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ACTIVE PHARMACEUTICAL INGREDIENT STANDS BETWEEN DUAL LAYERS IN SINGLE DOSAGE FORM

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ABSTRACT

In the new era, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bilayer tablet) has increased in the pharmaceutical industry, for promoting patient convenience and compliance. A bilayer tablet involves the compression of two formulations into a single solid oral tablet, while maintaining a physical separation of the formulations by layering on top of the other. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose. This article also provides an overview of different approaches and technologies introduced in bilayer tablet.

Keywords: Active Pharmaceutical Ingredients (API), bilayer tablet, sustained release, immediate release.

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INTRODUCTION:

Oral dosage forms are usually the most convenient and commonly employed route of drug delivery. As known worldwide, taking a medicine via oral route is one of the best options as it's the simplest and easiest way for any patient to take medication. It is safe to the patient and no nursing is required, which means the patient can take it with no help. Toxicity is delayed due to the late onset of action which permits easier recovery than in case of other dosage forms. There are many ways to design modified release dosage forms for oral administration; from tablets, capsules or lozenges to more sophisticated delivery systems such as osmotically driven systems, systems using three–dimensional printing technology and systems controlled by ion exchange mechanism. The most renowned oral dosage form among all has been the matrix type such as tablets and capsules where the drug is uniformly dispersed throughout the polymer, because of its effectiveness, low cost, easy to administer and prolonged delivery time period.[1]

Bilayer tablets, sometimes called double layered tablets, can be a primary option to avoid chemical incompatibilities between APIs by physical separation, and to enable the development of different drug release profiles. Despite of their advantages, the manufactures of bilayer tablets have become quite intricate, due to the use of different materials and complex geometric boundaries

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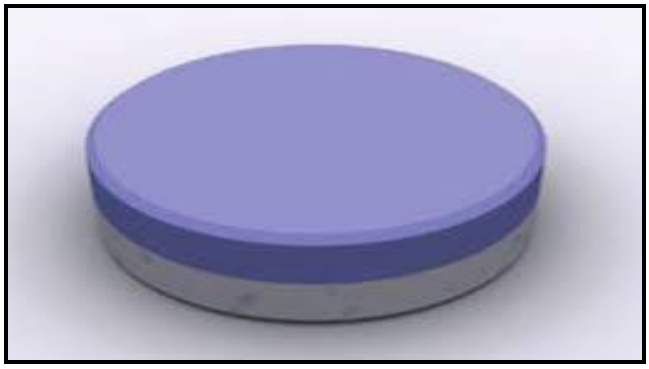
between the adjacent layers. Bilayer tablets offer definite advantages over the conventional monolayer tablets. For instance, such tablets are commonly used to avoid chemical incompatibilities of formulation components by physical separation. Also, objection able odor and bitter taste can be masked by coating technique. They are easy to swallow with fewer tendencies to hang–up.

1A



1B

Figure 1 A & B: Bi-Layer Tablets

Bi–layer tablets are developed for the following reasons:[1]

1. For administering fixed dose combinations of different APIs, prolong the drug product life cycle; fabricate novel drug delivery systems such as chewing device, buccal/muco adhesive delivery systems, and floating tablets for gastro–retentive drug delivery.
2. For separating incompatible Active pharmaceutical ingredient (APIs) from each other, to control the release of API from one layer by utilizing the functional property of the other layer (such as, osmotic property).
3. To control the delivery rate of either single or two different active pharmaceutical ingredient(s).
4. To modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swell able/erodible barriers for modified release.
5. They have been developed to achieve controlled delivery of different drugs with pre–defined release profiles.

Advantages of bilayer tablets:

1. They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
2. These tablets are commonly used to avoid chemical incompatibilities of formulation components by physical separation.
3. Cost is lower compared to all other oral dosage form.
4. Easy to swallowing with least tendencies to hang–up.
5. They are lighter and compact.
6. Easiest and cheapest to package and strip.
7. Suitable for large scale production.
8. Greatest chemical and microbial stability over all oral dosage form.
9. Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.
10. Flexible concept.
11. Bi–layer tablet is suitable for preventing direct contact of two drugs and thus to maximize the efficacy of combination of two drugs.
12. Bi–layer tablets can be designed in such a manner as to modify release as either of the layers can be kept as extended and the other as immediate release.
13. Maintain physical and chemical stability.

General properties of Bi–layer tablets:

1. The bilayer tablets should have physical and chemical stability.
2. The bi–layer tablet must release drug in an expectable and reproducible manner.
3. It must have a chemical stability shelf life, so as not to follow alteration of the medicinal agents.
4. It should have graceful product identity free of defects like chips, cracks, discoloration, and contamination.
5. It should have sufficient strength to with stand mechanical shock during its production, packaging, shipping and dispensing.

Manufacturing Process:

Bilayer tablets are prepared with one layer of the drug for immediate release with the second layer designed to release the drug later, either as a second dose or in an extended–release form. Compressing separate layers of each drug so as to minimize the area of contact between two layers is another method of preparation for bilayer tablets with two incompatible drugs. To produce adequate tablet formulation, specific requirements, such as sufficient mechanical strength, and the desired drug release profile, must be met. These drug delivery devices have proved to be mechanically complicated to design or manufacture and harder to predict their long–term mechanical properties.

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This is due to the poor mechanical and compression characteristics of the constituent materials in the compacted adjacent layers, elastic mismatch of the layers, insufficient hardness, inaccurate individual mass control, cross contamination between the layers, reduced yield, and their tendency to delaminate at the interface between the adjacent compacted layers during and after the various stages of production downstream of the compaction process.

One of the major challenges is lack of sufficient bonding and adhesion at the interface between the adjacent compacted layers which is often the result of an interfacial crack driven by residual stresses in the tablet. This leads to layer–separation which may not always be apparent immediately after compaction (e.g., during storage, packaging, shipping). In addition, if the compacted layers are too soft or too hard, they will not bond securely with each other which can lead to compromised mechanical integrity. Other challenges during development include establishing the order of layer sequence, layer weight ratio, elastic mismatch of the adjacent layers, first layer tamping force, and cross contamination between layers. These factors, if not well optimized can impact the bilayer compression and the quality attributes of the bilayer tablets (sufficient mechanical strength to maintain its integrity and individual layer weight control).

Bi–layer tablets can be visually appealing because the manufacturing process makes a clear demarcation between the layers, assuming the finished tablet is not coated. But there are also practical reasons to choose bi–layer manufacturing, such as:

- It can sometimes improve the intended therapeutic effect by separating two actives.
- There is a work–around for compatibility issues, which includes a way to combine ingredients that cannot easily be blended into the final formulation.
- It can prevent abuse of a constituent ingredient by using an "antagonist" layer that foils the potential abuser's attempts at extracting certain ingredients.

The steps in the bi–layer manufacturing process include:

- A tablet press that has two different feed hoppers is charged with the different formations that are necessary for the finished product.
- The first–layer granulation, which is the bottom layer, feeds into the die as the cavity passes under the first feed frame.
- The cavity continues through the initial compression stage, where the bi–layer tablet is "tamped" to form the first layer. However, it's not hard enough to inhibit good cohesion with the second layer fill.
- Next, the dies pass under the second feed frame and fill with the second layer granulation, which is appropriate for the desired total weight of the tablet when combined with the first layer.
- The tools pass through final compression rolls that apply the appropriate amount of force to achieve the intended hardness of the tablet.
- The process finishes as the tools proceed through the ejection stage of the press. The upper and lower punches are raised through the usage of raising and ejection cams, which eject the finished tablets from the die cavities.[3]

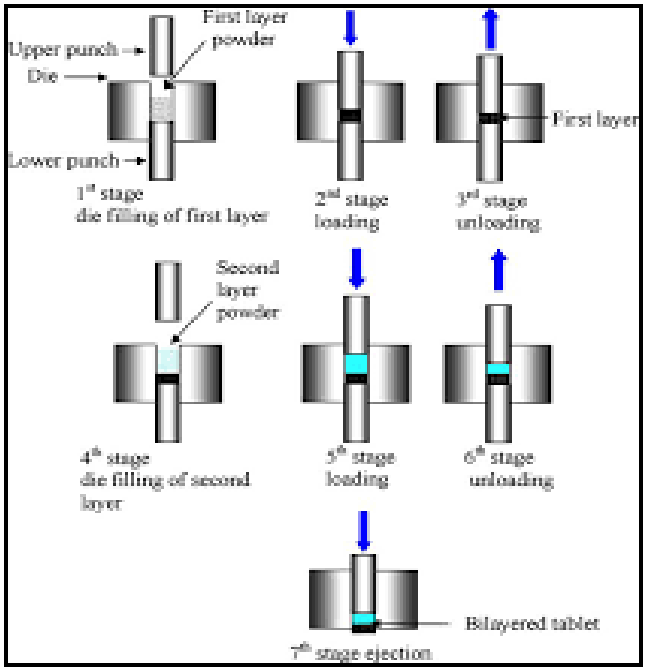

Figure 2: Preparation of Bi–Layer Tablets

Types of Bi–Layer Tablets[2]

1. Single sided tablet press.
2. Double sided tablet press
3. Bilayer tablet press with displacement monitoring.
4. Multilayer compression basics.

Single Sided Tablet Press:

This contains two chambers with double feeder separation from each other. Each chamber is gravity or forced fed with different powder, thus producing the two individual layers of the tablets. When the die passes under the feeder, it is first loaded with the first–layer powder followed by the second layer powder. Then the intact tablet is compressed in one or two steps.

Limitations of the single sided press

- No weight monitoring / control of the individual layers.
- Very short first layer dwell time due to the small compression roller, possibly ensuing in poor deaeration, capping and hardness problems. This may be corrected by reducing the turret–rotation speed (to extend the dwell time) but with the result of lower tablet output.
- Very difficult first–layer tablet sampling and sample transport to a test unit for in–line quality control and weight recalibration.
- No distinct visual separation between the two layers.

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Figure 3: Single Sided Tablet Press Machine

Double Sided Tablet Press: Most of the double–sided tablet press, which automates production control use the compression force to monitor and control the weight of the tablet weights. A double–sided press offers an individual fill station, pre–compression and main compression for each layer. In fact, the bi–layer tablet will go through four compression stages before being ejected from the press. The effective compression force exerted on each individual tablet with the help of the compression system at the main compression of the layer. This system helps into reject out the tolerance tablets and correct the dies fill depth when required.[4]

Advantages of the double sided tablet press:[3]

- Increased dwell time at pre compression of both first and second layer to provide sufficient hardness at maximum turret speed.
- Displacement weight monitoring for accurate and independent weight control of the individual layer.
- Low compression force exerted on the first layer to avoid capping and separation of the individual layer.
- Maximum prevention of cross contamination between two layers.
- A clear visual separation between the two layers.
- Maximized yield.

Limitations of the double sided tablet press:

Separation of the two individual layers is the consequence of insufficient bonding between the two layers during final compression of the bi–layer tablet. Correct bonding is only obtained when the first layer is compressed at a low compression force so that this layer can still interact with the second layer during final compression of the tablet. Bonding is restricted if the first layer is compressed at a too–high compression force. The low compression force required when compressing the first layer unfortunately reduces the accuracy of the weight monitoring/control of the first layer in the case of tablet presses with "compression force measurement". Most double–sided tablet presses with automated production control use compression force to monitor and control tablet weight. The effective peak compression force exerted on each individual tablet or layer is measured by the control system at main–compression of that layer.

Figure 4: Double Sided Tablet Press Machine

The exponential relationship between the measured peak compression force [F] and layer or tablet weight [W] is shown in the figure below–

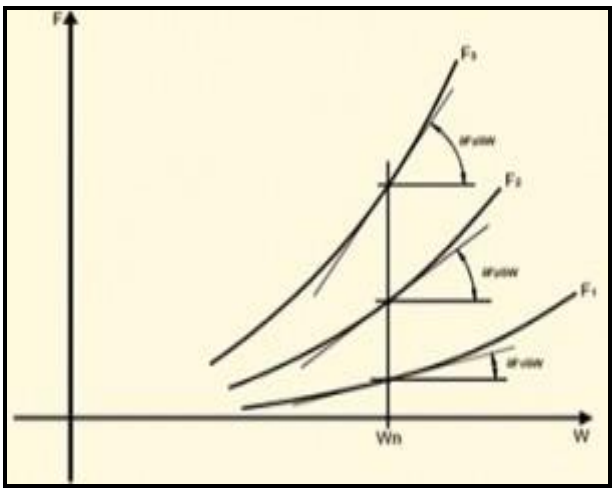

Figure 5: Force Vs Weight Sensitivity at Different Compression Force Levels

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This measured peak compression force [F] is the signal used by the control system to reject out–of–tolerance tablets and correct the die fill depth when required. This graph indicates that the sensitivity decreases with decreasing compression force (i.e., when the distance between the compression rollers is made greater). This decreasing sensitivity is inherent to an exponential relationship and therefore inherent to the compression force–controlled system. The rate at which the sensitivity decreases depend on the formulation or powder characteristics. That is why the compression force control system is always based on measurement of compression force at main–compression and not at pre–compression since a higher compression force is required to obtain sufficient sensitivity, thus allowing a more accurate control.[5]

A compression force–controlled system requires a minimal compression force of several hundreds of daN. However, many bi–layer formulations require a first layer compression force of less than 100 daN in order to retain the ability to bond with the second layer. Above 100 daN, this ability may be lost, resulting in low hardness of the bi–layer tablet and separation of the two layers.

Bilayer Tablet Press with Displacement Monitoring[5]

The basic problem of compression force monitoring can be overcome by a different approach known as 'Displacement measurement'. Displacement measurement has the advantage that accuracy increases with reduced compression force. At higher production speed, the risk of separation and capping increases but can be reduced by sufficient dwell time at all four compression stages. It also provides increased dwell–time in addition to good bonding between the two layers, with improved and accurate weight monitoring/control of the first layer. A double–sided tablet press with "displacement measurement" is thus the preferred press to produce bi–layer tablets. This double–sided tablet press has been specifically designed and developed for the production of quality bi–layer tablets and provides:

- 'Displacement' weight monitoring/control for accurate and independent weight control of the individual layers
- Low compression force exerted on the first layer to avoid capping and separation of the two individual layers.
- Increased dwell time at precompression of both first and second layer to provide sufficient hardness at maximum turret speed.
- Maximum prevention of cross–contamination between the two layers.
- A clear visual separation between the two layers.
- Maximized yield.

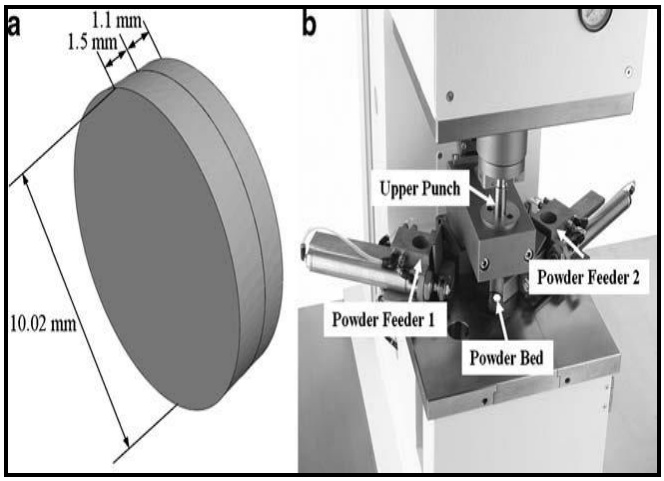

Figure 6: Bi-Layer Tablet Pressing

Multilayer Compression Basics:

Presses can be designed specifically for multilayer compression or a standard double press can be converted for multipliers. The multilayer tablet concept has been long utilized to develop sustained release formulations. Such tablets have fast releasing layer and may contain players or triple layers to sustain the drug release from the tablet. The advantage of pharmacokinetics is that the drug release from fast releasing granules leads to sudden rise in blood concentration. However, the blood level is maintained at a steady state as the drug is released from the sustained granules.[6]

Bilayer tablets[6]:

Quality and GMP requirements –To produce a quality bi–layered tablet, in a validated and GMP way, it is important to select a bilayer tablet press is capable of:

- Preventing capping and separation of the two individual layers that constitute the bi–layer tablet.
- Providing sufficient tablet hardness.
- Preventing cross contamination between the two layers.
- Producing a clear visual separation between the two layers.
- High yield.
- Precise and individual weight control of the two layers.

VARIOUS APPROACHES OF BILAYER TABLETS

A. **Floating drug delivery system: –**These are designed to have a low density and thus float on gastric contents after administration until the system either disintegrates or the device absorbs fluid to the point where its density is such that it loses buoyancy and can pass more easily from the stomach with a wave of motility responsible for gastric emptying. The bilayer tablet is designed in such a manner that, one layer gives the immediate dosing of the drug which gives faster onset of action while another layer is designed as a floating layer which floats in the stomach.

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Disadvantages

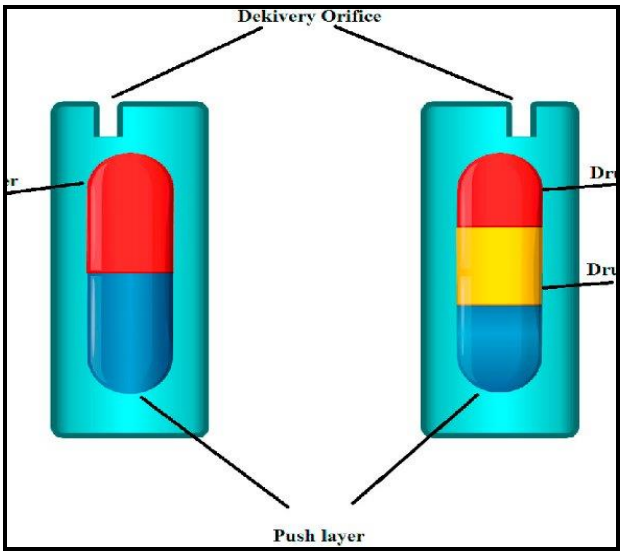
The floating drug delivery system may not have the controlled loss of density which is required for it to exit the stomach. Floating tablets are not applicable to higher dose of water–soluble drugs where large amounts of polymer are needed to retard drug release. The performance of floating formulation may also be posture dependent. A patient sitting upright may ensure prolonged gastric residence of a buoyant dosage form, whereas a supine patient might allow ready presentation of the floating dosage form to the pylorus and thus allow rapid exit of the dosage form from the stomach.

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

C. Swelling System: These are designed to be sufficiently small on administration so as not to make ingestion of the dosage form difficult. On ingestion they rapidly swell or disintegrate and passage through the pylorus until after drug release has progressed to a required degree. The simple bilayer tablet may contain an immediate release layer with the other layer as extended release.[7]

DIFFERENT TECHNIQUES OF BILAYER TABLETS[7]

1. **O R O S®push pulls Technology–** This system consists of mainly two or three layers among which the one or more layer is essential of the drug and other layer are consist of push layer. The drug layer mainly consists of drug along with two or more different agents. So, this drug layer comprises of a drug which is poorly soluble form. There is a further addition to suspending agent and osmotic agent. A semipermeable membrane surrounds the tablet core.



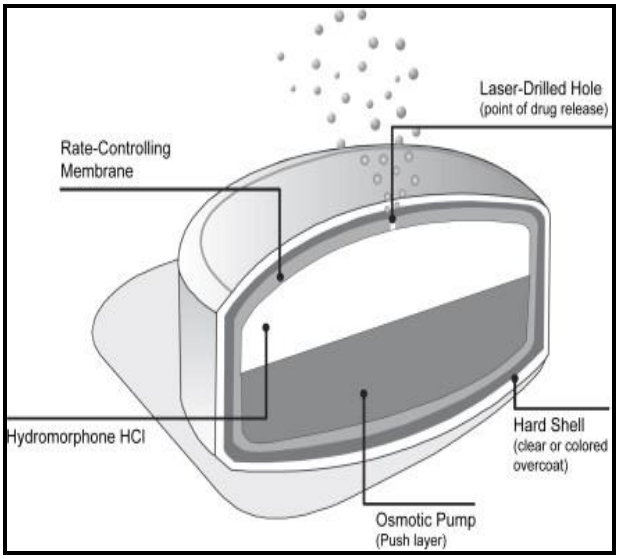


Figure 7: O R O S®push pulls Technology

2. L–OROS tm technology– This system used for the solubility concern Alza developed the L–OROS system where a lipid soft gel product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, then osmotic push layer and then a semi permeable membrane, drilled with an exit orifice.

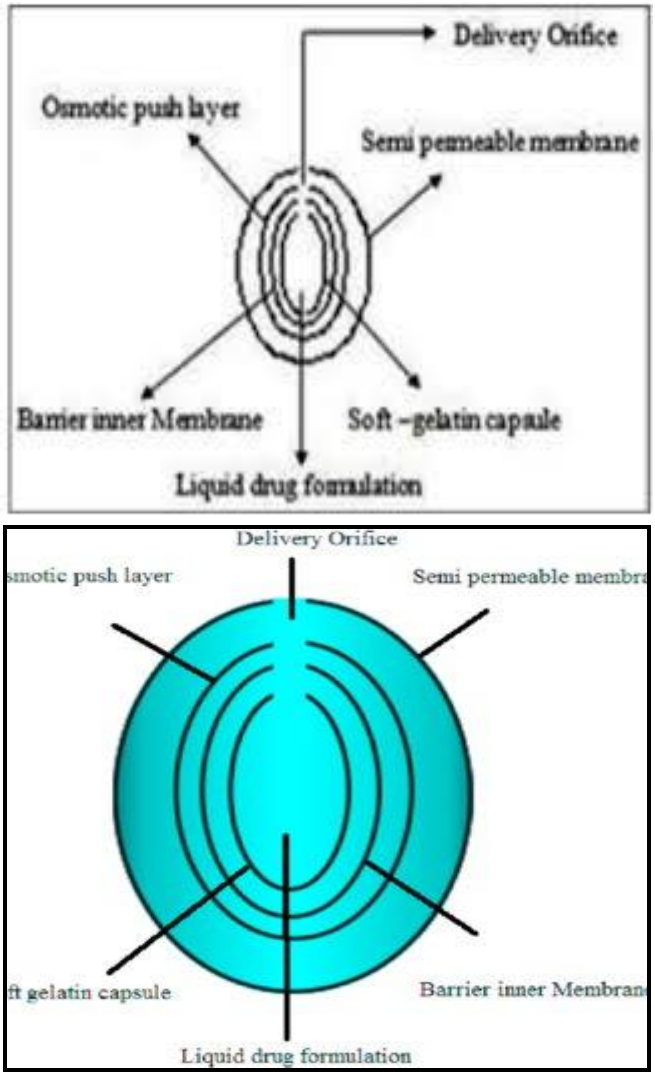


Figure 8: L–OROS tm technology

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3. DUROS technology

It is based on implant technology, which provides an alternative for the delivery of a wide range of therapeutic compounds, including peptides, proteins and other bioactive macromolecules. Following implantation, DUROS implants enable continuous, precise delivery of the therapeutic compound at rates as low as 1% of a drop of water per day. The system consists from an outer cylindrical titanium alloy reservoir. This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the minuscule drug dispensing system that opposes like a miniature syringe and regions minute quantity of concentrated form. Recently, Viadur (leuprolide acetate implant), which is based upon this technology, has been approved for once–yearly palliative treatment of advanced prostate cancer.[8]

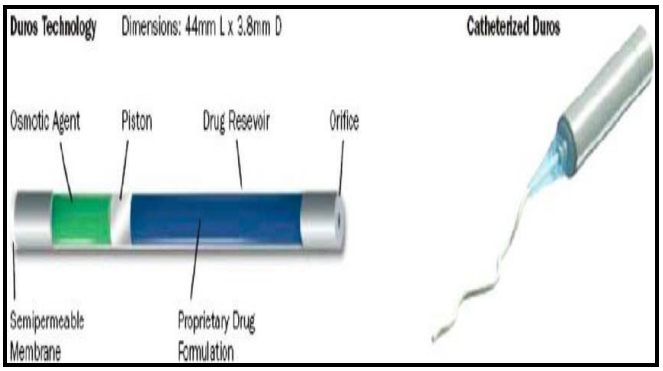
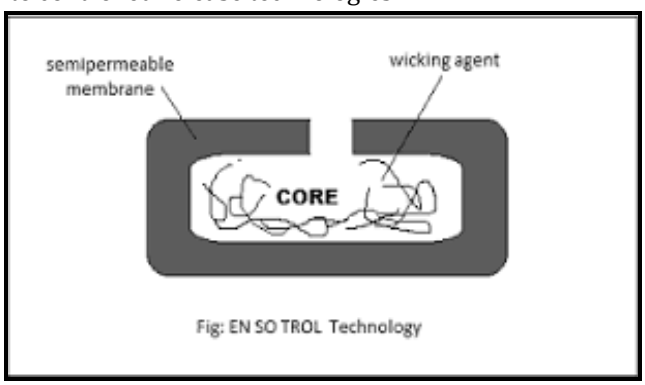


Figure 9: DUROS technology

1. ENSOTROL technology–

Solubility enhancement of an order of magnitude or creates optimized dosage forms hire laboratory use an integrated approach to drug delivery. It focuses on identification and incorporation of the identified enhancer into controlled release technologies.



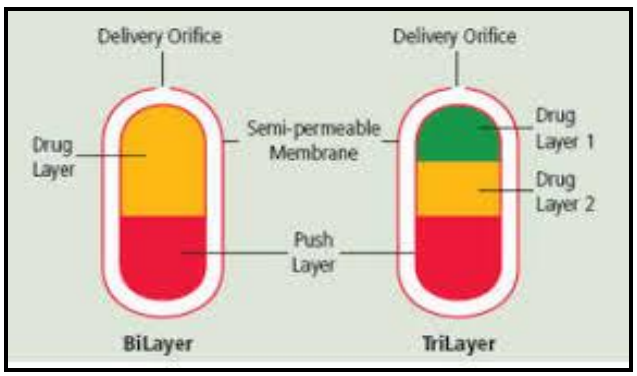


Figure 10: Ensotrol Technology

2. DUREDAS Technology–

This technology provides immediate or sustained release of two drugs or different release rates of the same drug in one dosage form. The tableting process can provide an immediate release granulate and a modified–release hydrophilic matrix complex as separate layers within the one tablet. 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 technology.
- Ability for immediate release and modified release components in one tablet.
- Unit dose tablet presentation.
- Ability of two different CR formulations combined.
- Modified release rate of two drug components.

3. GEMINEX technology–

It is a dual drug delivery technology that can deliver one or more drugs at different times. This technology controls the release rate of the two drugs to maximize their individual therapeutic effect and minimize the side effects.

EVALUATION OF BILAYER TABLETS

1. General Appearance– The general appearance of a tablet, its visual identity and overall "elegance" is essential for consumer acceptance. Includes in are tablet's size, shape, color, presence or absence of an odor, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

2. Size and shape– The size and shape of the tablet can be dimensionally described, monitored and controlled. A compressed tablet's shape and dimensions are determined by the tooling during the compression process. The thickness of the tablet is the only dimensional variable related to the process.

3. Weight variation– Standard procedures are followed as described in the official books.

4. Friability– Friability is the measure of tablet strength. A friabilator is used for testing the friability using the procedure:

Twenty tablets are weighed and placed in a tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 minutes, the tablets were weighed and the percentage loss in tablet weight is determined by the formula given below–

% loss= (initial weight– final weight) × 100 / (initial weight of tablets).

5. Hardness– The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The Monsanto or Stokes hardness tester measures the force required to break the tablet when the force generated by a coil spring is applied diametrally to

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the tablet. The Strong–Cobb Pfizer and Schleuniger apparatus which were later introduced measures the diametrically applied force required to break the tablet. Hardness or crushing strength determinations are made during tablet production and are used to determine the need for pressure adjustment on tablet machine. If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specifications; if it is too soft, it may not be able to withstand the handling during subsequent processing such as coating or packaging and shipping operations.[9]

6. Stability study– The bilayer tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

Table1: Table of storage conditions of bilayer tablet[8]

Study	Storage condition	Minimum time period covered by data at submission
Long term	25°C±2°C/60% RH±5% RH or 30°C±2°C/65% RH±5% RH	12 months
Intermediate	30°C±2°C/65% RH±5% RH	6 months
Accelerated	40°C±2°C/75% RH±5% RH	6 months

The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability and Dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25°C.[10]

Marketed bilayer tablets

Table 2: Market preparation [9]

Brand name	Name of the Drug	Manufacturer
Pioglu	Pioglitazone, Metformin hydrochloride	Emcure pharmaceuticals ltd.
Volise– M	Voglibose, Metformin hydrochloride	Ranbaxy laboratories ltd.
Zyrtec– D	Cetrizine HCL/Pseudophedrine HCL	DR. Reddy's Lab
Istamet	Sitagliptin, metformin hydrochloride	Ranbaxy laboratories ltd.
Augmentin	Amoxicillin/ Clavulanate	Janssen pharmaceuticals
Alprax plus	Sertraline, alprazolam	Torrent pharmaceuticals ltd.
Gluconorm	Glimepride, metformin hydrochloride	Lupin pharmaceuticals

CONCLUSION:

Bi–layer tablet is improved beneficial technology to overcome the limitation of the single layered tablet. There is various application of the bi–layer tablet it consists of monolithic partially coated or multilayered Matrices. Bi–layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. The objective of the dosage form is to ensure that the drugs available to its citizen are not only safe and effective, but are also properly manufactured and packaged to meet the established quality target product profile over it shelf life. Bi–layer tablet quality and GMP–requirements can vary widely. This explains why many different types of presses are being used to produce bi–layer tablets, ranging from simple single–sided presses to highly sophisticated machines.

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