



A NOVEL APPROACH OF BILAYER TABLET TECHNOLOGY: A REVIEW

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ABSTRACT

Over the past 30 years as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. Bilayer tablet is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. . So use of bilayer tablet is a very different aspect for anti-inflammatory and analgesic. 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. This article explains about different techniques of bilayer tablet and why the development and production of quality bi-layer tablets needs to be carried out on purpose-built tablet presses to overcome common bi-layer problems, such as layer-separation, insufficient hardness, Inaccurate individual layer weight control, cross-contamination between the layers, reduced yield etc.

Keywords- Bi-layer tablet, push pull technology, various tablet press, OROS push pull technology, DUROS technology, GMP Requirements for bilayer tablets.

INTRODUCTION^{1,2}

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 pre-determined release profiles by combining layers with various release patterns, or by combining slow-release with immediate-release layers. 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.

NEED OF BILAYER TABLETS^{2,3,4}

1. For the administration of fixed dose combinations of different APIs, prolong the drug product life cycle, buccal/mucoadhesive delivery systems, fabricate novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery.
2. Controlling the delivery rate of either single or two different active pharmaceutical ingredient(s)
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 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).

ADVANTAGES OF THE BI-LAYER TABLET DOSAGE FORM

1. Bi-Layer execution with optional single-layer conversion kit.
2. Cost is lower compared to all other oral dosage form.

3. Greatest chemical and microbial stability over all oral dosage form.
4. Objectionable odor and bitter taste can be masked by coating technique.
5. Flexible Concept.
6. 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.
7. Easy to swallowing with least tendency for hang-up.
8. Suitable for large scale production.

DISADVANTAGES OF BI-LAYER TABLET DOSAGE FORM ARE

1. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
2. Bitter tasting drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating.
3. Difficult to swallow in case of children and unconscious patients.
4. 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.

VARIOUS TECHNIQUES FOR BILAYER TABLET

Duredas^{5,6}

Duredas or Dual Release Drug Absorption System (Elan Corporation) utilizes bilayer-tableting technology, which has been specifically developed to provide two different release rates or dual release of a drug from a single dosage form. The tablets are prepared by two separate direct-compression steps that combine and immediate-release granulate (for rapid onset of action) and a controlled-release hydrophilic matrix complex within one tablet. The controlled-release matrix remains intact and slowly absorbs fluid from the GI tract, which causes the matrix to expand and transforms the hydrophilic polymers into a porous, viscous gel that serves as

a barrier between the drug and the surrounding fluid. As the gel continues to expand, fluid penetrates further into the dosage form, dissolving the drug and allowing the resulting solution to diffuse out in a controlled manner.

Benefits offered by the DUREDAS technology include:

- Bilayer tableting technology.
- Tailored release rate of two drug components.
- Capability of two different CR formulations combined.
- Capability for immediate release and modified release components in one tablet.

Unit dose, tablet presentation

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 the drug release of each is controlled to maximize therapeutic effect of the combination. Again both immediate- release and controlled-release combinations of the two drugs are feasible.

Geomatrix Technologies⁶

Geomatrix system is a multilayer tablet with a matrix core containing the active ingredient and one or more modulating layers (barriers) applied to the core during the tableting process. The function of these barriers is to delay the interaction of the core with the dissolution medium. Eight Geomatrix technologies are designed to meet a wide range of therapeutic objectives: Zero-order release provides a constant rate of drug release over a defined period of time; binary release is used to provide the controlled release of two different drugs in a single tablet; quick–slow release provides a quick burst of drug release followed by a constant rate of release over a defined period of time; slow–quick release provides an initial constant rate of release followed by a quick burst of drug release at a predetermined time; positioned release delivers the drug to a predetermined position in the digestive system before it begins to release the active drug compounds; accelerated release provides a constantly accelerating rate of drug release; delayed release provides a predetermined time lag before it begins releasing drug molecules; multiple pulse provides an initial quick burst of drug release followed by a predetermined period of no release. Some of the drugs that are marketed based on this technology are diltiazem hydrochloride, nifedipine, and diclofenac sodium.

OROS® push pull technology⁷

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 (Fig.1). 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.

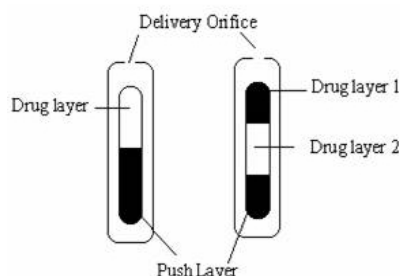


Fig. 1 OROS push pull technology

L-OROS tm technology⁷

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, than osmotic push layer and than a semi permeable membrane, drilled with an exit orifice

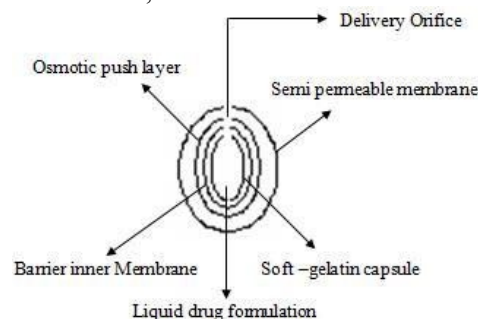


Fig.2 L-OROS tm technology

EN SO TROL technology^{7,8}

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.

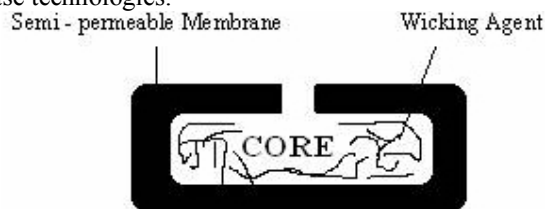


Fig. 3 EN SO TROL technology

Duros^{6,7}

DUROS (Alza Corporation) is based on implant technology, which provides an alternative for the delivery of a wide range of therapeutic compounds, including peptides, proteins, and other bioactive macromolecules. These implants are miniature titanium cylinders designed to provide continuous osmotically driven delivery of drugs within the body for up to one year.

Following implantation, DUROS implants enable continuous, precise delivery of the therapeutic compound at rates as low as 1% of a drop of water per day. The cylinder is manufactured from titanium because of the material's tolerability to human tissue and its long use in medical devices such as implantable defibrillators and joint replacements. The cylinder protects therapeutic agents from degradation in the body and enables a drug to remain stable for extended periods of time. Recently, Viadur (leuprolide acetate implant), which is based upon this technology, has been approved for once-yearly palliative treatment of advanced prostate cancer.

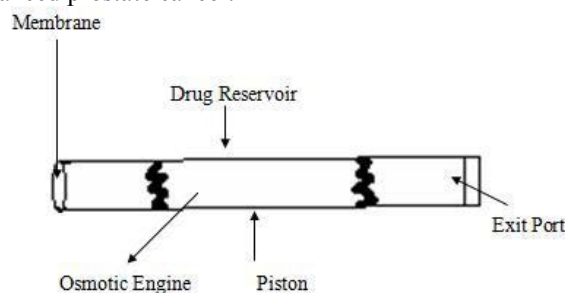


Fig. 4 Duros technology

Geminex⁹

Geminex is a dual drug delivery technology that can deliver one or more drugs at different times. The Geminex technology controls the release rate of the two drugs to maximize their individual therapeutic effect and minimize side effects. The benefit of Geminex to the pharmaceutical industry, and ultimately to patients, is that two different actives or the same active can be delivered at differing rates in a single tablet. Penwest is actively applying its Geminex technology to the following therapeutic areas: cardiovascular disorders, diabetes, cancer, and disorders of the central nervous system.

PRODAS or Programmable Oral Drug Absorption System⁶

Prodas or Programmable Oral Drug Absorption System (Elan Corporation) is a multiparticulate drug delivery technology that is based on the encapsulation of controlled-release minitables in the size range of 1.5 to 4 mm in diameter. This technology represents a combination of multiparticulate and hydrophilic matrix tablet technologies and thus provides the benefits of both these drug delivery systems in one dosage form. Minitables with different release rates can be combined and incorporated into a single dosage form to provide the desired release rates. These combinations may include immediate-release, delayed-release, and/or controlled-release minitables. In addition to controlled absorption over a specified period, PRODAS technology also enables targeted delivery of drug to specified sites of absorption throughout the GI tract. Combination products also are possible by using minitables formulated with different active ingredients.

Erodible Molded Multilayer Tablet¹⁰

Egalet erodible molded tablets is an erosion-based platform. It has the advantage of delivering zero-order or delayed release with minimal impact from the gastrointestinal conditions. Egalet erodible molded multilayered tablets are prepared by injection molding. Egalet technology contains a coat and a matrix. Drug release is controlled through the gradual erosion of the matrix part. The mode and rate of release are designed and engineered by altering the matrix, the coat, and the geometry to achieve either a zero-order release or a delayed release. For a zero-order release, a drug is dispersed through the matrix. The coat is biodegradable but has poor water permeability to prevent its penetration. The matrix tends to erode when in contact with available water. The erosion of the matrix is caused by GI fluids and promoted by gut movements in the GI tract. The drug release is mediated almost wholly by erosion because the dosage form is designed to slow down the water diffusion into the matrix. It is definitely more desirable for drugs with chemical and physical stability issues after contacting with water. Egalet delivery technology is developed based on standard plastic injection molding to ensure accuracy, reproducibility, and low production cost.

VARIOUS APPROACHES USED IN THE BILAYER TABLET¹¹

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 other layer is designed as a floating layer which floats in the stomach (GI-fluid).

Disadvantages: It may not have the controlled loss of density alternatively required for it to eventually exit from the stomach. Floating tablets are not applicable to higher dose levels of highly water soluble drugs where large amounts of polymer are needed to retard drug release, as in case of water soluble drugs. The performance of floating formulation may also be posture dependant. A patient sitting upright may ensure prolonged gastric residence of a buoyant dosage form, whereas a supine patient might allow ready presentation of the floating dosage form to the pylorus and thus allow rapid exit of the dosage form from the stomach. Hence, floating dosage forms might be expected to only have limited applications.

b) Polymeric Bioadhesive 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 bioadhesive property.

Disadvantages: The success seen in animal models with such system has not been translated to human subjects due to differences in mucous amounts, consistency between animals and humans.

The system adheres to mucous not mucosa. The mucous layer in humans would appear to slough off readily, carrying any dosage form with it. Therefore, bioadhesive dosage form would not appear to offer a solution for extended delivery of drug over a period of more than a few hours.

c) Swelling System

These are designed to be sufficiently small on administration so as not to make ingestion of the dosage form difficult (e.g., less than approximately 23 mm long and less than 11 mm wide for an oval or capsule-shaped tablet whereas 10- 12mm in diameter for round tablets). 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 stomach. The simple bilayer tablet may contain an immediate release layer with the other layer as extended release or conventional release.

BILAYER TABLETS: QUALITY AND GMP REQUIREMENTS¹²

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

SINGLE SIDED PRESS¹³

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 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.

Limitations of single-sided press^{12,18,19}

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- 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

DOUBLE SIDED TABLET PRESSES:¹³

Double-sided tablet presses have been specifically designed and developed for the production of quality bi-layer tablets and provide:

- 'displacement' weight monitoring/control for accurate and independent weight control of the individual layers
- low compression force exerted on the first layer to avoid capping and separation of the two individual layers
- increased dwell time at pre-compression of both first and second layer to provide sufficient hardness at maximum turret speed
- maximum prevention of cross-contamination between the two layers
- a clear visual separation between the two layers
- maximised yield

PREPARATION OF BILAYER TABLET^{14,15,16,17}

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 form⁸. 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.

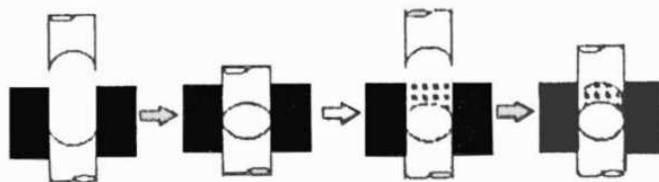


Fig 5 Preparation of bilayer tablet

Compaction

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 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 characteristic 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 major factor influencing tablet delamination.

DIFFERENT TYPES OF BILAYER TABLET PRESS

Piccola Bi-Layer

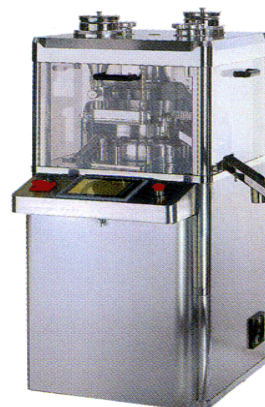


Fig.6 Piccola bilayer tablet press

This rotary press was designed to represent two-layer tablet production conditions at a small scale, according to the needs of new product development. Piccola Bi-layer press meets cGMP standards and can use type D or B tooling complying with TSM or EU standards, which allows the employment of the same punches used in production. For an appropriate adjustment in tablet production, there are totally independent systems for weight, height and hardness adjustment, both for the first and second layers. A PLC system having a touch screen and a software designed for Galenic Development and Production Control allows the integrated control of all parameters, including production rate and, separately, the rate of each of the star forced feeder. There are varied accessories and options for the software used; such as the possibility of weight control during production and the use of data obtained for calculation and statistics.

- Easy and quick assembly and dismantling of hoppers, feeders and dies for cleaning and product replacement purposes.
- Two product hoppers with paddle feeders.
- Pre-compression system.
- Easy access to the machine through eight removable doors, interconnected and equipped with safety switches.
- Two vacuum inlets for separate product recovery.
- Rate variation by an inverter.
- Pressure compensation hydro pneumatic system.
- Wipper seals on punches.
- Automatic lubrication.

Model	B - 10	D - 8
Tooling TSM or EU	B	D
Maximum tablet diameters	16 mm	25 mm
Number stations	11	11
Output	10000/33000	10000/33000
Compression force max.	60 KN	80 KN
Upper punch penetration	0-8 mm	0-8 mm
Depth of fill first layer (up to)	17 mm	17 mm
Depth of fill second layer (up to)	8 mm	8 mm
Pitch diameter	280 mm	280 mm
Power consumption	3 KW	3 KW
Net weight	880 Kg.	880 Kg.
Gross weight	1020 Kg.	1020 Kg.

The KORSCH XM 12 Bi-Layer Tablet Press

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 XM 12 Bi-Layer Tablet Press offers a new standard in GMP with extreme accessibility to the compression zone and a combination of quick disconnects and smooth surfaces that permit fast cleaning and changeover.

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.



Fig.7 Korsch XM 12

Advantages

- Flexible Concept
 - Bi-Layer execution with optional single-layer conversion kit
 - Exchangeable turret
 - Turret sizes for product development, scale-up, and mid-range production
 - Full production capability in a scale-up machine
 - Self-contained, fully portable design
 - Fast and Easy Changeover
 - Internal turret lift device for extreme simplicity in turret removal and installation
 - Clean compression zone with quick-disconnect design
- Design Advantages
 - Small-scale bi-layer capability
 - Robust caster base permits full portability
 - Large touch screen flush mounted
 - Unique structural design eliminates vibration and noise
 - Zero clearance feeder for maximum yield and optimal layer separation
 - Retractable second layer feeder for automatic first layer sampling
 - Full instrumentation
 - Tamping force
 - Pre/Main compression force
 - Ejection force
 - Touch Screen Control
 - Integrated control cabinet
 - Press force control and single tablet rejection capability
 - Comprehensive data collection and analysis capability
 - Real time display and batch data documentation
 - Identical control and software concept

The Machine Concept

Pharma Research

- Integrated data acquisition and analysis
- Full instrumentation for tamping force, precompression force, main compression force and ejection force

Pharma control

- Touch screen HMI for user friendly operation
- Integrated system for automatic layer weight control and single tablet rejection
- Clearly displays key parameters and adjustments
- Fully compliant with 21 CFR Part 11
- Retracting second layer feeder for automated first layer sampling with hardening option

Carrier Plate

- Unique floating structure design for dramatic noise reduction at all operating speeds

New feeder Design

- Low-volume feeder paddle option for product development with minimum material quantities
- Zero clearance feeder design for maximum yields and layer separation

Compression Zone

- Open access to compression zone
- Quick disconnect design requires no tools
- Smooth surfaces for easy cleaning

Exchangeable Turret

- Turret sizes for product development, scale-up, and mid-range production
- Bi-layer execution with optional single-layer conversion kit

- c. Internal turret lift device for extreme simplicity in turret removal and installation
- d. Mixed turret offering D,B and BB press tools in a single turret

Machine Base

- a. Self contained design
- b. Robust caster base permits full portability
- c. Full accessibility to major components simplifies service

PharmaResearch Comprehensive Data Acquisition and Analysis

PharmaResearch is a Windows-based system that offers data acquisition and analysis for press force and punch displacement data. The system displays press force waveforms in real time and permits on-demand data collection. The system can collect data locally, or write the data to a networked SQL server for centralized data storage and analysis. The system can work with the following tablet press instrumentation:

- Precompression Force
- Main Compression Force
- Ejection Force
- Scrape-Off Force
- Die-Wall Force
- Punch Displacement

The data analysis is automatic and provides a statistical assessment of:

- Peak Force
- Area Under The Force-Time Curve
- Contact Time
- Rate of Force Application
- Rate of Force Decay

CONCLUSION

Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. There is various application of the bi-layer 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.

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