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# An overview on bilayer tablet dosage forms

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**Abstract**
These days various developed and developing countries move towards a combination therapy for treatment of various diseases and disorders requiring long term therapy such as hypertension, Diabetes and Cardiovascular diseases. Over 90% of the formulations, manufactured today are ingested orally. It shows that bilayer tablet formulation is the most popular worldwide and the major attention of the researcher is towards this direction. The major aim of controlled drug delivery is to reduce the frequency of dosing. The design of modified release drug product is to optimize a therapeutic regimen by providing slow and continuous delivery of drug over the entire dosing interval providing greater patient compliance and convenience.

**Keywords:** layer tablets, bilayer, sustained release, compression, tablet press

## 1. Introduction
The solid medicaments can be administered orally as powders, pills, cachets, capsules or tablets. These dosage forms contain a quantity of drug which is given as a single unit and they are known collectively as solid unit dosage forms, even in the case of sustained action preparations which, technically, contain the equivalent of several normal doses of drug. The stringent formulation requirements of modern medicaments, the many advantages of tablet and capsule medication, coupled with expanding health services and the commitment need for large-scale economic manufacture, have led to a steady decline in the prescribing of powders and pills. Tablets and capsules, on the other hand, currently account for well over two third of the total number and cost of medicines produced all over the world. Tablet may be defined as a compressed solid dosage form containing medicaments with or without excipients [1].

### 1.1 Layer tablets
Layer tablets are composed of two or three layers of granulation compressed together. They have the appearance of a sandwich because the edges of each layer are exposed. This dosage form has the advantage of separating two incompatible substances with an inert barrier between them. It makes possible sustained release preparation with the immediate release quantity in one layer and the slow release portion in the second. The weight of each layer can be accurately controlled, in contrast to putting one drug of a combination product in a sugar coating. Two layer tablets require fewer materials than compression coating tablet, weight less, and may be thinner. Monograms and other distinctive markings may be impressed in the surface of the multilayer tablet. Colouring the separate layers provide many possibilities for unique tablet identity. Analytical work may be simplified by a separation of the layers prior to assay. Since there is no transfer to a second set of punches and dies, as with the dry coating machines, odd shapes ( such as triangles, squares, and ovals ) presents no operating problems except for those common to keyed tooling [2, 3].

### 1.2 History of layer-tablet presses
F.J. stokes**,** in his 1917 patent indicate that his machine was a layer press, the first layer or tablet being compressed on another machine. The idea was apparently not pursued by the pharmaceutical industry at the time, but the electrical industry develops the idea for the production of bimetallic contacts, which are actually two layers of metal bonded together. The earliest machines fed controlled volumes of each separate granulation on top of each other and compressed them together at one pressing station. The later machines were engineered to compress each layer separately before the deposition of the next granulation, with a final compression for the complete tablet. Since, in these machines, the excess granulations from each feed frame could not be permitted to circulate around the turret and commingles. Wipe-off blades covering the entire face of the die table had to be installed. The excess was thus directed into pots at the side of the press and manually returned to the appropriate hopper. Suction tubes were needed to remove any fine dust that escaped under the scraper blades [4]. The latest refinement has been the force feeders which retain the individual granulations. But some powder escape from these also, and the same arrangement as described above is installed in the presses to prevent one granulation from contaminating the other [5].
In the operation of the older type of machine, the granulation for the first layer is placed in the hopper, & the machine is adjusted until the desired weight is achieved with consistency; then the 2nd hopper is filled with its granulation, & the same procedure is followed until the correct total tablet weight is obtained. In this, the single compression method, the delineation between layers tends to be a little uneven. It is also difficult to weight adjustment during a run [6].

### 1.3 Layer-Tablet Presses
Of the modern machine, there are two types which differ mainly in the way the layer are removed for the weight and hardness checking. In one, the first layer of the first two

layers are diverted from the machine; in the other, the first layer is made so hard that the 2nd layer will not bound to it or will bound only weakly; upon ejection of the completed tableted, the layers may be easily separated and tested individually [7].

Below figure (Figure 1), illustrates the operation of a three layer press with force feeder. The line (A) represents the die table. A granulation is placed in the first hopper and flows into the feed frame (B). The machine is started, and the volume of granulation in the die is adjusted by the weight adjustment cam (C). The upper and lower punches are broad together by the pre-compression rolls (D) and (E) to form a weak compact. Part of the lower cam track (F) is than raise hydraulically to eject the first layer, which is swept off the die table (A) by the wipe-off blade (G) affixed to the back edge of the second feeder (H).

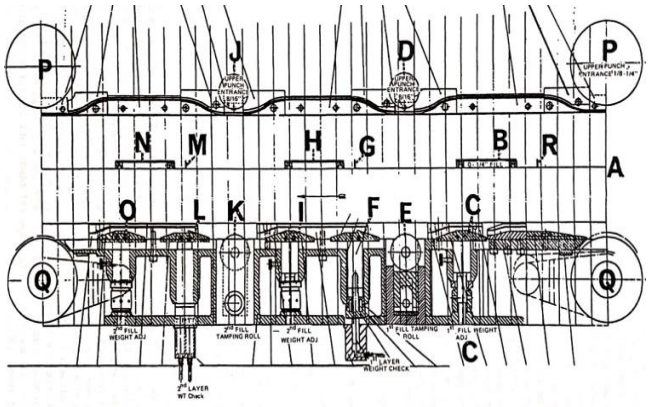


**Fig 1:** Schematic diagram of layer press

Samples are weighed and hardness is determined. The operator makes any necessary corrections. When conditions are satisfactory, the ejection cam is lowered, and the entire procedure is repeated for the second layer using feed frame (H), and weight adjusting cam (I), tamping rolls (J) and (K), ejection cam (L), and wipe-off blade (M). The weight of the second layer is determined by the difference between the two weighing. The sequence is again repeated for the 3rd layer by means of feed frame (N), weight adjustment (O) and the final compression rolls (P) & (Q), with the completed tablet being removed from the machine by the wipe-off blade (R) [to the right of the first feed frame (B)] [7].

When a layer is ejected, the upper tamping roll is lowered slightly to exert more pressure upon the layer. This action will prevent damage to the layer as strikes the take-off blade & is directed into the collection box. Once the lower punches have cleared the next filling station, they are quickly pulled down by a lowering cam so that they are not struck by the upper punches. The latter are already descending into the dies to make the next tamping or compression stroke.

The leading and trailing edges of each feed frame are equipped with wipe-off blades which divert any powder that escape from the feeders into collection boxes. The blade on the trailing edge of the first feed frame guides the completed tablet down the chute (G) to the collection bin. Vacuum tubes at each filling unit suck away any powder or granulation that remains in the lower punches faces during weight checks. Although the punches are raised flush with the die table

At this time and do not drop as they pass under the feed frame, they do trap a small amount of material in the depression in their tips. If an adjustment in the weight or thickness of the first or second layer is necessary, then the weight is related to the fill volume.

### 1.4 Formulations (Layer)

As with compression –coated tablets, the granulation for layer tablets should be readily compressible for good bonding between layers. Dust like fines should be kept a minimum; the less dust, the cleaner the scrape-off at each feed frame. It may be necessary to separate out that fraction of a granulation which is finer than 70 or 80 mesh. Such material is not discarded but added to the next lot and re-granulated. Lubricants, however, must be finely divided, their efficiency depending on the degree of fineness. Since these lubricants fines cannot be avoided, the quantities used should be kept minimal. The metallic stearate presents an additional difficulty in that they interfere with the bonding of the layers. Stearic acid and the hydrogenated fats are better lubricants from this point of view.

Granules should be small, less than half the thickness of the layers; otherwise, the lines of demarcation between layers will be uneven. Equal weight of granulation will not necessarily lead to equal thickness of the layers. That will depend on the compression ratios of the formulations. It may be compensated for by adjusting the weight required for each layer. The shape of the punches also plays a role: punches with bevelled edges or concave faces will make the top and bottom layers of a three-layer tablet appear thinner than the middle one. Flat-faced tooling will produce equal thickness of the layers, but unfortunately the edges of the tablets will tend to chip readily. If the upper punch faces have monograms or other marking, the bonding between layers will be strengthened because the devices will act as keys between the layers. Pre-compression lengthens dwell time and aids in bonding [8].

### 1.5 Bilayer Tablet

Bilayer tablet is suitable for sequential release of the two drugs in combination it is also capable of separating the two types of incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and the second player is maintenance dose. In certain cases bilayer tablets have two sustained release layers of different drugs (Figure 2).

Bilayer tablet is an improved technology to overcome the short coming of the single layered tablet. Player tablets contain immediate, sustained release layers, and the immediate release layer delivers the initial dose, it contains super disintegrates, which promotes the drug release rate and attains the onset of action quickly whereas sustained release(maintenance dose) layer releases the drug in a sustained manner for a prolonged time period.

The biphasic system is used mostly when maximum relief needs to be achieved quickly and it is followed by a sustained release phase. It also avoids repeated administration of a drug. Coronary vasodilators, antihypertensive, antihistamines, analgesics, antipyretics and antiallergenic agents are mainly suitable for this type of drug delivery. Some bilayer tablets have both the layers as the sustain release layers examples are a certain anti-diabetic agents [9].

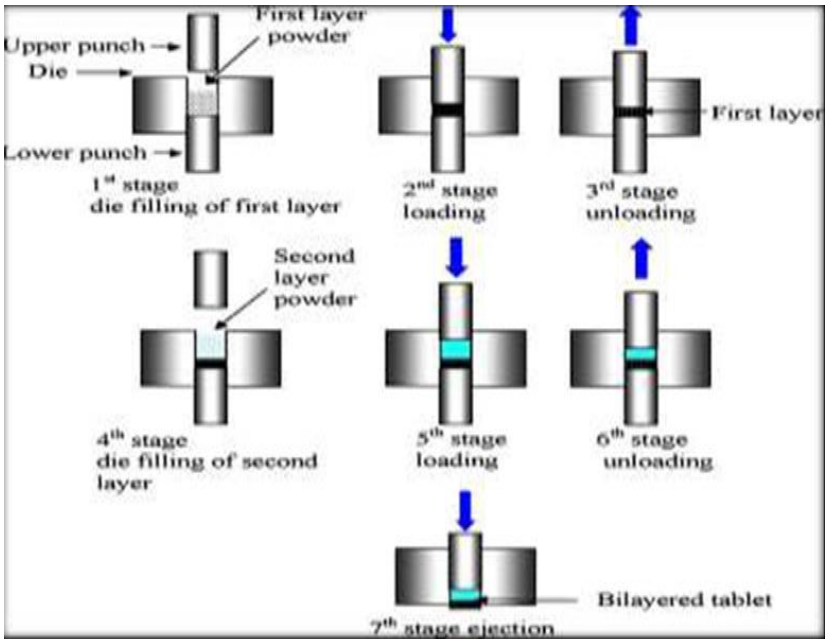


**Fig 2:** Preparation of bilayer tablet Compaction

### 1.6. Need of bilayer tablets

- For the administration of fixed dose combinations of different APIs, prolong the drug product lifecycle, vocal mucoadhesive delivery systems, fabricates novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery.
- To control the delivery rate of either single or two different APIs.
- To modify the total surface area available for API layer either by sand witching with one or two inactive layers in order to achieve swellable (or) erodible barriers for modified release.
- To separate the incompatible active pharmaceutical ingredient (APIs) from each other and control the release of API from one layer by utilizing the functional property of the other layer.
- To administer fixed dose combinations of different active pharmaceutical ingredients, prolong the drug product lifecycle, fabricating oral drug delivery systems such as chewing device buccal muco adhesive delivery systems, and floating tablets for gastro-retentive drug delivery [10].

### 1.7 Advantages of the bilayer tablets -

- Bi-Layer execution with optional single layer conversion kit.
- The cost is lower compared to all other oral dosage forms.
- Greatest chemical and microbial stability over all oral dosage forms.
- Objectionable odour and bitter taste can be masked by coating technique.
- Flexible concept.
- Zhey are a unit dosage form and offer the greatest capabilities of all oral dosage forms for the greatest dose precision and the least content variability.
- Easy to swallow with less tendency to hang-up.
- Suitable for large scale production

### 1.8 Disadvantages

- Due to the amorphous nature, low density character some drugs resist compression into dense mass.
- There is need of coating for masking unacceptable odour of drugs, bitter tasting drugs or drugs sensitive to oxygen.
- There is problem of swallowing, for children and unconscious patients.
- There is difficulty in formulating bilayer tablet with drugs having poor wetting properties, slow dissolution rate, optimum absorption high in GIT.
- There is possibility of cross contamination between the layers.
- For manufacturing of bilayer tablet required different tablet presses are required which adds complexity.
- Insufficient hardness, layer separation, reduced yield.

### 1.9 Kinds of Bilayer Tablets

1. Homogeneous Type
2. Heterogeneous Type

1. Homogeneous Type: These are preferred when drug Showing release profile different from each other. These are developed in such a manner that one layer acts as loading dose for immediate release and other layer for giving maintenance dose or extended release.
2. Heterogeneous Type: These are formulated with two incompatible substances in single dosage form separated from each other. Two drugs providing sequential release in combination are the example of this type.

### 2. Types of bilayer tablets

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

**1. Single sided tablet press:** Various types of bilayer presses have been designed over the years. The simplest design is a single sided press with both chambers of the double feeder separated from each other. Each chamber in gravity fed or force-fed with a different powder, thus producing the two individual layers of the tablet. When the

dye passes under the feeder, it is at first loaded with the first layer of powder followed by the second-layer powder then the entire tablet is compressed in one or two step. The two layers in the dye mix slightly at their interface and in most cases bond sufficiently so that no layer separation occurs when the tablet is produced this is the simplest way of producing a bilayer tablet.

**Limitations**
- No weight monitoring or control of the individual layers.
- No distinct visual separation between the two layers.
- Dwell time due to the small compression roller possible resulting in poor deaeration capping and hardness problems

**2. Double sided tablet presses:** 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. 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.

**Advantages**
- Low compression force exerted on the first layer to avoid chapping and separation of the individual layer.
- Increased dwell time at pre-compression of both first and second layer to provide sufficient hardness at maximum turret speed.
- Maximum prevention of cross contamination between two layers.
- A clear visual separation between the two layers.
- Displacement weight monitoring for accurate and independent weight control of the individual layer.
- Maximized yield.
- Separation of the two individual layers is due to insufficient bonding between the two layers during final compression of bi-layer tablet.

**Limitations**
- 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 a final compression.
- Bonding is too restricted if the first layer is compressed at a 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.

**3. Bi Layer tablets Presses with Displacement**

The principle of bilayer tablet press is fundamentally different from the principle of compression force. In this case, the accuracy increases with reduced compression force. At higher production Speed the risk of capping and separation increases, but can be reduced by sufficient dwell time a tall four compression stages.

**Advantages**
- Displacement weight monitoring /control for accurate independent weight control of the individual layers.
- Low compression force exerted on the first layer to avoid chapping and separation of the 2 individual layers.
- Increased dwell time at pre-compression of both first and second layer to provide sufficient hardness at maximum turret speed
- Maximum prevention of cross contamination between the layers.
- A clear visual separation of the layers.
- Maximized yield.

**4. Multilayer Compression:** Basics Presses can be designed specifically for multi-layer 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 pharmacokinetics advantage relies on the fact that 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.

**2.1 Preparation of bilayer tablets**

Bilayer tablets are prepared with one layer of drug for immediate release with the second layer designed to release drug later, either as a second dose or in an extended release form. The bilayer tablets with two incompatible drugs can also be prepared by compressing separate layers of each drug so as to minimize the area of contact between two layers (Figure 3).

**1. Compaction**

To produce an adequate tablet formulation, certain requirements such as sufficient mechanical strength and desired drug release profile must be met. At times, this may be a difficult task for the for emulator to achieve these conditions, especially in the bilayer tablet formulation where double compression technique is involved, because of Poor flow and compatibility characteristic of the drug which will result in capping and/or lamination. The compaction of a material involves both the compressibility and consolidation.

**2. Compression**

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

**3. Consolidation**

It is the property of the material in which there is increased mechanical strength due to inter-particulate interaction (bonding). The compression force on layer1 was found to be a major factor influencing tablets delaminating [11].

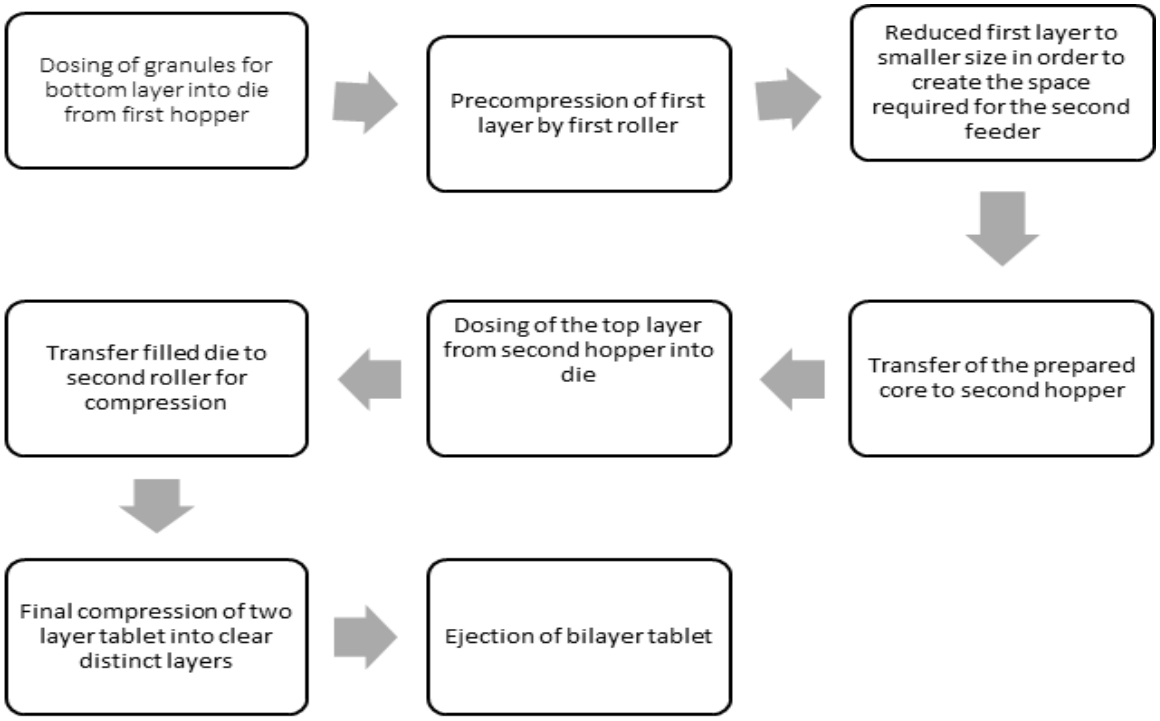


**Fig 3:** Steps involved in preparation of bilayer tablets.

## 3. Novel techniques of bilayer tablets

### 3.1. OROS ® push pull technology

This system consist 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 semi-permeable membrane surrounds the tablet core. Drug layer is of poorly soluble nature. Suspending agent and osmotic agent may be added further. A semi-permeable layer separates tablet core from surrounding (Figure 4).

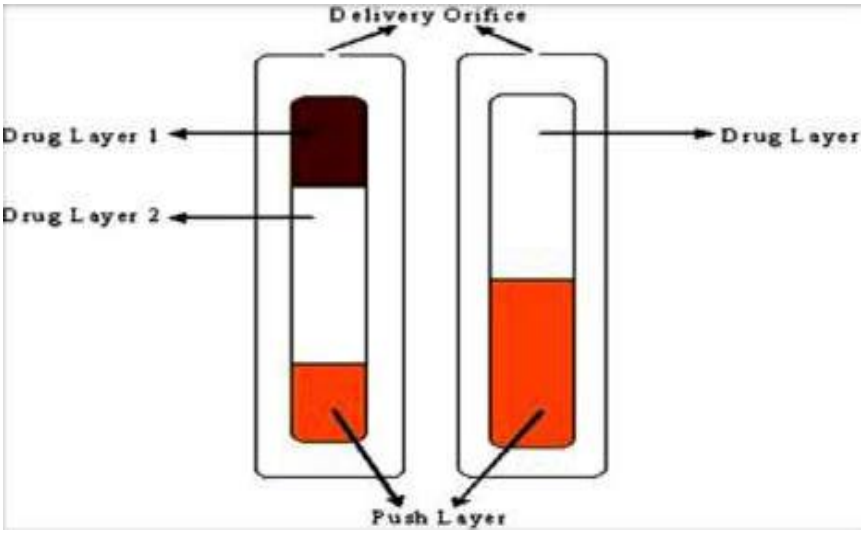


**Fig 4:** Bilayer and trilayer OROS push pull technology.

### 3.2 L-OROS time technology

This system is used for the solubility issue also developed the L-OROS system a lipid soft gel product containing drug in a dissolved State is initially manufactured and then coated with a barrier membrane, than osmotic push layer and then a semi permeable membrane, drilled with an exit orifice (Figure 5) [12].

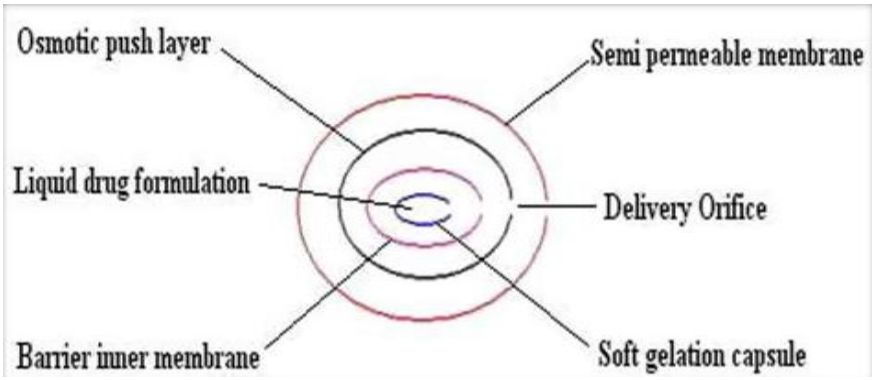


**Fig 5:** L–OROS TM Technology.

### 3.3 Ensotrol Technology

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

### 3.4 Duros Technology

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 miniature drug dispensing system that opposes like a miniature syringe and regions minute quantity of concentrated form in continuing and consistent from over months or years (Figure 6).

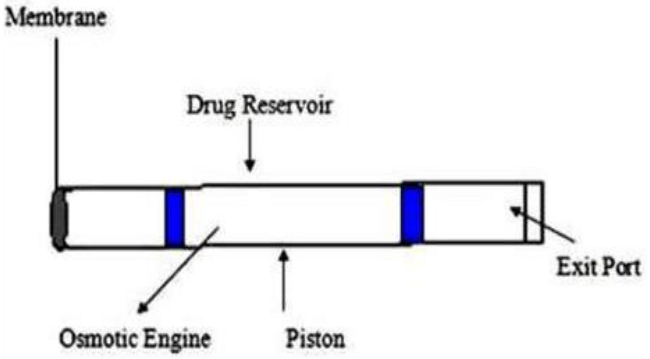


**Fig 6:** DUROS Technologies

### 3.5 E lan Drug. Technologies Dual Release Drug Delivery System

DUREDAS Technology is a bilayer tablet which can provide 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**

- Bilayer tableting technology.
- Tailored release rate of two drug Components.
- Capability for immediate release and modified release components in one tablet.
- Unit dose tablet [13].

### 3.6 EN So Trol

Technology Shire laboratory uses an integrated approach for drug Delivery system, with the help of identification and Incorporation of enhancer for getting optimized dosage form in controlled release system. This approach is useful in increasing solubility (Figure 7).

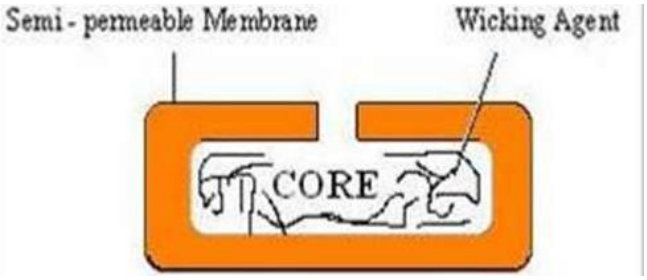


**Fig 7:** EN So Trol Technology.

### 3.7 Rotab Bilayer

1. Software its software of modular design, to which additional functions can be added. Fast graphical evaluations with accurate results can be achieved by one of the advanced system known, PC- system with 15” touch- screens.
2. Working Ro Tab bilayer is an automatically regulating system, when using for production mode switched towards it. With the help of it dose and compression force is automatically regulated by adjusting filling speed and die table. Hardness is also regulated when required.
3. R and D modified technique- R and D modified RoTab Bilayer are useful for graphical visualization and evaluation with measuring points on which there are. These playing important functions of controlling punch tightness. These have R and D plus with possibility of anytime upgration.
4. R and D Plus -R and D Plus showing great importance in tableting technology, provides improved standards. It is useful in controlling important functions such as control of punch tightness, force displacement display and scraper force of tablet, as shown in Figure 8.

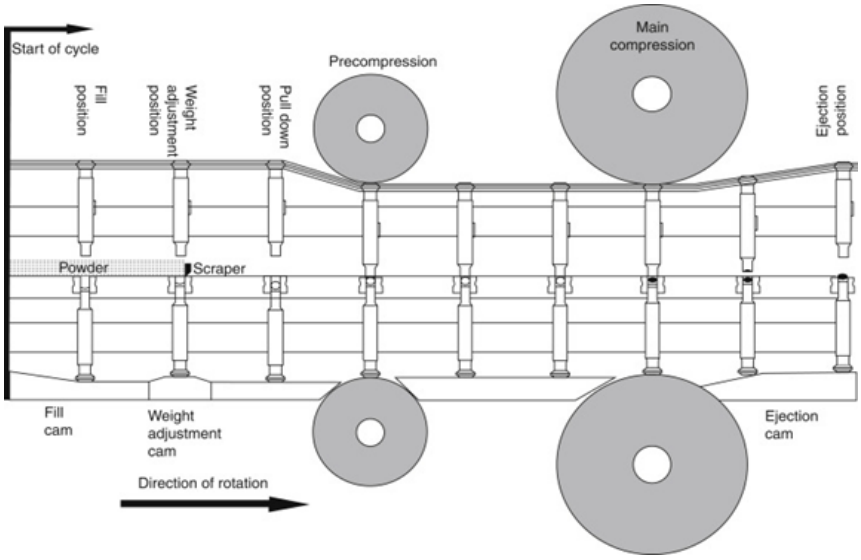


**Fig 8:** Rotab bilayer manufacturing process

### 3.8 Geminex Technology

This technology is very useful one. With help of this the therapeutic efficacy of drugs can be increased greatly, also useful in minimizing side effects. This technology delivers one or more drug with different release rate in single dosage form. It is very useful both for industry as well patients. Geminex Technology actively applied by pen west in following areas – diabetes, cardiovascular diseases, cancer and CNS disorders.

### 3.9 Prodas or programmable oral drug absorption system

PRODAS is also known as multi particulate drug technology (Elan Corporation). In this technology, controlled release mini tablets (size range 1.5 to 4 mm) are encapsulated. This technology has the combination of multi particulate and hydrophilic matrix tablet technologies, used to provide usefulness of above technologies in single dosage form. PRODAS technology is useful in targeted delivery of drug, for targeting to GIT. Different release rates Minitab (immediate-release, delayed-release, and/or controlled release) are combined together in single dosage form to provide desired release rate. Sometime Minitab let are combined with different API to form products of desired release pattern.

### 3.10 Erodible moulded multilayer tablet-

Eaglet delivery technology is erodible moulded multi layered tablet technique. This technology developed based on standard plastic injection moulding, containing coat and matrix. Egalet erodible molded tablets, having mechanism for release pattern is erosion of matrix part. This technique is useful in delivering zero order or delayed release pattern of drug without affecting GI conditions. Release pattern controlled by designing and engineering of geometry of coat and matrix. For zero order release drug dispersed in matrix. The coat used is of poor water permeability and biodegradable. Erosion of matrix takes place when come in contact with available water or by GI fluids and promote by gut movements in the GI tract. This technique is wholly desirable for drugs with stability issues while contacting with water i.e. Chemical and physical stability issues. This technology assures accuracy, reproducibility and low production cost [13].

## 4. Various novel 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 [14].

### 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 or unfold to a size that precludes passage through the pylorus until after drug release has progressed to a required degree Gradual erosion of the system or its breakdown into smaller particles enables it to leave the stomach. The simple bilayer tablet may contain an immediate release layer with the other layer as extended release or conventional release.

## 5. Summary and Conclusion

Bi-layer tablet is also used to overcome the limitation of the single layered tablet. Bi-layer tablet is a new era for successful development of controlled release formulation along with various features to provide successful drug delivery. Bi-layer tablets can be primary option to avoid chemical incompatibilities between APIs by physical separation and to enable the development of different drug release profiles. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. Several pharmaceutical companies are currently developing bi-layer tablets. For a variety of

reasons: patent extension, therapeutic, marketing to name a few. To reduce capital investment, quite often existing but modified tablet presses are used to develop and produce such tablets. Bi-layer tablet is suitable for sequential release of two drugs in combination and also for sustained release of tablet in which one layer is for immediate release as loading dose and second layer is maintenance dose. So use of bi-layer tablets is a very different aspect for antihypertensive, diabetic, anti-inflammatory and analgesic drugs where combination therapy is often used. Several pharmaceutical companies are currently developing bi-layer tablets, for a variety of reasons: patent extension, therapeutic, marketing to name a few.

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