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# Bilayer Tablets: An Emerging Drug Delivery System

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**ABSTRACT**

There are many approaches to supply drugs into the body, viz oral (through swallowing), sub mucosal (through buccal and sublingual mucosa), parenteral (through injection), transdermal (through the skin), pulmonary (through inhalation) etc. Despite disadvantages, oral drug shipping remains the preferred route of drug delivery. Novel applied sciences with extended performance, affected person compliance and better first-class have emerged in the latest past. Multilayer tableting is getting growing attention from a variety of industries for a variety of reasons: patent extension, therapeutic, advertising to identify a few. To reduce capital investment, quite frequently existing however modified pill presses are used to increase and produce such tablets. While general pill manufacturing principles continue to be the same, there is an awful lot extra to consider because making multi-layer pills entails multiple-often incompatible products, extra equipment and many formula and operation challenges. The current article affords a evaluation on the oral drug shipping system, sorts of tablets, and challenges in bilayer tablet manufacturing, a number tablet presses used, high-quality and GMP requirements for their manufacturing and latest developments in the area of bilayer technology.[1]

## INTRODUCTION

The bilayer tablet is a concept utilized by Skye Pharma PLC in their Geo-matrix tablet, which is composed of different layers. The system allows the incorporation of more than one drug into the dosage form.[1]

The improvement of sustained or managed drug delivery structures has bought momentum over the previous decade due to sizeable focus on the advertising of new drug molecules as the mixture of these new drug molecules has elevated to counter multiple illnesses that require special dosage regimens. [3]

Bilayer tablet has patient compliance and is recommended for both sequential launch of two capsules in mixture or sustained and immediate release of the identical drug one as preliminary and other as a protection dose. Therefore, this report aims to shed light on the significance of bilayer tablets in the drug delivery system and to counter the challenges that are faced in its manufacturing. Besides, numerous techniques for its formation and various bilayer tablets use for different diseases are also analyzed in this article.[3]

Formulation of layers from different polymers allows manipulation over more than one rate-controlling polymer, thus enabling different types of drug delivery of one or more drugs, i.e. where the drug may be released with a bolus and then at a controlled rate or by targeted drug delivery in the GI tract using pH-dependent polymers. There are clearly several issues of concern to the production of bilayered tablets.

While the mechanical strength of layered tablets has been observed not to be a controlling factor in drug release the determination of this property could be beneficial in understanding the adhesion between various layers and provide an improved characterization of the systems.

Bilayer Tablet Bi-layer tablets are prepared with one layer of drug for immediate release while second layer is designed to release drug, later, either as second dose or in an extended-release manner. 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 the maintenance dose.[2]

Monolithic Tablets (Matrix or Single layer): The term monolithic tablet refers to tablet containing no sub units that have different drugs. [1]

## NEED OF DEVELOPING BI-LAYER TABLETS

For the supervision of fixed-dose combinations of API's, prolong the drug product life cycle, buccal/mucoadhesive delivery systems, and manufacture novels drug delivery systems like chewing devices and floating tablets for gastro-retentive drug delivery systems.

1. Controlling the delivery rate of either single or two different API'S

2. To adapt the total surface area available for the API layer either by sandwiching with one or two inactive layers to achieve swellable/erodible barriers for controlled release.

3. To separate incompatible API's from each other, to control the release of one layer by utilizing the functional property of the other layer (such as osmotic property).[5]

## BILAYERED TABLET

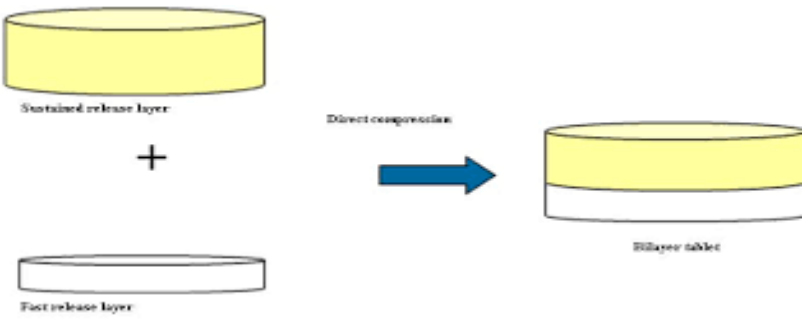
In the ultimate decade, interest in growing a mixture of two or extra Active Pharmaceutical Ingredients (API) in a single dosage form (bilayer tablet) has elevated in the pharmaceutical industry, advertising patient convenience and compliance. Several pharmaceutical corporations are in modern times creating bi-layered drugs for a variety of reasons effective extension, therapeutic, advertising to a name, a few Bilayer are novel drug delivery structures where a combination of two or extra drugs in a single unit.

## TYPES OF BILAYER TABLET

The term bilayered tablets contains subunits that may be either the same (homogeneous) or different (heterogeneous).

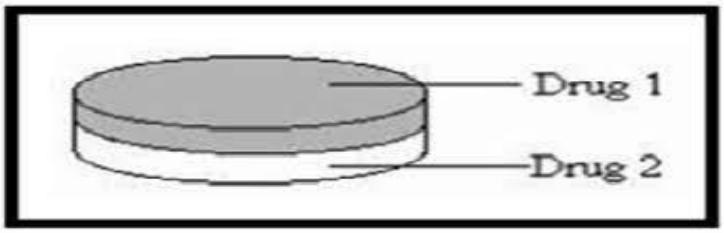
## HOMOGENOUS TYPE

Bilayer tablets are preferred when the release profiles of the Drugs are different from one another. Bilayer tablets allow for designing and modulating the dissolution and release characteristics. Bilayer tablets are prepared with one layer of drug for immediate release while second layer designed. To release drug, later, either as second dose or in an Extended release manner.



- **HETEROGENEOUS TYPE**

- Bilayered tablet is suitable for sequential release of two drugs in combination, separation two incompatible substance. [4]




**ADVANTAGES OF BILAYERED TABLET**

1. The administration of Sustained-release preparation as one layer with the immediate release preparation as the second layer is possible.

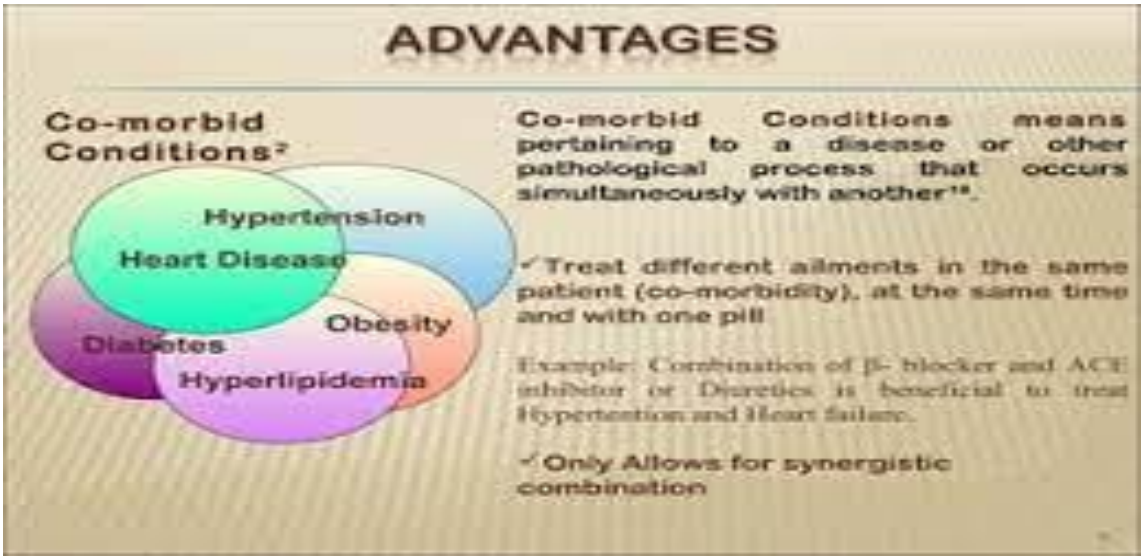
2. The separation of two incompatible substances with addition of any barrier layer between them is possible.

3. The widths of each layer can be accurately controlled.

4. Preventing of cross-contamination between two layers.

5. Producing a clear visual separation between two layers.

6. Accurate and individual weight control of two layers.[1]




**DISADVANTAGES**

1. Adds complexity and bilayer rotary presses are expensive.

2. Insufficient hardness, layer separation reduce yield.

3. Inaccurate individual layer weight control Cross contamination between the layers.[5]

**APPLICATION OF BILAYERED TABLET**

Bilayer tablet is appropriate for sequential launch of two drug in combination. Separate two incompatible substances. Sustained release tablet in which one layer is instant launch as preliminary dose and 2d layer is preservation dose.

Bilayer tablet is increased advisable technology to overcome the quick coming of the single layer tablet.

Bilayer tablet are used to supply the loading dose and sustained dose of identical or extraordinary drugs.

Bilayer tablet are used for bilayer floating tablets in which one layer is floating layer the drug. Any other one is the instantaneous launch layer of Bilayer tablet are used to supply the two exclusive tablet having different launch profiles.

## GENERAL PROPERTIES OF BI-LAYER TABLET DOSAGE

It should have graceful product identity free of Defects like chips, cracks, discoloration, and Contamination should have sufficient strength to withstand Mechanical shock during its production, packaging, Shipping and dispensing.

should have physical and chemical stability. The bi-layer tablet must release drug in an expectable and reproducible manner.

Must have a chemical stability shelf life, so as not to follow alteration of the medicinal agents.[4]

## TYPES OF BILAYER TABLET PRESS

1. Single-sided tablet press.

2. Double-sided tablet press or “compression force” controlled tablet press.

3. Bilayer tablet press with displacement monitoring.

Single sided tablet presses the simplest design is a single sided press with both Chambers of the doublet feeder separated from each other each chamber is gravity or force-fed with different powers, thus producing the two individual layers of the tablets. When the die passes under the feeder, it is at first loaded with the first layer powder followed by the second layer of powder then the entire tablet is compressed in one or two steps. [4]

### Limitations of Single sided tablet press

- No weight monitoring/ control of the individual layers.
- No distinct visual separation between the two layers.
- Very short first layer dwell time due to the small compression roller, possibly resulting 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 consequence 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.

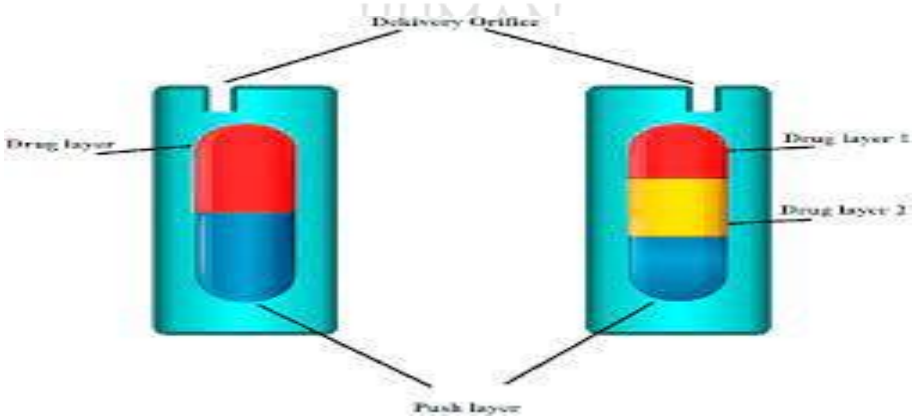
**Double-sided tablet presses**

A double-sided press offers an individual fill station pre-compression and main compression for every layer. In reality the bi-layer tablet will go through four compression levels earlier than being ejected from the press. Most double-sided tablet presses with automated production manipulate compression pressure to display and manage pill weight. The advantageous top compression pressure exerted on every individual pill or layer is measured by way of the management system at the principal compression of the layer. This measured height compression force is the sign used by way of the manipulated system to reject out of tolerance tablet and correct the die fill depth when required.

**Various Techniques for Bilayer Tablet**

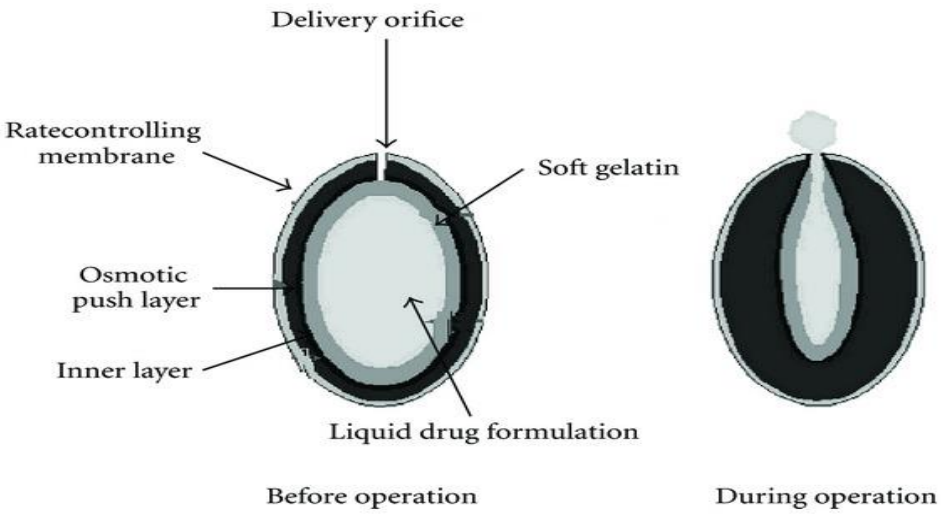
**OROS® Push Pull Technology**

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 drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi-permeable membrane surrounds the tablet core.



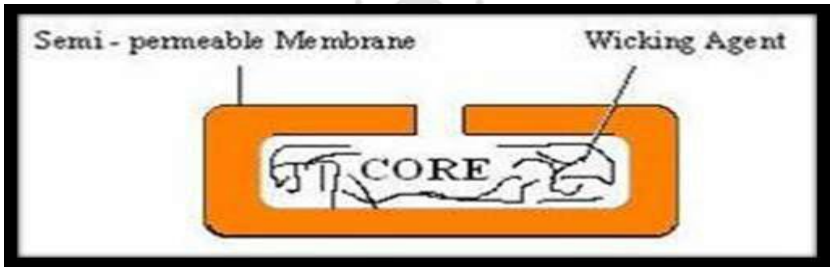

**L-OROS TM Technology**

This system used for the solubility issue 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 than a semi-permeable membrane, drilled with an exit orifice."



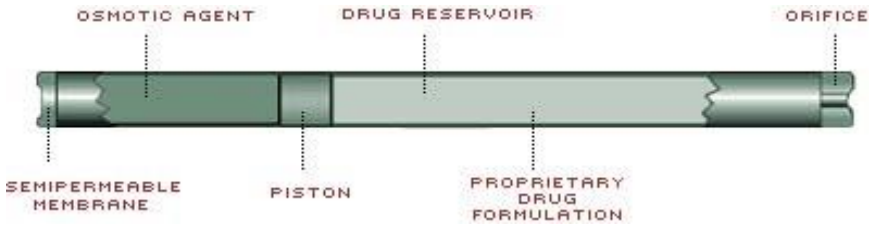

**EN SO TROL Technology**

Solubility enhancement of a magnitude or to create optimized dosage form Shire laboratory uses an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies.




**DUROS Technology**

The system consists of 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, a system that opposes like a miniature syringe and religious minute quantity of concentrated form in continues and consistent from over months or year."



**Elan Drug Technologies' Dual Release Drug Delivery** System

(DUREDAS™ Technology) is a bilayer tablet that 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 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**

1) Bilayer tableting technology

2) Tailored release rate of two drug components

3) Capability of two different CR formulations combined

4) Capability for immediate release and modified release components in one tablet

5) Unit dose tablet presentation. [2]

The DUREDAS™ system can easily be manipulated to allow the incorporation of two controlled release formulations in the bilayer. Two different release rates can be achieved from each side. In this way greater prolongation of sustained release can be achieved. Typically, an immediate release granulate is first compressed followed by the addition of a controlled-release element which is compressed onto the initial tablet. This gives the characteristic bilayer effect to the final dosage form. A further extension of DUREDAS™ technology is the production of controlled-release combination dosage forms whereby two different drugs are incorporated into the different layers and drug release of each is controlled to maximize the therapeutic effect of the combination. Again both immediate release and controlled release combinations of the two drugs are possible. Several combination products utilizing this technology approach have been evaluated. The DUREDAS™ technology was initially employed in the development of several OTC controlled-release analgesics. In this case a rapid release of analgesic is necessary for a fast onset of therapeutic effect. Hence one layer of the tablets is formulated as immediate releases granulate. By contrast, the second layer of the tablet, through use of hydrophilic polymers, releases drug in a controlled manner. The controlled release is due to a combination of diffusion and erosion through the hydrophilic polymer matrix. [1]

## LIMITATIONS

The separation of the two individual layers is due to insufficient bonding between the two layers during final compression of 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. Bonding is too restricted if 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". Most of the double-sided tablet presses with automated production control use compression force to monitor and control tablet weight. The compression force control system is always based on the measurement of compression force at main compression but not at pre-compression.

Bilayer Tablet Press with Displacement Monitoring

The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied pre-compression force. In fact the lower the pre-compression force, the more the monitoring control system and this ideal for good interlayer bonding of the bi-layer tablet.

- **Challenges in the formation of bilayer tablets**

Nevertheless, these mediums of drug delivery are mechanically Difficult to manufacture and it is not easy to foretell their long-term mechanical properties because of the inferior mechanical and Compression characteristics of the basic materials used in the Manufacturing of the drug layers, the elastic disparity of the layers, inadequate hardness, imprecise individual mass control, cross-Contamination amongst the layers, decreased yield, and their affinity Of delaminating at the interface between the layers throughout and after The different production stages following the compaction process. Thus, the main issue that has to be dealt with in the proper and detailed understanding of the main sources of the issues in both macro and microscales and the development of effective remedies for their solution during the solid dosage delivery design. Among the main issues are the insufficient adhesion and bonding at the interface between the adjacent compacted layers that are mostly caused by an interfacial crack resulting in residual stresses in the tablet, spreading a finite distance in the tablet and

resulting in delamination, or Layer-separation, that is not visible instantly after compaction, such as During packaging, storage, or shipping. Moreover, if the compacted Layers are excessively hard or soft, they won't be able to adhere firmly Which could result in negotiated mechanical integrity. Some other issues in the development process are the establishment of the layer sequence Order, the elastic disparity of the adjacent layers, layer weight ratio, the Damping force of the first layer, and cross-contamination between layers. If these factors are not controlled, they will somehow affect the bilayer compression per se (uncontrolled or inefficient process) and the quality characteristics of the bilayer tablets, i.e., adequate mechanical Strength for maintaining its usefulness and the weight control of the Individual layer. Thus, the proper attainment of a detailed understanding of the main causes is important for enabling the design of a robust Process and product. As the adjacent compacted layers within a Bilayer tablet adhere to each other mechanically, the understanding of the things influencing the stress state, the mechanical attributes of every Layer and the overall bilayer tablet, and compression parameters, as well As the dedicated methods for predicting failure as a function of Compression conditions and layer properties, are elemental for the successful development of the bilayer.

Areas to be addressed during the formation of bilayer drugs In the introduction of this article, some of the challenges were Mentioned which can deteriorate the process of formation of bilayer Tablets and also the produced drug once it's produced. The following eight Areas should be addressed during the production of bilayer tablets. [3]

**Material properties**

The material properties such as plasticity, brittleness, and visco-elasticity are vital in the successful formation of bilayer tablets. These properties are categorized into two distinct groups, i.e. Active pharmaceutical ingredients (APIs) and excipients. Depending upon the chemical composition of the tablets either the active pharmaceutical ingredient or excipient influences the compactness of the tablet. The plasticity deformation and the brittleness of material have importance regarding the compression process. This means that the plasticity would not affect the compression process as long as the elasticity of the plastic material does not go beyond the bond limit. Besides, the particle deterioration in the central area of die is greater in comparison to the outer layer, hence it is vital to focus on the material properties of the substance before employing it in the formation of bilayer tablets.

**Compression forces**

The compression force on the first layer influences the interfacial strength and adhesion between the two layers, which results in mechanical attraction among the layers in the tablet. So, if the first layer of the bilayer drug was more elastic, then the stress and tension introduced in the whole system due to it, causes the strength of the bilayer tablet to weaken. This can lead to the breakage of the bond between the two layers at the interface of the bilayer tablet. Therefore, it is necessary to focus and check the compression forces while preparing the bilayer tablets.

**Lubricant**

It is researched that a substance having greater lubricity will have lower friction among its particles and with die when it comes into contact because all the matter will be evenly distributing. However, in the case of bilayer substances to achieve greater interaction and strength between the two layers low lubricant level is compulsory. The impact of lubricant level has more influence than the brittle substance Therefore, these attributes of the substance should be kept in mind while dealing with the formation of bilayer tablets.

**Laer ratio and layer sequence**

This area has the least research; however, it is found that generally, the ratio between the first and second layers could be 1:1, 1:2, and even 1:3 in some circumstances. But it is difficult to make the weight of the second layer consistent with that of the first layer which is mostly heavy, and it causes a problem during the formation of bilayer drugs.

**Environmental conditions**

Environmental conditions like humidity and moisture can affect the compactness of bilayer tablets. The hygroscopic materials can absorb or desorb the moisture from its structure through its pores, whereas the substances such as starches, microcrystalline cellulose, hydroxypropyl Methylcellulose, etc. tend to absorb moisture from the surrounding. The Intake of moisture causes weak compactness of the substance, due to the enlarging of the basic structures. This, in turn, will cause a weak Bond between the two layers at the interface, hence, contributing to the Time-based delamination.

**Layer weight control**

To ensure the content uniformity of the active pharmaceutical ingredients in the bilayer tablets some precursors play a significant role, such as material flow property, particle size distribution, and the ability Of the bilayers to press accurately. Hence, a commercial press is used to measure the weight of the first layer and second layer, however, a press used to individually monitor the weight of the second layer is not available. This generates a huge challenge while manufacturing the bilayer tablets.

Therefore, a way should be developed to minimize this effect.

**Bilayer tablet compression machines**

Several bilayer compression machines, such as Oyestar magnets, Hata, korsch, kilian, etc. are available for the researchers working on Bilayer tablets, whereby they provide many features like; first layer Sampling, pre-compression rollers, sealed feeders, and many more. All these features have a certain influence on the binding between the two layers of the bilayer tablet. Therefore, compression machines are very important in the formation of a bilayer tablet, as they can help in making the desired quality of the dosage or they can reduce the quality of the tablet. Hence, this area should be focused significantly during the formation of the bilayer tablet [40].

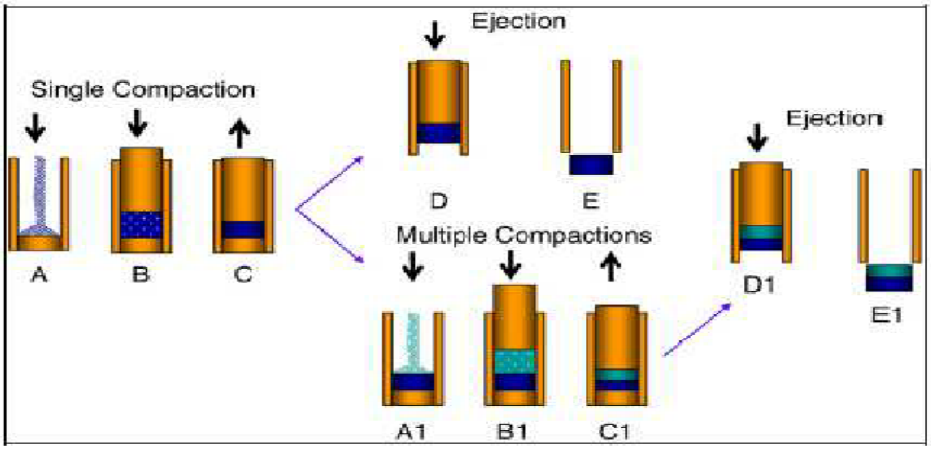
**Bilayer tablet characterization**

It is one of the most influential areas which should not be neglected in any case while discussing the bilayer tablets. While it is theoretically preferred to have a material, which can be compressed without deformation and compact on its own when compression is applied to it, which will lead to a stronger bond between the two layers of the bilayer tablet, however, other elements play a role in the formation of the desired quality of bilayer tablets. This is known as characteristics, wherein particle size distribution, angle of the response, photo microscopic study, density, compressibility, and moisture sorption capacity are included. [3]

**BI-LAYER COMPRESSION BASICS**

A) Initial layer die filling and compaction.

B) Initial layer compaction showing the predominant stress transmission profile.




C) Density profile of initial layer before die filling of the final layer.

D) Final layer die filling and compaction.

E) Final layer compaction showing the predominant stress transmission profile.

F) Density profile of bilayer tablet before ejection.

G) Ejection of a bilayer tablet. [4]

**CONCLUSION:**

The Bilayer tablet is an improved beneficial technology to overcome the shortcoming of the single-layered tablet. There is the various application of the bilayer tablet it consists of monolithic partially coated or multi-layered matrices. A Bilayer tablet is suitable and one of the important design approaches where incompatible drugs, with different indications, and same drug with different release rate (e.g. IR and SR) can be incorporated in a single unit in the immediate-release layer as initial dose and Sustained Released layer is maintenance dose. To develop a bilayer, tablet a complete mechanistic understanding must be developed through the application of scientific and quality risk management tools. The main purpose of this drug delivery system is to guarantee that the drug is effective and has the least side effects, is properly manufactured keeping in view all GMP parameters to maintain its quality throughout its shelf life. To meet these criteria, different approaches are applied and different presses are used to maximize their efficacy and minimize the side effects. The manufactured tablet is evaluated both physically and chemically to ensure its effectiveness and stability throughout its shelf life. Nowadays different bilayer tablets are produced that have different APIs for combination therapy or the same API to be given in a single unit having both Immediate and Sustained released drug profiles. [1]

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