, double-side presses, and bilayer tablet displacement presses, as well as their uses, advantages, and disadvantages. In addition, the review paper discusses the several ways and procedures used to manufacture bilayer tablets, so readers may have a comprehensive understanding of these tablets. In the last paragraph, the whole essay is evaluated critically.

Keywords: Bilayer tablets, immediate release, Sustain release, Drug delivery system

Introduction:

Over the last decade, there has been a significant uptick in the commercialization of novel pharmacological compounds, with an even greater emphasis on their combination in order to combat numerous illnesses, each of which requires a unique dose regimen. As a result, research into sustained or controlled drug delivery systems has gained steam. Bilayer tablets are well-received by patients and may be used for the sequential release of many medications at once or for the immediate and sustained release of a single drug at two

different doses: the initial and maintenance doses. More than nine in ten modern formulations are meant to be taken orally. The fact that the researcher is focusing mostly on this class of formulations indicates how popular they are globally. In light of the difficulties encountered during production, this study intends to illuminate the role of bilayer tablets as a drug delivery system component. This article also examines the several methods for its production and the many bilayer tablets used for various ailments. Less frequent dosing is the primary goal of controlled medication delivery systems. Ensuring safety, improving therapeutic effectiveness, and increasing patient compliance are the main goals of sustained release drug administration [1]. Tablets The solid unit dose form of a medicine, a tablet might be granular, powder, crystalline, or crushed into a disc. The APIs or medications may or may not include excipients. Tablets are the most popular dosage form because to their many advantages, including their portability, stability, convenience of administration, accurate dosing, and ease of manufacturing, transportation, and storage. Tablets are a viable form of administration for most pharmaceutical substances. [2]. they are categorised into different categories based on their release profile, coating type, and administration route which is shown in following figure 1. Types of multilayer tablets Bi-layer tablets to quadruple layered tablets are available. Bilayer tablets: Bilayer tablets allow for the sequential and simultaneous delivery of two different APIs. An immediate-release layer and a maintenance-dosing sustained-release layer are present. With no pharmacological or behavioural interactions, the bi-layer tablet may deliver two drugs simultaneously. Triple layer tablet: One layer of a triple-layer tablet is designed for rapid drug release, while the other two layers work together to provide a more gradual release of the active ingredient over time. These two layers are separated by the intermediate barrier layer. When administering two drugs with known interactions, this is the way to go [3].

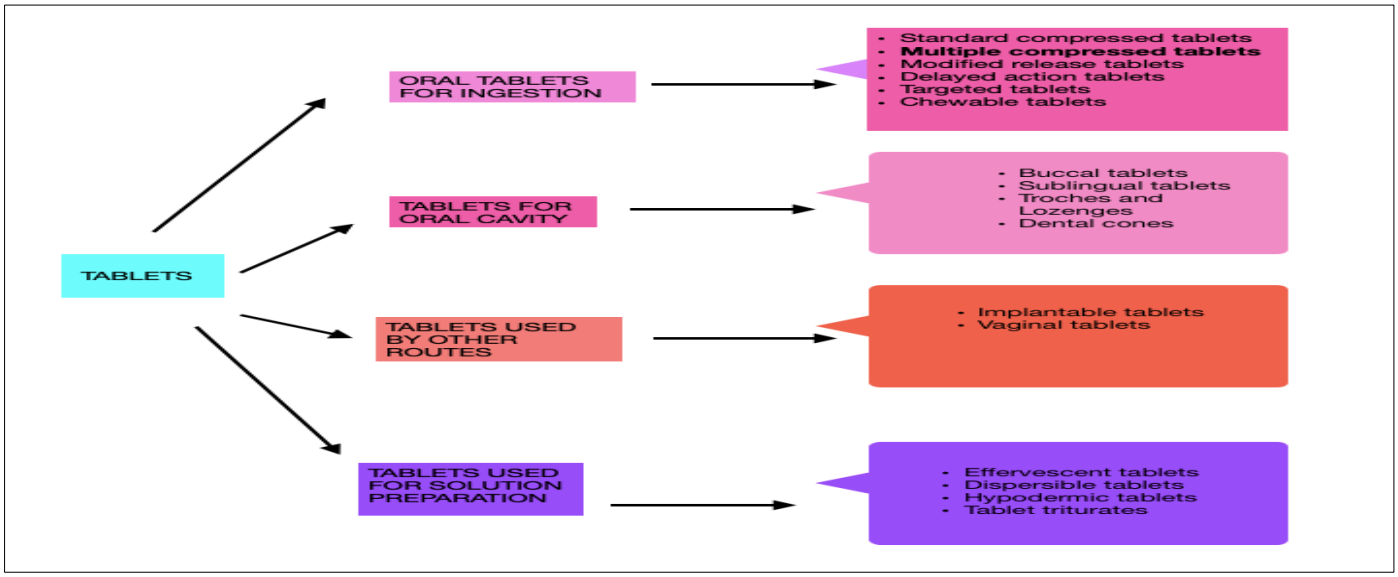

Figure 1: Types of Tablet.

Bilayer tablet

A bilayer tablet is an FDC that is designed to be used orally. The first layer provides the traditional or immediate release of one or more active ingredients, while the second layer provides the controlled or sustained release of the same or more active ingredients. An acronym for "Bilayer tablets" describes them. Two medicines were identified using distinct colours. As an improvement over the single-layered tablet, the bilayer tablet represents a significant step forward. The first layer of a bilayer tablet is the immediate release layer, which includes super disintegrates to speed up the drug's release and get the loading dosage out of the way as soon as possible. The second layer is the sustained release layer, which releases the medication over time. An immediate goal of one of its layers is to get a high serum concentration quickly by guaranteeing the drug's extraction. In contrast, the maintenance dosage layer employs a variety of polymers as release retardants to ensure the drug's steady release over an extended length of time. Long-term maintenance of an effective plasma level is the goal of the second layer, which is a hydrophilic matrix with controlled release capabilities [4].

The majority of drugs that work well with this method of administration include those that treat diabetes, hypertension, allergies, pain, fever, and antihistamines. The rapid increase in blood concentration that follows the first layer's rapid release is the pharmacokinetic advantage. However, after medication release from the second supporting layer, the blood level becomes more stable. Reducing dosage frequency or enhancing medication effectiveness are the goals of selecting for controlled or sustained delivery systems [5].

Advantages [6]

- They are incorporated into more traditional technological systems
- The possibility of using feed granules for a single entity.
- Separating components that are anti-compatible.
- The effectiveness of pharmacological regimens is improved as a result of increased patient compliance. as it requires fewer dosages each day than the conventional method of distribution.
- Maintain physical and chemical stability.
- Retain potency and ensure dose accuracy

Disadvantages [7]

- Makes things more complicated and costly to use dual rotary presses.
- Inadequate decreased production.
- hardness,
- layer separation,
- Inaccurate individual layer weight control.
- Cross contamination between the layers.

Applications [8]

- If you need to release two medications at once, a bi-layer tablet is the way to go.

- Make Two Distinct Substances Work Alone.
- A two-layer sustained-release tablet with an immediate-release layer for the starting dosage and a maintenance-dose layer on top.
- Encouraging Ease of Use and Compliance for Patients.
- In order to address the drawbacks of the single-layered tablet, bilayer tablets have been developed.
- Both the loading dosage and the sustained dose of the same or different medications may be delivered by means of bilayer tablets.
- Bilayer floating tablets include two layers: one for the drug's quick release and one for the tablet's floating action.
- Bilayer tablets are used to deliver the two different drugs having different release profiles

Types of bilayer tablets:

There are four types of bilayer tablets differing on the mechanism employed to produce them. The first type is the simplest design termed as single side press it is produced with the simple technique of pressing with the help of gravity or sometimes force. The second type is known as Double-sided press which is generated with the process of compression, the third type is bilayer tablet press produced under the process of displacement. And the fourth type is Multilayer compression basics [9]. All types are explained below:

Single sided tablet press.

Double sided tablet press

Bilayer tablet press with displacement

Multilayer compression basics.

Single sided press

The years have seen the development of several varieties of bilayer presses. Separating the two chambers of the double feeder makes for the simplest design of a single-sided press. Two separate layers of tablet are created when each chamber is either force-fed or gravity-fed with a distinct powder. In one or two steps, the dye is loaded with the initial layer of powder as it goes beneath the feeder. Then, the tablet is crushed. When making a tablet, the two dye layers usually connect well enough that there is no separation of the layers, even when they mix somewhat at the interface. Making a bilayer tablet has never been easier than this [10].

Limitations of single-sided press [11]

- There is no way to control the separate layers.
- There does not seem to be any apparent separation between the layers.
- Due to the short stay duration of the first layer, capping and de-aeration issues arise.
- The transmission towards the testing unit makes it harder to assess the first layer sampling quality control.

- There is no way to keep track of the weight of the two layers independently.
- It is not immediately apparent where one layer ends and the other begins.
- Brief dwell time for the first layer because of the small compression roller, causing the possibility of reduced de-aeration, hardness, and capping.

Dwell time

The duration during which the compression force remains more than 90% of its maximum value is called the dwell period. In the case of complicated formulation compression, in particular, long dwell durations lead to the manufacture of high-quality tablets.

Compression force

In order to maintain their capacity to connect with the second layer, most bilayer formulations need the compression force for the first layer to be lower than 100 daN. This is because it might deteriorate beyond this value. The tablet's diminished hardness is due to the layers' poor bonding. Furthermore, in the end, the layers do split from one another [12].

Double sided tablet presses

Each film of this bilayer pill has its own fill station and core compression. The bilayer tablet goes through four distinct processes before it is ejected from the press. Most double-sided tablet presses with automated production control employ compression force to monitor and manage tablet weight. At the primary layer compression, the control system determines the effective peak compression force that is delivered to each tablet or layer of tablets. The control system then uses this peak compression force to reject tablets that are not within tolerance and adjust the die's filling depth as needed. Better weight monitoring and individual layer mass management are two benefits of using double-sided tablets rather than single-sided ones. Additionally, they do not cap the initial layer since they provide little compression. In order to achieve a necessary level of hardness, they possess enhanced dwell duration capabilities; yet, these features are not without their restrictions [13].

Advantages [14]

- To prevent chapping and layer separation, the initial layer is subjected to a low compression stress.
- To achieve the desired hardness at maximum turret speed, the dwell time at pre compression was increased for both the first and second layers.
- Two layers are protected from pollution to the maximum extent possible.
- The two layers are visually distinct from one another.
- Accurate and independent weight management of each layer is achieved using displacement weight monitoring.
- Maximized yield.
- When the bi-layer tablet is finally compressed, the two layers separate since there was not enough bonding between them.

Limitations [15]

- Proper bonding can only be achieved
- When the first layer undergoes compression with a little compression force, allowing it to continue interacting with the subsequent layer at final compression.
- Applying too much pressure while compressing the initial layer limits bonding.
- The low compression force required
- Regrettably, while compressing the first layer, tablet presses that detect compression force have less accurate weight monitoring and control of the first layer.

Bi Layer Tablets Presses with Displacement

There is a major difference between the principles of compressive force and the bilayer tablet press. Here, less compression force improves precision. Capping and separation become more likely at faster production speeds, although they may be mitigated with enough dwell time in the four compression phases [16].

Advantages [17]

- Accurate independent weight management of the different layers is achieved by displacement weight monitoring and control.
- In order to prevent chapping and the separation of the two layers, a low compression force is applied to the first layer.
- To achieve the desired hardness at maximum turret speed, the dwell time at pre compression was increased for both the first and second layers.
- Ensure that no contaminants may penetrate between the layers to any degree.
- The layers are visually separated. clear visual separation of the layers.
- Maximized yield.

Multilayer Compression Basics

You may get presses designed for multiple layer compression or adapt a regular double press to use multipliers. For quite some time, the idea of multilayer tablets has been used to create sustained release formulations. These tablets typically have a fast-releasing layer and either two or three layers of medication to ensure that the medicine is released slowly but steadily over time. The pharmacokinetic benefit is based on the fact that the drug's concentration in the blood rises sharply upon release from fast-releasing granules, but remains constant upon release from sustained granules [18].

Principles and Considerations of Bi-Layer Formulation:

It is common practice to utilize the more freely flowing formulation for the first layer as it determines the fill control and weight for the second and subsequent layers. Thermoplastic lubrication, main compaction force, and first layer tamping force optimization: Just enough tamping power to produce densification or make room for the second layer's filling should be applied to the

first layer. The interface strength is significantly affected by the degree to which the first layer compaction force produces elastic and plastic deformation. Due to the fact that bi-layer tableting subjects the first layer formulation to twice compression, the interface strength decreases as the compaction force applied to the first layer rises. To get the most out of compression and layer adhesion, as well as other tablet compositional considerations like choosing plastic, brittle, and other desired components, it's best to make layers with comparable properties and compactibility. Interaction adhesion strength and dwell duration are influenced by process-related factors such as tableting speed and compaction pressure. A happy medium between fast speed efficiency and excellent tablet yield may be achieved with adequate compression dwell durations. Another factor that could influence the adhesive strength of the layers is the concentration of lubricant in the mixture [19].

By compressing individual layers of each medicine to minimize the area of contact between them, bilayer tablets containing incompatible substances may also be manufactured.

Compaction

Some criteria, such the required mechanical strength and the intended drug release profile, must be satisfied in order to make a suitable tablet. Because of the drug's poor flow and compatibility characteristics, which will lead to capping and/or lamination, it may be challenging for the formulator to attain these conditions, particularly in the bilayer tablet formulation that involves the double compression process. Both compressibility and consolidation play a role in the compaction process.

Compression

It is defined as reduction in bulk volume by eliminating voids and bringing particles into closer contacts.

Consolidation

Increased mechanical strength as a result of intraparticle connection (bonding) is a feature of this substance. One of the most important factors affecting tablet delamination was the compression stress on layer 1[20].

Multi-layer tablet dosage forms are designed for variety of reasons [21]

- Floating tablets and chewing gadgets are two examples of innovative medication delivery mechanisms that might be developed to extend the life cycle of medical items. Fixed dose combinations of different active pharmaceutical ingredients (APIs) may be administered by buccal or mucoadhesive delivery systems.
- Managing the dose of a therapeutic substance or substances.
- One may alter the API layer's total accessible surface area by creating active layers for modified release and sandwiching one or two swellable/erodible barriers in between.
- To keep process control intact, it is required to distinguish between APIs that are incompatible with each other. Layer-to-

layer API extraction using a functional feature (like the osmotic property) of a higher-level layer.

General properties of bilayer tablet dosage forms [22]

- Defects such as chips, fractures, discoloration, and contamination should not be present in a bilayer tablet, which should also have an exquisite product identity.
- Must be sturdy enough to endure mechanical stress while being manufactured, packaged, transported, and administered.
- Both its physical and chemical stability are crucial.
- The bi-layer tablet's drug release should be consistent and predictable.
- Must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

Bilayer tablets: quality and GMP-requirements [23]

To produce a quality bilayer tablet, in a validated and GMP-way, it is important that the selected press is capable of:

- The two layers that make up the bilayer tablet must not cap each other or separate.
- Make sure the tablets are firm enough.
- Maintaining separation between the two layers to avoid contamination.
- Making the contrast between the two levels stand out.
- Excellent production.
- Accurate and individual weight control of the two layers. These requirements seem obvious but are not as easily accomplished as this article aims to demonstrate.

Various approaches to bilayer tablets

Floating drug delivery system

The lower density of these is designed to allow them to float on top of gastric contents. Once administered, they will continue to float until the system breaks down or the device absorbs the fluid, reducing its density and buoyancy. At that point, it will be able to pass easily from the stomach through a motility wave, causing the stomach to empty. The two layers of the bilayer tablet are designed such that one layer delivers the medicine instantly, causing its effects to kick in quicker, while the other layer floats in the stomach. Both intra-gastric bilayer floating tablets and multiple-unit type floating pills are the two main ways that floating doses are made [24]. The following details both of these:

Intra gastric bilayer floating tablets

There are two main compressed layers to these tablets: the immediate layer, which is used to rapidly affect the target area, and the sustained release or expanded release layer, which is used to affect the target after the first layer is finished.

Multiple unit types floating pills

Pills encased in two layers make up the expanded/sustained release component of these

tablets. Chemically, the inner layer consists of effervescent chemicals, while the outer layer is formed of a swellable membrane. These tablets, when dissolved in water at room temperature, first sink to the bottom, then inflate to balloon proportions owing to their low density, and then float to the top [25].

Polymeric bio-adhesive system

After administration, they absorb the fluid thanks to their special manufacturing process. The outer layer then becomes sticky and thick, adhering to the mucus layer in the stomach. Because of this, stomach preservation is encouraged to tilt as the adhesiveness weakens. One layer has the bio-adhesive characteristic, while the other is for quick dosage. Nevertheless, this dose has never been used on people; it has only been tested on animals. The physiological differences between the human and animal bodies account for this, as does the fact that mucus production and consistency vary greatly between the two [26].

Swelling system

These are designed to be very little when given so that the dosage may be more easily swallowed. Once consumed, they quickly expand, dissolve, or unroll until they reach a size that blocks the pylorus channel, allowing the drug release to advance to the appropriate level. After slowly eroding or breaking down into tiny pieces, it exits the stomach. The basic bilayer tablet may have one layer that releases the drug immediately and another layer that releases it over a longer period of time, similar to a regular tablet [27].

Techniques of bilayer tablets

The necessary quality of bilayer tablets is achieved by using several bilayer tablet processes. The following methods are employed in this procedure: erodible multilayer drug system, programmable oral drug absorption system (Prodas), osmotic-release oral system (OROS) push-pull technology, En so troll technique, L-OROS Tm technology, DUROS technology, Duredas technology/Elan drug technology, Geomatrix technologies, Geminix technology, and Geomatrix technologies. These are shown using illustrations and described below [28]

OROS ® push-pull technology

Typically, this technique consists of two or three layers, with the active pharmacological component included in the first one or two layers and the push layer being the final one. The drug layers are formed of insoluble substance and consist only of the drug with a few excipients. It may also include an osmotic agent and a suspending agent (fig. 2) According to [29], the tablet core is kept apart from its surroundings by a semipermeable covering.

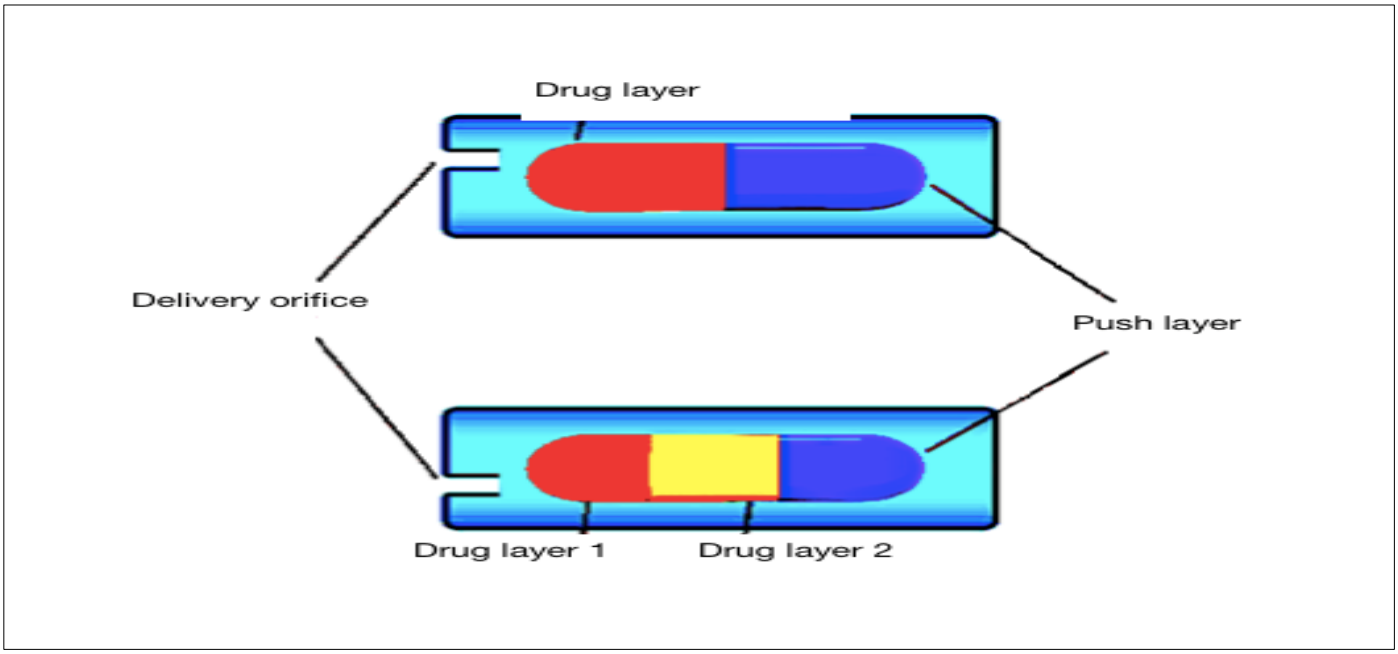

Figure 2. OROS Push-Pull technology.

L-OROS Tm technology

Alza has developed a technological solution to a serious issue with solubility. The medication was first created as a dissolved lipid soft gel. After that, a barrier membrane was placed on top, then the osmotic push layer, and finally, an exit chamber was created by puncturing the semipermeable membrane (Fig. 3).

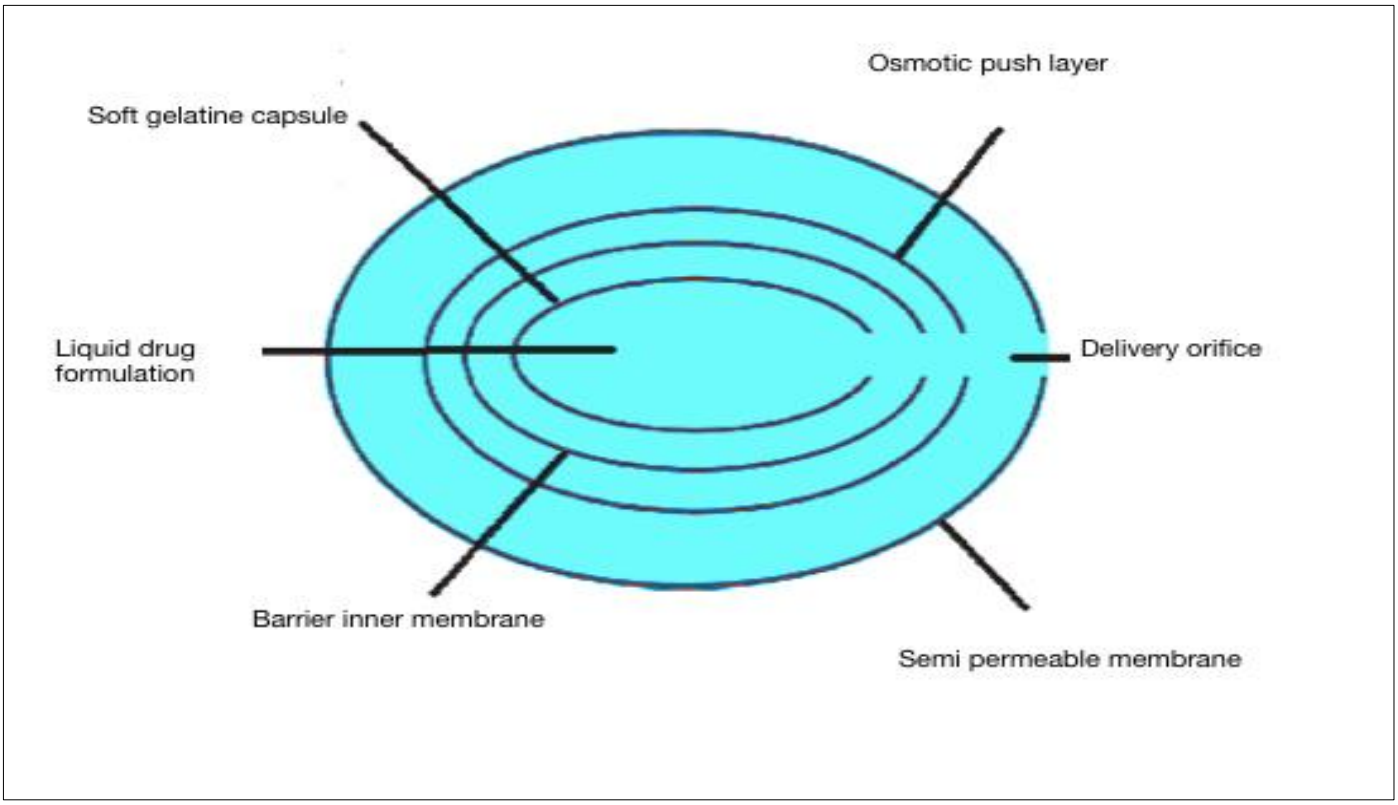

Figure 3. L-Oros tm technology.

DUROS technology (Alza Corporation)

A variety of biological compounds, including peptides, proteins, and others, may be transduced using the Duros technology's reliance on the implant approach. This method, which is also called "Miniature drug dispensing technology," is essentially a small syringe that dispenses a concentrated version of the medicine constantly and reliably over an extended period of time. These cylinders prevent the medicinal chemicals from entering the human body and causing them to be resistant to human tissues for an extended length of time (Fig. 4). Utilising this technique, Viadur (leuprolide acetate implant) is administered annually as a palliative therapy for advanced prostate cancer [31].

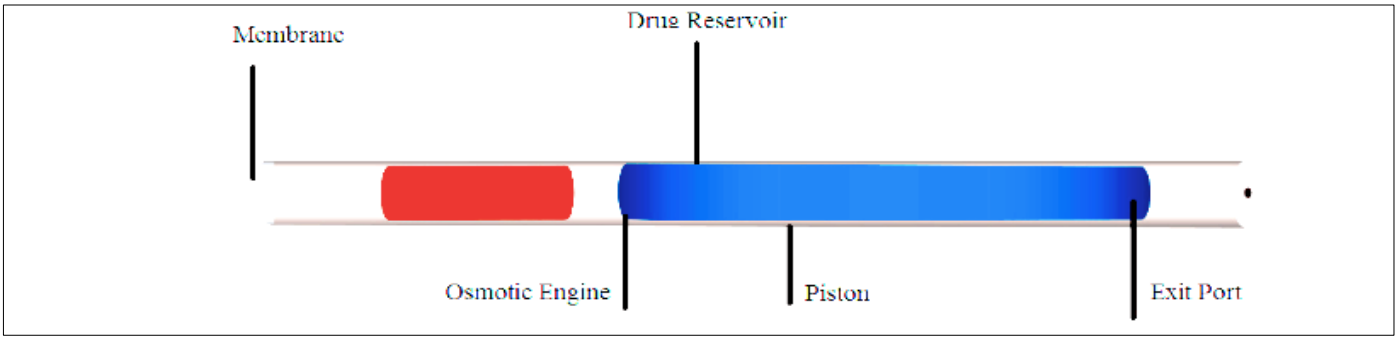

Figure 4. DUROS

Elan drug technologies' dual release drug delivery system (DUREDASTM technology)

Elan Corporations use a technique called DUREDAS, which stands for dual drug delivery system, to distribute a single dose in two different ways. With this innovation, you may get a medicine with either a quick or a prolonged release pattern. This method combines the immediate-release and hydrophilic layers of a tablet in a single tablet via two separate direct compression procedures. In doing so, it creates a complicated controlled-hydrophilic matrix that stays compact while slowly absorbing fluids from the GI tract. The hydrophilic matrix transforms into a sticky, permeable gel as it absorbs fluid. This gel then functions as a barrier between the dose and the surrounding fluid, preventing the medicine from being dissolved when the gel expands and permeates the surrounding fluid [32].

To put it simply, this technique provides a combination of quick and sustained release, or a pattern of drug release. Two medications may be delivered with a combined release pattern, or one drug can be delivered with a distinct pattern. It uses a mixture of hydrophilic polymers to create the varied release patterns. The system's many advantages include, among other things, the ability to mix the releases of two medications into a single dosage or two tablets. The DUREDASTM Technology is used to make the bilayer tablet, with the compressed layer being ground first by the instant release and the sustained release layer following. The development of over-the-counter controlled release anesthetics was the first use of this technology [33].

EN SO TROL technology

The Shire laboratory employs an integrated approach to the drug delivery system, which involves determining the optimal dosage form for the controlled release system and then adding the enhancer (Fig. 5). Solubility is improved using this method [34].

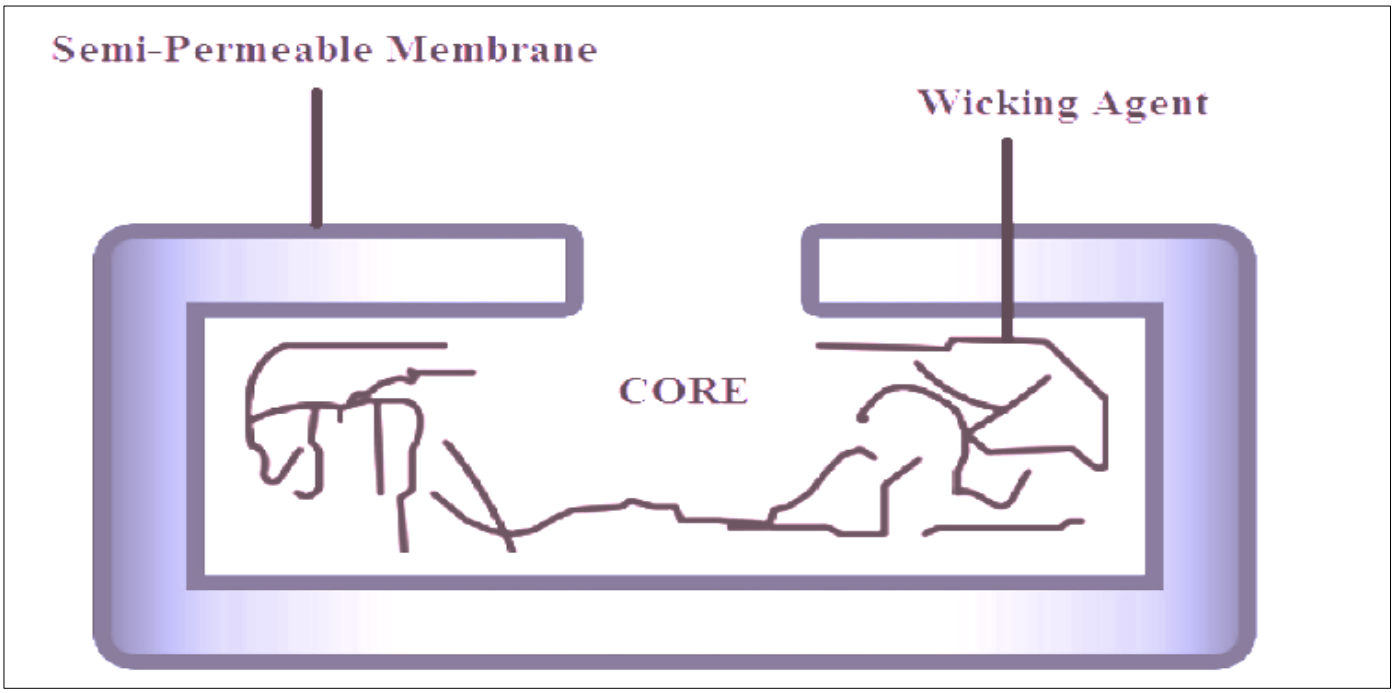

Figure 5. EN SO TROL technology.

RoTab bilayer

The software in question is modular in nature, meaning it may have new features added to it at a later date. Thanks to the state-of-the-art PC-system with a 15-inch touch-screen, exact findings may be obtained quickly via graphical examinations.

Whenever its production mode is switched to Working-RoTab bilayer, the system automatically controls itself. By adjusting the filling speed and die table, it assists in automatically regulating the dosage and compression force. Additionally, it is useful for controlling the hardness as needed.

R&D updated method— R&D updated Thanks to the measurement points they provide, RoTab Bilayer aids in graphical visualization and assessment. These serve important purposes, such as modifying the tightness of the punch. These include R and D plus, as well as the possibility of an unexpected upgrade.

R and D plus—R and D Plus offer enhanced standards and are a vital part of tableting technology. Important features, such as the force-displacement display, the tablet's scraper force, and punch tightness, may be controlled with their assistance [35].

Geminex technology

The therapeutic efficacy of the medications is much enhanced using this technique, which also significantly reduces their negative effects. It is able to de-liver several medications with varying release rates all at once. Pen west mostly uses it for CNS illnesses, diabetes, cancer, cardiovascular disease, and other conditions that benefit both patients and the business [36].

Programmable oral drug absorption system (PRODAS)

Encapsulating controlled-release mini-tablets (1.5–4 mm) of medication is the basis of PRODAS, or multi particulate drug technology (Elan Corporation). These medications may now be administered in a single dosage thanks to a technological advancement that combines multi-particle and hydrophilic matrix tablet technologies. The targeted delivery of medications to the GIT is facilitated by PRO-DAS technology. To achieve the desired release rate, a single dose is prepared by combining mini-tablets with different release rates, such as immediate, delayed, or controlled release. Products with predicted release patterns are often created by combining Minitab with multiple APIs [37].

Erodible molded multilayer tablet

Tablets that are molded and have many layers are part of the Eaglet delivery system. A coat and matrix are components of this technology, which is manufactured using the conventional method of plastic injection molding. Eaglet erodible molded tablets release its active ingredient by eroding the matrix. Without interfering with gastrointestinal issues, this method aids in administering the medication in a zero-order or delayed-release pattern. This technology's release pattern is modulated by the geometric design and engineering of the coat and matrix. Matrix dispersion allows for zero-order release of the medicine. As an added bonus, the coat is both biodegradable and very water-resistant. Matrix erosion occurs when it comes into touch with preexisting water or gastrointestinal fluids and is accelerated by gastrointestinal motility. This method works well for pharmaceuticals that suffer from chemical or physical stability problems when exposed to water. Low manufacturing costs, precision, and repeatability are also promised [38].

Geomatrix technologies

Using Geomatrix technology, a multilayer tablet may be created. During this process, a matrix core encases an active component, and one or more modulating layers, which function as barriers, are attached to the central matrix. These barriers primarily serve to keep the core and dissolving medium from coming into touch with one another. Medications including diclofenac sodium, nifedipine, and diltiazem hydrochloride are marketed using this technique [39]. The eight Geomatrix methods, developed to achieve a wide variety of therapeutic goals, are:

- Zero-order release Geomatrix technology is employed for a constant medicine discharge rate over a long duration of time.
- Binary-release Geomatrix technology is utilized for the measured discharge of two distinct drugs present in a particular dosage.
- Quick-slow release Geomatrix technology involves a fast discharge of dosage tailed by a continual discharge for a specific period.
- Slow-quick release Geomatrix technique, this is anti-parallel to the quick-slow release technique. It involves a slow constant release of drug followed by an immediate discharge at a fixed time.

- Positioned released geomatrix technique involves the transport of the medicine to a specific location in the gastrointestinal tract earlier to the discharge of the main dosage.
- Accelerated release geomatrix technology includes the constant accelerating release of the core drug.
- The delayed-release geomatrix technique is utilized when a pre- arranged time delay of the actual dosage is required.
- Multiple pulse geomatrix technology is employed whereby a prior quick burst is required followed by a prearranged time of no release.

Challenges involved in manufacturing of bilayer tablet:

The production of bilayer tablets is susceptible to cross-contamination between layers if certain conditions are not met, such as an inadequate hardness, layer sequence, layer weight ratio, an elastic mismatch between adjacent layers, or an excessive tamping force given to the first layer. Improper management of these elements will have a significant influence on bi-layer compression pressure as well as qualitative attributes such as mechanical strength and layer weight regulation. Therefore, it's critical to focus on the robust design of a product or process. Bilayer tablets are much more difficult to produce than single-layer ones, even though they are essentially two single-layer tablets compressed into one [40].

The physical and chemical characteristics of the API and excipients play a significant role in the manufacture of bilayer tablets. Bilayer tablet strength and fracture mode are highly dependent on the tablet's material composition. How something compresses depends on its plasticity, brittleness, and viscoelasticity. The impact of compression on a material's plasticity and brittleness must be carefully considered. Compression is unaffected by plasticity as long as the material's elasticity stays below the bond limit.

Since particle disintegration is more significant in the inner layer of the die compared to the outer layer, it is necessary to analyses the material properties of the substance before making bilayer tablets. Multilayer tablet formulations need appropriate volume reduction in addition to mechanical, long-lasting, and cohesive cohesiveness between all layers. Compressibility (a substance's capacity to reduce in bulk when compressed) and compatibility (the ability of powdered substances to transform into tablets) dictate that they should be very compact. To optimize the compression capabilities, flow characteristics, and particle size distribution of the material, stacking tablets need meticulous control over the weight of each layer [41].

The key to a successful bilayer tablet manufacturing process is carefully controlling the compression force of the first layer. This force affects the strength of the interfacial bond and the adhesion between the two layers. The interlayer mechanical aeration may then take place. Alternately stated, the structural integrity of a bilayer tablet is compromised by the stress and

strain created throughout the system if the initial layer of the tablet is more elastic. Because of this, the layers' adhesion might be at risk if their contact breaks down. Pressure and speed have a major role in determining the compactibility of the die. Compaction of the powders and grains and smoothing of the surface of the first layer using compression forces (usually 2 to 18 KN) creates a void that may be filled with a second layer.

Compression improves both the tensile strength and the surface roughness. If the intermolecular adhesion between successive layers is reduced, delamination may be enhanced by smoothing the surface of the original layer. When the tablet is finally compressed, the first and second layers engage with each other at a moderate compression force, which ensures appropriate bonding. Crushing the initial layer with a strong compression force significantly hinders bonding [42].

Because the lubricant is distributed more uniformly, the die and lubricant particles experience less friction when they come into contact. To enhance contact and strength between two layers in a bilayer formulation, a lower lubricant component is required. Because of their greater impact, lubricant levels are more critical for bilayer tablets than brittle materials.

It is necessary to estimate the quantity of lubricant required to keep the initial layer from picking up and adhering throughout product development. As the grains encounter the die and punches during compression, a blended lubricant is distributed or "coated" onto their surface. As a result, the components experience less friction and wear due to the lubrication. This aids in decreasing intergranular adhesion, which impacts dissolving and breaking forces of tablets, two quality indicators. To test the effects of lubricant on critical tablet quality parameters, researchers did not use it directly on the granules but rather applied it to dies and punches. According to the books, this is called external lubrication. External lubrication, in which lubricant is sprayed over the die and punches during each compression cycle instead of being mixed with the bulk powder, may boost crushing strength by 40%. A scanning electron microscope was used to determine that the tablet had a magnesium stearate coating. Although this novel method works best with monolayer tablets, it may help us understand how lubricant affects the quality features of bilayer tablets [43].

It is not always necessary to ensure that the two layers of a bilayer tablet have an identical weight when developing it. Their weight ratios will often be significantly different. It may be difficult to create bilayer medications with a consistent second-layer weight when there is evidence that the first and second layers often have a 1:1, 1:2, or even 1:3 ratio to each other.

Humidity and moisture levels in the formulation environment have a significant impact on the compactness of bilayer tablets. Curiously, the impact of moisture on the strength of bilayer tablets has received very little attention from researchers. In response to changes in ambient humidity, tablets containing hygroscopic substances in their bilayer layer may either collect or release water from their

pore structure.

In addition to starches, microcrystalline cellulose, sodium starch glycolate, cross povidone, polyvinylpyrrolidone, and colloidal silicon dioxide, compacts composed of these materials may also leach water. Porosity allows water to penetrate and enlarge particles and/or compacts. As time passes and the layers' thicknesses fluctuate, the contact between them decreases, and delamination occurs. It was suggested that the material be preconditioned to match the relative humidity of the production area and that compacts be packaged in sealed, water-resistant blisters.

Consideration of physical stability, in addition to formulation design and manufacturing process considerations, should be given to the creation of bilayer tablets. This is because physical stability may impact quality characteristics including tensile strength, adhesion between layers, friability, and dissolving. Researchers observed that bilayer tablets containing lactose had a decreasing interfacial strength with increasing humidity and storage time, whereas bilayer tablets with MCC in the first layer had an increasing interfacial strength with increasing humidity and storage time [44].

Achieving uniform dispersion of active medicinal components in bilayer tablets is influenced by material flow characteristics, particle size distribution, and the bilayers' ability to press efficiently. The instrumented bilayer press uses a weight-balancing mechanism that varies from vendor to vendor. Prior research and commercial presses are considered in two separate bilayers. Not a single bilayer press on the market has a way to determine how much weight is in the second layer. This greatly complicates the process of making bilayer tablets.

Among the bilayer presses that bilayer tablet formulators may find commercially available are the Kilian, Piccola, Oystar Manesty, Hata, Korsch, Courtoy, and Fette. Compression force and punch displacement are often computed automatically in instrumented bilayer presses. Thanks to developments in compression machine design and accessory technologies, it is now feasible to customize product characteristics such as initial layer sampling, sealed feeders, pre compression rolls, sensitivity of the layer strain gauge, and maximum upper punch penetration. The time required for consolidation and relaxation, in addition to variables like pre compression force and punch velocity, must be carefully considered. Compression machines have the potential to either enhance or degrade the dose's quality.

Despite the theoretical benefits of a material that compresses without distortion and compacts independently, other variables impact the production of high-quality bilayer tablets. Particle size distribution, response angle, photomicrographs, densities, compressibility’s, and moisture sorption capacity are all part of this [45].

Recent advancement in the field of bilayer tablet technology in drug combination therapy

Bilayer tablets have revolutionized the pharmaceutical business by allowing for the inclusion of incompatible active components into a single unit dosage form and the production of pre-

determined release patterns of active ingredients. This area has seen a great deal of research. The previous table 1 explains some of the most recent results.

The complicated nature of hypertension makes it often uncontrollable with a solo treatment. To achieve their target blood pressure, most individuals need to take a mix of medications from different classes. It is possible to get much better outcomes when two blood pressure medications are used simultaneously. Even with a higher dose, some people with mild hypertension may not get better.

Sodium excretion by the kidneys and the subsequent changes in plasma and total body volume, as well as cardiac function and vascular tone, are the main variables that influence blood pressure. Blood pressure (BP) is directly affected by three hemodynamic variables: intravascular volume, cardiac output, and systemic vascular resistance. The sympathetic nervous system (SNS) and RAAS work together to dynamically alter these parameters. Although some individuals may have their hypertension caused by a single factor, the complex nature of BP elevation makes it very difficult, if not impossible, to restore normal pressure by affecting only one presser mechanism [46].

Rationale of combination therapy [47]

• There may be many advantages to using two drugs from different classes in a low-dose combination if certain conditions are satisfied.

• Due to individual differences in hypertension response, it is more likely that a patient may have a positive outcome when two medications are taken together.

• Each medication may have an enhanced antihypertensive impact; in fact, when taken at the ideal dosage and timing, they may have a synergistic effect rather than an additive one.

• The antihypertensive effects of the two drugs are different, which means that they may take longer to take effect and have a slower onset.

• To reduce the likelihood of adverse effects, it is best to keep the dosage of each therapy low.

• It is very uncommon for the synergistic effects of two drugs to outweigh those of one another; for instance, -blocker treatment may reduce the palpitations brought on by certain CCBs.

• Reducing blood pressure is only one of several potential positive effects on target organs that may result from various procedures. The prognosis of a hypertension patient worsens when harm occurs to the end organs of the heart, kidneys, or brain. It is possible to delay disease progression using combination therapy. To improve adherence, it is usually best to give combination medications once day, especially at modest dosages.

• There will be less need for frequent doctor's appointments, faster achievement of blood pressure goals, and easier handling of dosage adjustments and titration. The end result is solutions that are easier to understand and implement. Starting medication for high blood pressure in primary care.

• It is possible to reduce the total cost of the therapy. It's possible that low-dose combination medications will be more cost-effective than the individual components. It may be more cost-

effective to prescribe only one medicine in certain nations than to prescribe two separate ones.

Compared to traditional monotherapy, fixed-dose combination therapy offers a number of benefits, such as a simplified dosage schedule that leads to better treatment outcomes (due to increased patient compliance), fewer side effects, less development of resistance in microbes, and possibly lower manufacturing, handling, packing, and shipping costs. The invention of prolonged drug administration was inspired by the wide range of medication concentrations in the circulation caused by the typical dose form. Creating sustained delivery systems may help with a few different goals: decreasing dosage frequency, increasing therapeutic efficacy, or ensuring uniform medication distribution.

Specific Drug Combinations [48]

A. β Blockers with diuretics

Research has shown that diuretics may enhance the antihypertensive effectiveness of β1-blockers in cases of low-renin hypertension. Cholorthalidone and atenolol are two examples. Bisoprolol fumarate and HCTZ are two more.

B. Angiotensin-converting enzyme (ACEIs) inhibitor and angiotensin receptor blocker (ARB) with Diuretics

Compared to taking either hydrochlorothiazide or an ARB alone, the combination is safer and more effective. Additionally, an ARB will lessen the metabolic effects of thiazide diuretics, such as hypokalemia and hyperglycemia.

C. Renin-angiotensin system (RAS) and Calcium channel blocker (CCB)

The different ways that CCBs, ARBs, and ACE inhibitors work are probably the reason why they have complementary or synergistic effects. It is possible that a RAAS blocker could lessen the dose-dependent peripheral edoema caused by CCBs.

D. Angiotensin-converting enzyme inhibitor /Calcium channel blocker (ACEI/CCB)

Patients with diabetes and hypertension who take an ACEI may not see a reduction in blood pressure as a side effect of the medication's therapeutic benefits. The study findings for amlodipine/benazepril combination treatment indicate that it is a safe, effective, and well-tolerated medicine for hypertension patients who do not react well to amlodipine or who have severe edoema.

E. Combination ARB with CCB

An excellent rationale exists for the use of CCBs and diuretics in combination with RAAS inhibitors. Amlodipine, valsartan, and hydrochlorothiazide are a fixed-dose combination of antihypertensive medications that were authorized in 2009.

F. ACEIs with ARB

The benefit of a more thorough RAAS blockage may be achievable with an ACEI/ARB regimen. There will be a decrease in the occurrence of the ACEI escape phenomenon with ARB. This occurs when angiotensin II levels return to their pretreatment levels while taking continuous ACEI medication. Another way that ARBs prevent ACEI-independent mechanisms from reducing angiotensin II production is by themselves.

G. Combination of CCBs and diuretics

Taking diuretics or calcium channel blockers to treat hypertension may raise the risk of myocardial infarction, but it won't put you at risk of stroke.

Table 1: Various Advancements in the Field of Bilayer Tablets [49]

Drug(s)	Dosage Form	Rationale
Atorvastatin, Atenolol	Bilayer Gastroretentive Matrix Tablet	Treatment of hypertension and hypercholesterolemia
Nifedipine	Gastro- Retentive Floating Bilayer Tablets	Treatment of hypertension and angina pectoris
Aspirin, Isosorbide 5- mono-nitrate	Sustained Bilayer tablets	Treatment of pain, fever and other inflammatory conditions
Pioglitazone HCl, Gliclazide	Bilayer Tablets	Treatment of Type II Diabetes
Losartan potassium	Bilayer tablet	Treatment of hypertension
Trimetazidine HCl, clopidogrel bisulphate	Bilayer tablets	Cytoprotective anti-ischemic, platelet inhibitor in acute coronary syndromes
Diclofenac, Cyclobenza-prine	Bilayer tablets	Synergistic effect in pain
Granisetron HC1	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects
Metformin HCL, Glimipiride	Bilayer tablets	Synergistic effect in diabetes
Indomethacin	Bilayer floating tablets	Biphasic drug release
Metformin HC1, Atorvastatin Calcium	Bilayer tablets	To develop polytherapy for the treatment of NIDDS & hyperlipidemia
Cefixime Trihydrate, Dicloxacilline Sodium	Bilayer tablets	Synergistic effect in bacterial infections
Piracetam, Vinpocetin	Bilayer tablets	Synergistic effect in Alzheimer disease
Paracetamol Diclofenac	Bilayer tablets	Synergistic effect of drugs in pain
Misorostol, Diclofenac	Bilayer tablets	To minimize contact b/w drugs

Evaluation of Bilayer Tablets [50]

General Appearance

A Tablet's visual identity, overall elegance, and general appeal are crucial for customer adoption. This includes the following aspects of the tablet: its size, Shape, colour, odor, taste, Surface Texture, physical defects and the readability and consistency of any identifying marking.

Size and Shape

You may manage and monitor the tablet's size and form using its dimensions.

Tablet thickness

For accurate visual reproduction and accurate counting with filling equipment, tablet thickness is a crucial attribute. The consistent thickness of the tablets is used as a counting mechanism by certain filling equipment. A micrometer, Verneir Calliper, or Screw Gauge was used to record the thickness of ten tablets.

Weight variation

The weight variation test involves randomly selecting twenty tablets, calculating their average weight, and then comparing their weight variation to The official books detail the standard processes that are followed.

Friability

The tablets often chip, cut, or shatter due to factors such as friction and stress. Tablet hardness and the friability test are closely connected; the friability test determines how well a tablet can withstand abrasion during transportation, handling, and packing. The Roche friabilator is the standard tool for this measurement. After being weighed, a number of tablets are loaded into the equipment and subjected to rolling shocks, falling 6 inches with each revolution. We compare the original weight of the pills with their final weight after four minutes of treatment, which is equivalent to 100 rotations. A tablet's friability may be measured by its loss owing to abrasion. The percentage represents the value. It is widely accepted that the friability test should not pick up any broken or shattered tablets and that the weight loss should not exceed 1% of the weight of the tablets being evaluated. It is not common practise to compute friability values when capping takes place. The decrease in tablet weight is a measure of variability stated as a percentage. Thicker tablets are less likely to cap, but thinner ones with a larger diameter commonly exhibit considerable cupping. This suggests that thicker tablets have less internal tension.

%Friability=1-(loss in weight/Initial weight)X100

Hardness

Depending on its hardness, a tablet's resistance to capping, abrasion, or fracture during storage, transit, and handling prior to utilization is determined. Monsanto developed and presented the compact hardness tester in the middle of the 1930s. The name has changed, and it's now known as the Stokes or Monsanto hardness tester. When a coil spring is applied diametrically to a tablet, the device measures the force that is needed to shatter the tablet. The later-introduced strong-Cobb Pfizer and Schleuniger device determines the amount of force needed to break the tablet by applying a diametric force. When making tablets, it is necessary to measure hardness—now more correctly referred to as crushing strength—to ascertain if the tablet machine's pressure needs adjusting. Tablets that are too hard won't dissolve in the time needed to satisfy dissolving requirements, while tablets that are too soft won't be able to endure the treatment that comes after them, in processes like coating or packing and shipping. In general, tablets are regarded to be of sufficient quality if they have a crushing strength of at least 4 kilogram's (Kg). The hardness of oral tablets ranges from 4 to 10 kg, whereas that of hypodermic and chewable tablets is typically considerably softer at 3 kg, and that of some prolonged release tablets is much harder at 10 to 20 kg. Along with density and porosity, tablet hardness has been linked to other tablet qualities. Depending on the form, chemical characteristics, binding agent, and compression pressure, tablet hardness typically rises with moderate to rage tablet size.

Particle size distribution

The particle size distribution was measured using sieving method

Photo-microscope study

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

Angle of repose:

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

Tan ø=h/r

Where, h = Height, r = Radius of the powder cone.

Moisture sorption capacity:

The ability of all disintegrants to absorb atmospheric moisture impacts medications that are sensitive to it. The stability chamber was maintained at 37±1°C and 100% relative humidity for 2 days to measure the quantity of moisture absorption. 1 gram of disintegration was evenly dispersed in the petri dish.

In-vitro Dissolution Studies

The capacity of the bilayer formulations to provide the necessary controlled medication delivery is evaluated using in-vitro drug release tests in simulated gastric and intestinal fluids. Using the official monograph's protocol or a USP dissolving apparatus type-II set to a certain rpm, researchers conduct in vitro drug release investigations.

Stability Study

The bilayer tablets are placed in appropriate containers and kept in a controlled environment for the duration specified by the ICH guideline for expedited research. After 15 days, the tablets were taken out and examined for drug content, visual flaws, hardness, friability, and dissolution. To find the degradation kinetics, the collected data is fitted into the first set of equations. The shelf life at 25°C is calculated by plotting the accelerated stability data according to the Arrhenius equation [51].

Conclusion:

In conclusion, the study explains that bilayer pills are a new kind of medicine that successfully treats illnesses by bonding together many ingredients. Traditional bilayer tablets feature two layers: one for delayed release and one for instant release. One of these layers is designed to provide rapid drug release, allowing for a rapid increase in serum concentration. Designed to maintain an effective plasma level for a long time, the second layer is a regulating release hydrophilic matrix. This drug delivery system's primary goal is to ensure that the medicine is safe, effective, and made in accordance with all Good Manufacturing Practise (GMP) standards so that it retains its quality throughout time. To achieve these goals, many methods are used, each with its own set of advantages and disadvantages, in order to maximize effectiveness and minimize adverse effects. Physical and chemical tests are performed on the produced tablet to guarantee its efficacy and stability over time. These days, you can get bilayer tablets with a variety of active pharmaceutical ingredients (APIs) for combination treatment, or you can have two different doses of the same API one for loading and one for maintenance so you can keep your plasma concentration effective for a long time.

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