

BILAYER TABLET-TECHNOLOGY- A REVIEW

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ABSTRACT

Several pharmaceutical companies are currently developing bi-layer tablets, for a variety of reasons: patent extension, therapeutic, marketing to name a few. Bi-layer tablet is a new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system and it 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. 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. The present article provides a review on the oral drug delivery system, types of

tablets, Bilayer tablet manufacturing, various tablet presses used, quality and GMP requirements for high production output and recent developments in the field of Bilayer technology and why development and production of quality bi-layer tablets need to be carried out on purpose built tablet presses to conquer common Bilayer problems, such as layer separation, insufficient hardness, inaccurate individual layer weight control, cross contamination between the layers, reduced yield.

KEYWORDS: Bi-layer tablet, Approaches, GMP requirement for bi-layer tablets, various tablet presses.

INTRODUCTION

Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease of administration. Conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable

toxicity and poor efficiency. The aim in designing sustained or controlled delivery systems is to decrease the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required. The main objective of sustained release drug delivery is to make sure safety and to improve effectiveness of drugs as well as patient compliance.^[1]

Now a day's various developed & developing countries move towards combination therapy for treatment of various diseases & disorders requiring long-term therapy such as hypertension, diabetes and Cardio vascular diseases. Bi-layer tablets are 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.^[2]

Bilayer tablets have some key advantages compared to conventional monolayer tablets. For instance, such tablets are commonly used to avoid chemical incompatibilities of formulation components by physical separation. In addition, Bilayer tablets have enabled the development of controlled delivery of active pharmaceutical ingredients with predetermined release profiles by combining layers with various release patterns, or by combining slow-release with immediate-release layers.^[3] However, these drug delivery devices are mechanically complicated to design/manufacture and harder to predict their long term mechanical properties 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. Therefore, the major problem, that has to be overcome, is to understand in detail the sources of these problems in micro- and macro scales and to develop remedies to solve them during solid dosage delivery design.^[4, 5]

Need of Bilayer Tablet

- 1) Controlling the delivery rate of either single or two different API'S.
- 2) To separate incompatible active pharmaceutical ingredient 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 administer fixed dose combinations of different APIs, prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device, buccal/mucoadhesive delivery systems, and floating tablets for gastroretentive drug delivery.
- 4) To modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable / erodible barriers for controlled release.

Bilayer Tablets

A multi-layered tablet is a tablet that has more than one individually compacted powder layers within its final single body e.g. a bi-layered tablet consists of two sequentially compressed layers that form a single final coherent tablet body at the end of the compression process. Multi-layered tablets are favoured due to their controlled release profiles of the active ingredients.^[7] The target of any drug delivery system is to supply a therapeutic amount of the drug to the appropriate site in the body to achieve quick and/or sustain the required drug concentration. Combination therapy is more effective as compared to monotherapy because in this we can minimize the dose dependent side effects. Low dose combination of two different drugs reduces the side effect of single drug in high dose.^[8]

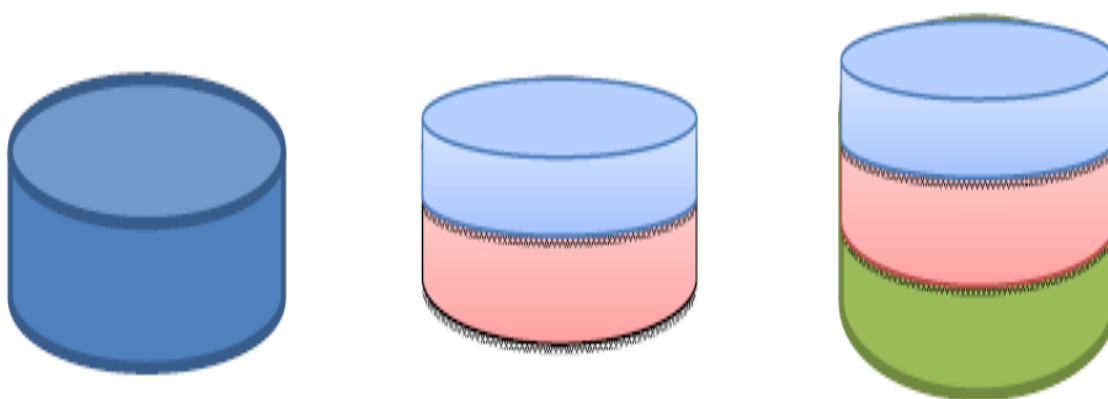


Fig.1 A) Single Layer Tablet

B) Bilayer Tablet

C) Multilayer Tablet

Applications^[6]

- 1) Bi-layer tablet is suitable for sequential release of two drugs in combination.
- 2) Separate Two Incompatible Substances.
- 3) Sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose.
- 4) layer is maintenance dose.
- 5) Promoting Patient Convenience and Compliance.

- 6) Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet
- 7) Bilayer tablets are used to deliver the loading dose and sustained dose of the same or different drugs.
- 8) Bilayer tablets are used for bilayer floating tablets in which one layer is floating layer another one is immediate release layer of the drug.
- 9) Bilayer tablets are used to deliver the two different drugs having different release profiles.

Advantages of Bilayer Tablets^[9, 10]

- 1) Objectionable odor and bitter taste can be masked by coating the tablets.
- 2) Chemical and microbial stability is more as compared to other oral dosage form.
- 3) This is unit dosage form with various capabilities for highest dose precision and least content variability.
- 4) Easy to swallow with fewer tendencies to hang-up.
- 5) It is suitable for large scale production.
- 6) Cost is low as compared to other oral dosage form.
- 7) Product identification is easy.
- 8) Maintain physical and chemical stability.
- 9) Patient convenience is improved because fewer daily doses are required compared to traditional delivery system
- 10) Potential use of single entity feed granules.

Disadvantages of Bilayer Tablet Dosage Form^[9]

The drug which resists the compression or drug which is amorphous in nature or low density drugs cannot be incorporated into bilayer tablet.

- 1) Bitter drugs, drugs which are sensitive to oxygen or drugs which have objectionable odor, they requires additional step of coating.
- 2) Difficulty in swallowing in case of unconscious patients and children.
- 3) Drugs which have poor wetting, slowly dissolves in GIT.

General Properties of Bilayer Tablets^[11]

- 1) Bilayer Tablet should be elegant with free of defect, cracks, discoloration and contamination
- 2) It should have sufficient strength to resist mechanical shock during production, packaging and shipping.

- 3) It must be physically and chemically stable.
- 4) It should release the drug in predictable and reproducible manner.
- 5) It should be chemically stable to resist the alteration of chemical nature of drug substance in shelf life.

Bilayer Tablets Quality and GMP Requirements^[11]

To create a quality bilayer tablets it is important to choose Bilayer Tablet Press which is capable of.

- 1) Providing sufficient tablet hardness
- 2) Preventing cross contamination between two layers
- 3) Producing bilayer tablet with distinct visual separation of two layers
- 4) Preventing capping and separation of two layers
- 5) Accurate and individual weight control of both the layers
- 6) Producing tablets with minimum weight variation.

Challenges in formulation of Bilayer Tablets^[10, 12]

Challenges during development of Bilayer tablets include the order of layer sequence, layer weight ratio, and elastic mismatch of the adjacent layers, first layer tamping force and cross contamination between layers. If these factors not well controlled in one way or other will affect the bi-layer compression pressure and the quality attributes like mechanical strength and individual layer weight control. Therefore care must be taken to enable design of a vigorous product and process. Some Challenges in formulation of Bilayer Tablets are as follows.

- 1) Lamination i.e. layer separation is major problem in production of layered tablets.
- 2) Mixing of both the layers i.e. Cross-contamination.
- 3) Lack of sufficient bonding and adhesion at adjacent layers.
- 4) Difficult to maintain integrity of final Tablets.
- 5) Individual layer weight control is difficult.
- 6) Insufficient hardness.
- 7) Production yield of Bilayer tablet is very low compared to single layer tablet.
- 8) Bilayer tableting is more expensive than single layer tableting

Types of Bilayer Tablet Press

- 1) Single sided tablet press.
- 2) Double sided tablet press.

3) Bilayer tablet press with displacement monitoring.

1) Single Sided Tablet Press^[14]

The simplest design is a single sided press with both chambers of the doublet feeder separated from each other. Each chamber is gravity or forced fed with different power, producing the two individual layers of tablets. When die passes under the feeder, it is first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps.



Fig.2 Single Sided Tablet Press.

Limitations of the Single Sided Press^[15, 16, 17]

No weight monitoring / control of the individual layers.

1. No distinct visual separation between the two layers.
2. Very short first layer dwell time due to the small compression roller, possibly resulting in poor Deaeration, capping and hardness problems.
3. This may be corrected by reducing the turret rotation speed (to extend the dwell time) but with the consequence of lower tablet output.

2) Double Sided Tablet Press^[14]

In 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 the layer.

This measured peak compression force is the signal used by the control system to reject out of tolerance and correct the die fill depth when required.



Fig.3 Double sided tablet press.

3) Bilayer Tablet Press with Displacement Monitoring^[14]

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 precompression force.



Fig.4 Bilayer tablet press with displacement.

Advantages

- 1) Weight monitoring / control for accurate and independent weight control of the individual layers.
- 2) Low compression force exerted on the first layer to avoid capping and separation of the two individual layers.
- 3) Independence from the machine stiffness.
- 4) Increased dwell time at Precompressional of both first and second layer to provide sufficient hardness at maximum turret speed.
- 5) Maximum prevention of cross-contamination between the two layers.
- 6) Clear visual separation between the two layers and maximized yield.

Ideal Properties of Bilayer Tablet Press

- 1) It should produce maximum yield and accurate individual layer weight control.
- 2) Should produce clear visualization between two layers.
- 3) It should prevent the cross-contamination between two layers.
- 4) It should prevent capping and separation of two individual layers.
- 5) There should be a system to separate two layers to check and control the weight of individual layer.

Various Techniques for Bilayer Tablets^[18, 19]

OROS® Push Pull Technology

This system consist of mainly two or three layer among which the one or more layer are 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.

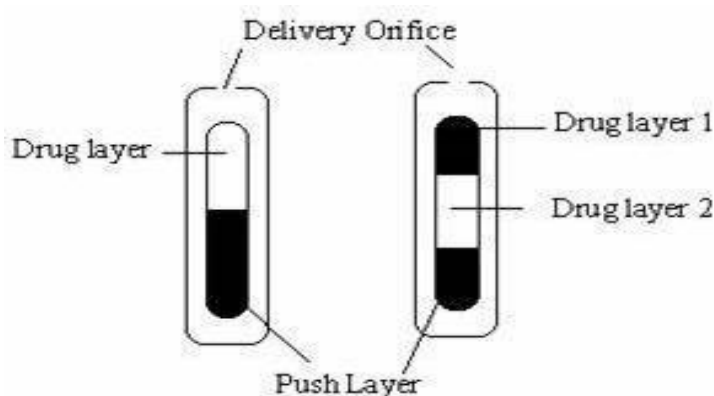


Fig.5 Bilayer and Trilayer OROS Push pull technology.

L-OROSTM Technology

This system used for the solubility issue Alza developed the L-OROS system. This system is mainly used for solubility problem, where a lipid soft gel product containing drug in a dissolved condition initially prepared and then coated with barrier membrane then osmotic push layer and then semi permeable membrane drilled with exit orifice for drug release.

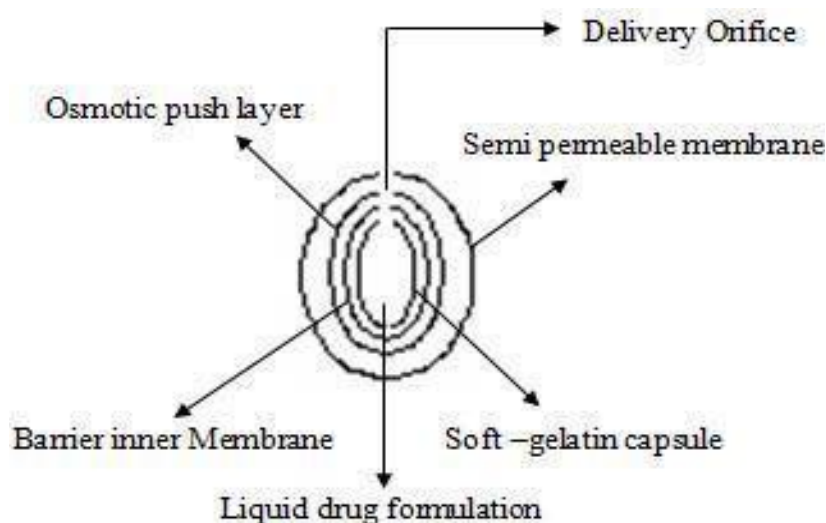


Fig.6 L – OROStm technology.

DUROS Technology (Elan drug technologies dual release drug delivery System)

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 release minute quantity of concentrated form in continues and consistent from over months or Year.

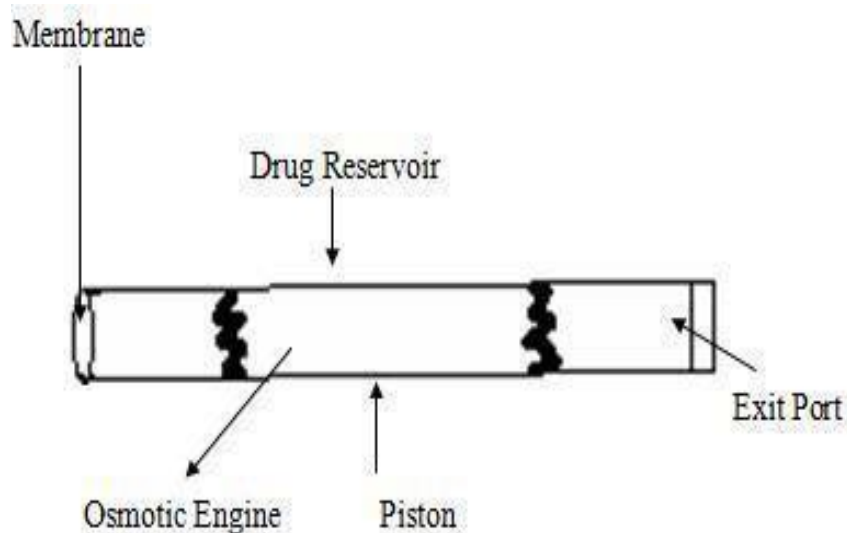


Fig.7 DUROS Technology.

EN SO TROL Technology

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

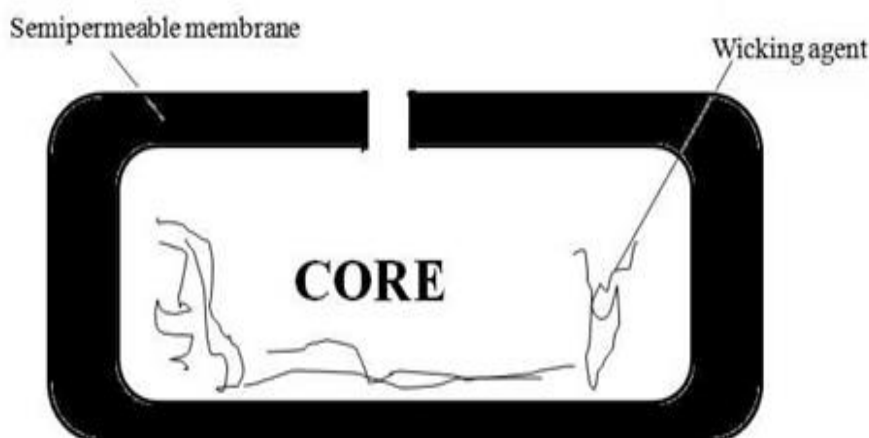


Fig.8 EN SO TROL Technology.

Duredas Technology

Duredas or Dual release drug absorption system (Elan Corporation) utilizes bilayer tableting technology. This is specifically developed to provide two different release rates or dual release of drug from single dosage form. Tablets prepared as immediate release layer and controlled release layer within single tablet. Controlled release matrix remains intact and slowly absorbs fluid from GI tract, which causes matrix to expand and transform hydrophilic matrix into porous, viscous gel which acts as barrier releases drug in controlled manner.

Benefits offered by the DUREDAS™ Technology Includes

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.

Geminex Technology

It is dual drug delivery technology, which can deliver one or more drugs at different times. This technology controls the release rate of two drugs to maximize their individual

therapeutic effect and minimize side-effects. The benefits of this technique are that two different actives can be delivered at different rates in a single tablet.

PRODAS or Programmable Oral Drug Absorption System

PRODAS or Programmable Oral Drug Absorption System (Elan Corporation) is a multiparticulate drug delivery technology that is based on encapsulation of controlled release minitables in the size ranging from 1.5 to 4 mm in diameter. This technology is a combination of multiparticulate and hydrophilic matrix technology thus shows benefits of both. Minitables with different release rates can be combined and incorporated into single dosage form to present different release rates. These combinations may include immediate release, delayed release and/or controlled release minitables.

Preparation of Bilayer Tablets^[20]

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 area of contact between two layers. An additional intermediate layer of inert material may also be included. To produce 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 formulator to achieve these conditions especially in bilayer tablet formulation where double compression technique is involved, because of poor flow and compatibility characteristics of the drug which will result in capping and/or lamination. The compaction of a material involves both the compressibility and consolidation.

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

Consolidation: it is the property of the material in which there is increased mechanical strength due to interparticulate interaction (bonding). The compression force on layer 1 was found to be a major factor influencing tablet delamination.

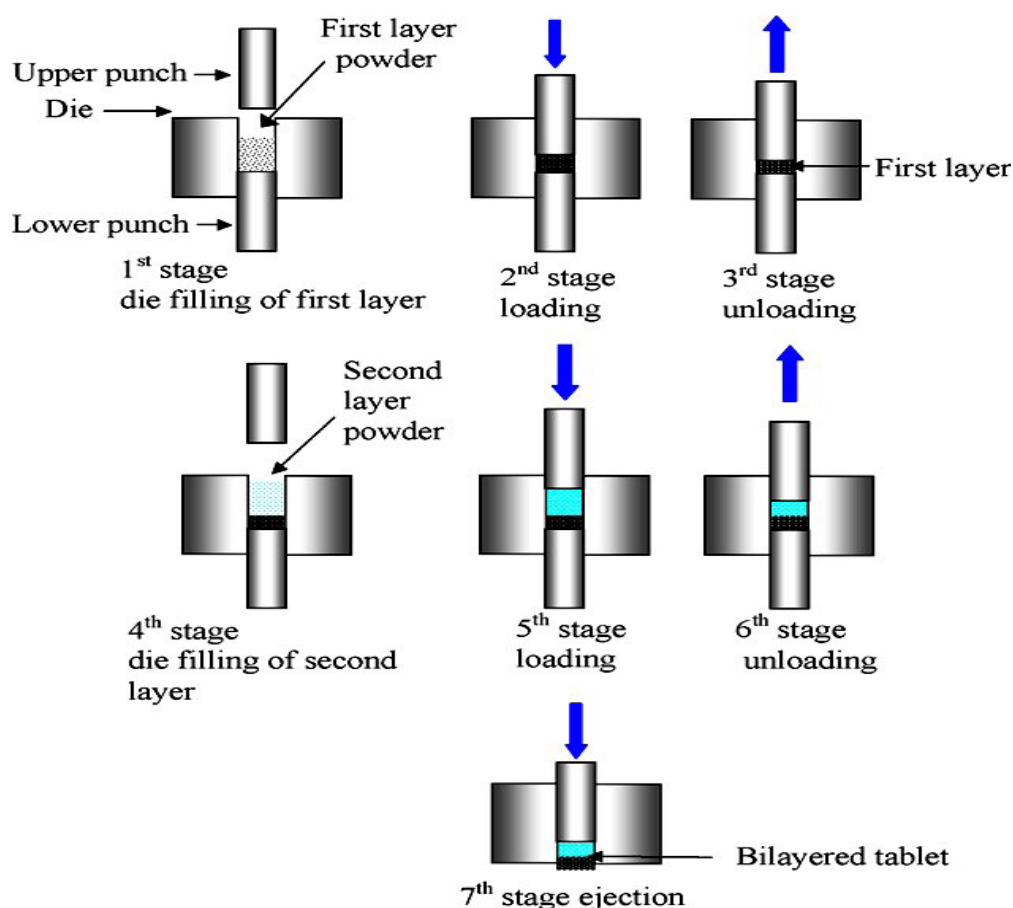


Fig.9 Preparation of bilayer tablet Compaction.

CONCLUSION

Bilayer tablet is improved beneficial technology to overcome the shortcoming of single layered tablet. Bilayer tablets provide one of the important design approaches where incompatible drugs, with different indication, and same drug with different release rate can be incorporated in a single unit. 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. To develop a dynamic bi-layer tablet a complete mechanistic understanding must be developed through the application of scientific and quality risk management tools. Pharmaceutical development and quality risk management. Bi-layer tablet quality and GMP requirements can vary widely. This explains why many different types of presses are being used to produce bilayer tablets, ranging from simple single-sided presses to highly sophisticated machines.

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