

REVIEW ARTICLE

Bi-Layer Tablets: An Emerging Trend

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ABSTRACT

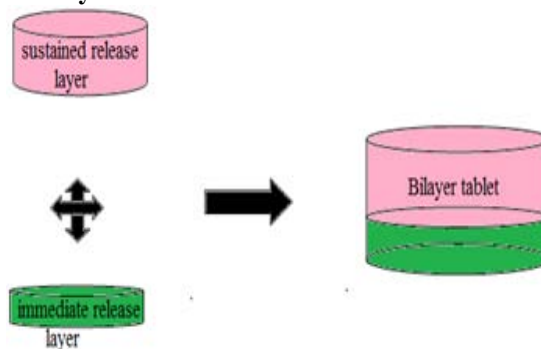
Bi-layer tablets have been developed to achieve controlled delivery of different drugs with pre-defined release profiles. In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bilayer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance. 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. 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.

Key words: Bilayer tablet, RoTotab push technology, OROS® push pull technology, DUROS technology.

INTRODUCTION

Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance. 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 [2]. There is various application of the bi-layer tablet it consist of monolithic partially coated or multilayered matrices. In the case of bi-layered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper non-adhesive layer its delivery occurs into the whole oral cavity.

Fig 1: Bilayer Tablet



Multi-layer tablet dosage forms are designed for variety of reasons:

1. To control the delivery rate of either single or two different active pharmaceutical ingredient(s).
2. To separate 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 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 modified release.
4. To administer fixed dose combinations of different APIs, prolong the drug product life cycle, fabricate novel drug delivery systems

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such as chewing device, buccal/ mucoadhesive delivery systems, and floating tablets for gastro-retentive drug delivery.

The advantages of the bi-layer tablet dosage form are:

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. Cost is lower compared to all other oral dosage form.
3. Lighter and compact.
4. Easiest and cheapest to package and strip.
5. Easy to swallowing with least tendency for hang-up.
6. Objectionable odour and bitter taste can be masked by coating technique.
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.

Disadvantages of Bi-Layer Tablet Dosage Form are:

1. Difficult to swallow in case of children and unconscious patients.
2. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
3. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
4. Bitter tasting drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.

General properties of Bi-Layer Tablet Dosage Forms:

1. A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration, and contamination.
2. Should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
3. Should have the chemical and physical stability to maintain its physical attributes over time. The bi-layer tablet must be able to release the medicinal agents in a predictable and reproducible manner.
4. Must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

Bi-layer tablets: quality and GMP-requirements

To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the selected 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.
- Accurate and individual weight control of the two layers.

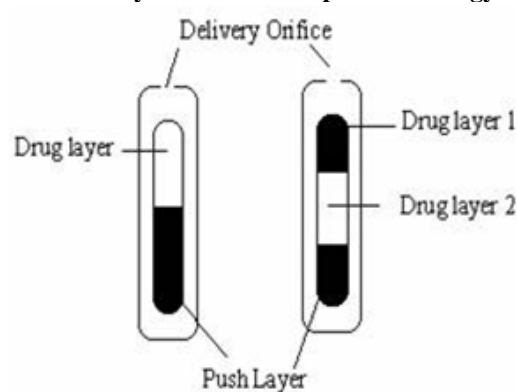
These requirements seem obvious but are not as easily accomplished as this article aims to demonstrate.

VARIOUS TECHNIQUES FOR BILAYER TABLET

OROS® push pull technology

This system consist of mainly two or three layers among which one or more layers are essential of the drug and other layers 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.

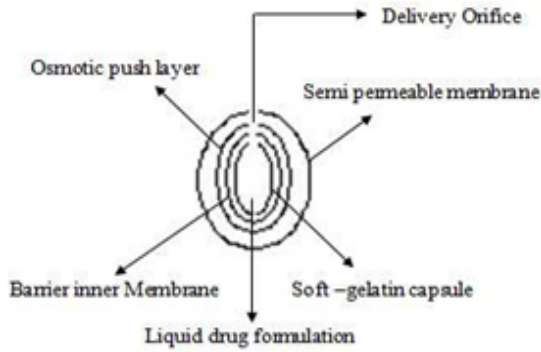
Bilayer and trilayer OROS Push pull technology



L-OROS™ 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 then a semi permeable membrane, drilled with an exit orifice.

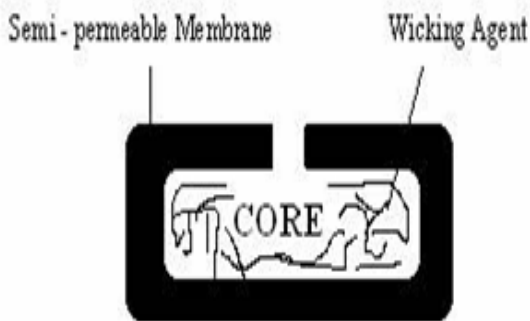
L – OROS™ technology



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.

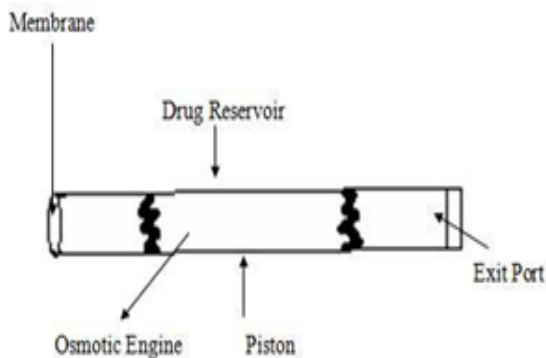
EN SO TROL Technology



DUROS technology

The system consists 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 reglious minute quantity of concentrated form in continues and consistent from over months or year.

DUROS technology



Benefits offered by the DUREDAS™ technology includes:

- 1) Bilayer.tabletting.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

The DUREDAS™ system can easily be manipulated to allow 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 the 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.

A number of combination products utilizing this technology approach have been evaluated. The DUREDAS™ technology was initially employed in the development of a number of 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.

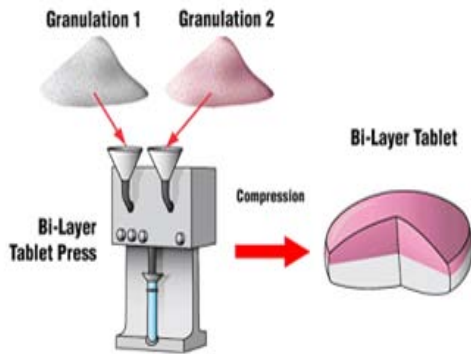
Manufacturing Process:

Manufacturing processes such as wet granulation/roller compaction and addition of binders increases the level of complexity in understanding the critical factors governing compression and tablet breaking force. Thus, the tablet breaking force and the tablet’s propensity for delamination/capping either during manufacturing or during storage need to be carefully observed. Apart from the critical material attributes of individual components and final blend, the tablet press has large influence on the manufacture of multilayer tablets.

Bilayer tablets are composed of two layers of granulation compressed together. They have appearance of a sandwich because the edges of each layer are exposed. They have the appearance of a sandwich because the edges of each layer are exposed. Bi-layer tablets are prepared with one

layer of drug for immediate release with second layer design to release drug, later, either as second dose or in an extended release manner.

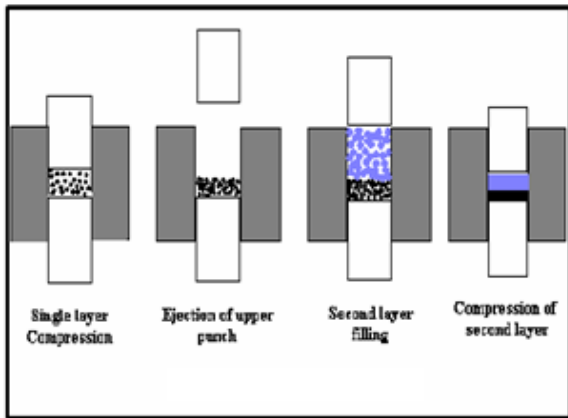
Bi-layer tablet press



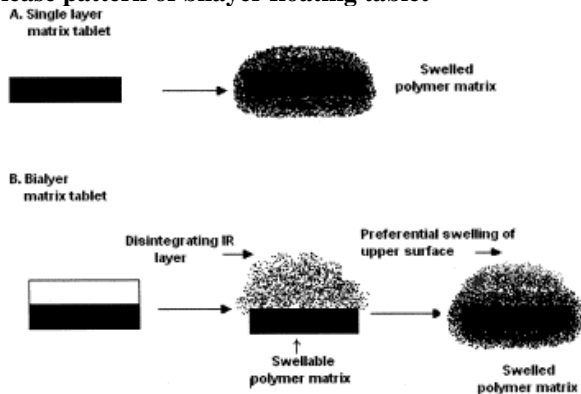
Compression cycle for bilayer tablet:

Bi-layer tablets are tablet, made by compressing two different granulations fed into a die succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet press can be set up for two or three layers. More are possible but the design becomes very special. Figure 6 represents compression cycle of bi-layer tablet.

Compression cycle of bilayer floating tablet



Release pattern of bilayer floating tablet



Bilayer tablets are prepared by compressing two different blend fed into a die succession, one on the top of another, in layers. Each layer comes from separate fed frame with individual weight control. Rotary tablet press can be set up for two layers.

A.) RoTab Bilayer

1) Software

This software is modular designed and can be upgraded with additional functions at any time. An advanced industrial PC-system with 15" touch-screen guarantees precise results and fast graphical evaluations. The wide range of instrumentations allows a nearly perfect simulation of production machines in laboratory scale.

2) Basic technique

Software package for prevailing use of RoTab Bilayer in production mode. Operation with 15" touch-screen display, by automatically dosing regulation by compression force and adjustment die table and Optifiller speed. Optional independent hardness regulation available.

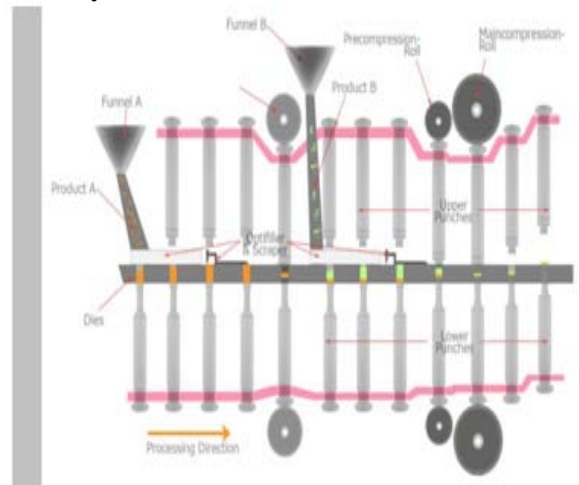
3) R&D modified technique

Basic package for galenical R&D on the RoTab Bilayer contains evaluation and graphical visualization of instrumented measuring points, as compression 1st layer pre main compression and ejection force on a 15" touch screen display. Punch tightness control can be selected as an additional alarm function. Upgrade to R&D Plus is possible at any time.

4) R & D Plus

Contains all functions of Basic possibility to evaluate and visualize the following special instrumentations on the 15" touch-screen display, punch tightness control, tablet scraper force and display of force displacement. With R&D Plus the RoTab Bilayer sets new standards in tableting technology [18].

RoTab Bilayer



B) BI-LAYER TABLET PRESS 6

The XM 12 Bi-Layer Tablet Press features a retractable second layer feeder that permits automated first layer sampling at production speeds. The first layer sampling capability also offers a hardening feature, in which the main

compression station will automatically compress the first layer tablet for in-process measurement. The two feeders are zero clearance and are configured with an integrated dust extraction manifold which cleans the die table and completely eliminates any potential for cross contamination. WipCon® solution available for potent for Small-Scale Bi-layer applications. The KORSCH XM 12 Bi-Layer Tablet Press is a small-scale press which is ideal for product development scale-up, clinical trials and midrange production. The bi-layer execution, single-layer conversion kit and exchangeable turret offer unprecedented flexibility. The XM 12 Bi-Layer Tablet Press offers a new standard in GMP with extreme accessibility to the compression zone and combinations of quick disconnects and smooth surfaces that permit fast cleaning and changeover. The machine features a 5 KN tamping station, 40 KN precompression station, 80 KN main compression station, and a unique structural design that eliminates vibration to the head piece and base frame. The result is an extreme reduction in the operating noise level.

1) Small-Scale bi-Layer

- a) 5 KN First Layer Tamping Force.
- b) 40 KN Precompression Force.
- c) 80 KN Main Compression Force.
- d) Single-Layer Conversion Capability.

2) Bi-layer application

The XM 12 features an exchangeable turret capability to permit a single machine to run all press tool sizes to provide maximum flexibility and versatility. An internal lift arm eliminates the cost and space requirement of a large external turret removal device.

- a) Single layer conversion kit adds yet another dimension of flexibility.
- b) Single Layer Conversion.
- c) 30 Minute Conversion Time.
- d) High Speed Single-Layer Capability (120 RPM)

3) Advantages

- a) Flexible Concept.
- b) Bi-Layer execution with optional single-layer conversion kit.
- c) Exchangeable turret.
- d) Turret sizes for product development, scale-up, and mid-range production.
- e) Full production capability in a scale-up machine.
- f) Self-contained, fully portable design.
- g) Fast and Easy Changeover.
- h) Internal turret lift device for extreme simplicity in turret removal and installation.

i) Clean compression zone with quick-disconnect design.

LIMITATIONS OF THE SINGLE SIDED PRESS BI-LAYER TABLETS

Various types of bi-layer 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 is having gravity- or forced-fed with a different powder, thus producing the two individual layers of the tablet. When the die passes under the feeder, it is at first loaded with the first-layer powder followed by the second-layer powder. Then the entire tablet is compressed in one or two steps (two = pre- and main compression). The two layers in the die 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. It undergoes certain limitation as follow.

- 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 de-aeration, 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 to eliminate these limitations, a double-sided tablet press is preferred over a single-sided press. 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 4 compression stages before being ejected from the press.

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, colour, presence or absence of an odour, 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.
3. **Tablet thickness:** Tablet thickness is an important characteristic in reproducing

appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

4. Weight variation: Standard procedures are followed as described in the official books.

5. Friability: Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator. A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked up. Normally, when capping occurs, friability values are not calculated. A thick tablet may have less tendency to cap whereas thin tablets of large diameter often show extensive capping, thus indicating that tablets with greater thickness have reduced internal stress the loss in the weight of tablet is the measure of friability and is expressed in percentage as:

$$\% \text{ Friability} = 1 - (\text{loss in weight} / \text{Initial weight}) \times 100$$

6. Hardness (Crushing strength): The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The small and portable hardness tester was manufactured and introduced by Monsanto in the Mid 1930s. It is now designated as either the Monsanto or Stokes hardness tester. The instrument measures the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet. The Strong-Cobb Pfizer and Schleuniger apparatus which were later introduced measures the diametrically applied force required to break the tablet. Hardness, which is now more appropriately called 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. The force required to break the tablet is measured in kilograms and a crushing strength of 4 Kg is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10 kg; however, hypodermic and chewable tablets are usually much softer (3 kg) and some sustained release tablets are much harder (10 -20 kg). Tablet hardness have been associated with other tablet properties such as density and porosity. Hardness generally increases with normal storage of tablets and depends on the shape, chemical properties, binding agent and pressure applied during compression.

7. Stability Study (Temperature dependent):

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. 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.

Recommended Long Term and Accelerated Storage Condition

Study	Storage Condition	Time Period
Long Term	25 °C±2 °C/60%RH±5% OR 30 °C±2 °C/65%RH±5%RH	12 months
Intermediat	30 °C±2 °C/65%RH±5%RH	6 months
Accelerated	40 °C±2 °C/75%RH±5%RH	6 months

CONCLUSION

Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. There are various applications of the bilayer tablet, it consist of monolithic partially coated or multilayered Matrices. 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. The preparation of tablets in the form of multi layers is used to provide systems for the administration of drugs, which are incompatible and to provide

controlled release tablet preparations by providing surrounding or multiple swelling layers. Bilayer 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 such as the Courtoy-R292F. Whenever high quality bilayer tablets need to be produced at high speed, the use of an 'air compensator' in combination with displacement control appears to be the best solution.

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