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BILAYER TABLET – AN EMERGING TREND

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ABSTRACT

Bilayer tablet is new era for successful development of controlled release formulation along with various features to provide successful drug delivery system. Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles. The manufacture of bi-layer tablets, produced by sequential compaction of loose powder layers has become of increased interest within the pharmaceutical industry due to the tailored release profiles of active ingredients that may be obtained. 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 loading dose and second layer is maintenance dose. In case of bilayered tablets drug release can be rendered almost unidirectional if drug can be incorporated in the upper non adhesive layer its delivery occurs into the whole oral cavity. The immediate release layer of bilayer tablet has worked as the loading dose and the sustained release layer has maintained therapeutic plasma drug concentration for prolonged time. This article explains why 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. Using a modified tablet press may therefore not be the best approach in producing a quality bi-layer tablet under GMP-conditions, especially when high production output is required.

Key words: Bilayer tablet, OROS® push pull Technology, EN SO TROL Technology, DUROS Technology.

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INTRODUCTION

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. Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation and to enable the development of different drug release profiles (immediate release with extended release). Despite their advantages, due to the use of different materials and complex geometric boundaries between the adjacent layers, the mechanical structures of this drug delivery system have become quite intricate, requiring complicated tablet architectures as well as patient-friendly administration which pose serious challenges to the pharmaceutical scientists/engineers. This oral presentation details the major challenges associated with bilayer compression and rational strategy to deliver the desired bilayer tablet performance.

One of the major challenges is lack of sufficient bonding and adhesion at the interface between the adjacent compacted layers which is often the result of an interfacial crack driven by residual stresses in the tablet propagating a finite distance within the tablet and leads to delamination (layer-separation) which may not always be apparent immediately after compaction (e.g., during storage, packaging, shipping). In addition, if the compacted layers are too soft or too hard, they will not bond securely with each other which can lead to compromised mechanical integrity. Other challenges during development include establishing the order of layer sequence, layer weight ratio, elastic mismatch of the adjacent layers, first layer tamping force, and cross contamination between layers. These factors, if not well controlled/optimized, in one way or another will impact the bilayer compression per se (inefficient or uncontrolled process) and the quality attributes of the bilayer tablets (sufficient mechanical strength to maintain its integrity and individual layer weight control). Therefore, it is critical to obtain an insight into the root causes to enable design of a robust product and process^[1,2].

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Objectives behind designing Bilayer Tablet:

1. To control the delivery rate of either single^[3] or two different active pharmaceutical ingredient(s)^[4,5].
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^[6,7].
4. To administer fixed dose combinations of different APIs^[8], prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device^[9], buccal/ mucoadhesive delivery systems^[10], and floating tablets for gastro-retentive drug delivery^[11].

Advantages of the bilayer tablet are:

- It is the dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
- Cost is lower compared to all other oral dosage form.
- Lighter and compact.
- Easiest and cheapest to pack and strip.
- Easy to swallow with least tendency for hangup.
- Objectionable odour and bitter taste can be masked by coating technique.
- Suitable for large scale production.
- Greatest chemical and microbial stability over all oral dosage form.
- Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.

Disadvantages of bilayer tablet are:

- Difficult to swallow in case of children and unconscious patients.

- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
- 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.
- Bitter tasting drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.

Ideal characteristics of bilayer tablet:

- A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration and contamination.
- It should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
- It 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.
- It must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

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.

The level of pre-compression force, punch velocity, consolidation time (time when punches are changing their vertical position with reference to the rolls as the distance between the punch tips are decreased), dwell time (time when punches are not changing their vertical position in reference to the rolls), relaxation time (time when both punches are changing their vertical position in reference to the rolls as the distance between the punch tips increases before losing contact with the rolls), and the applied force can have significant effect on the critical quality attributes of the tablet^[12]. For instance, the extent of compact densification and resistance to compressibility within the die cavity was impacted by compaction pressure and the punch velocity. It was demonstrated that increase in the punch velocity between of 50 and 500mm/s decreased the porosity reduction on individual layers^[13].

VARIOUS TECHNIQUES FOR BILAYER TABLET**A) 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^[14]. A semi permeable membrane surrounds the tablet core (Figure 1).

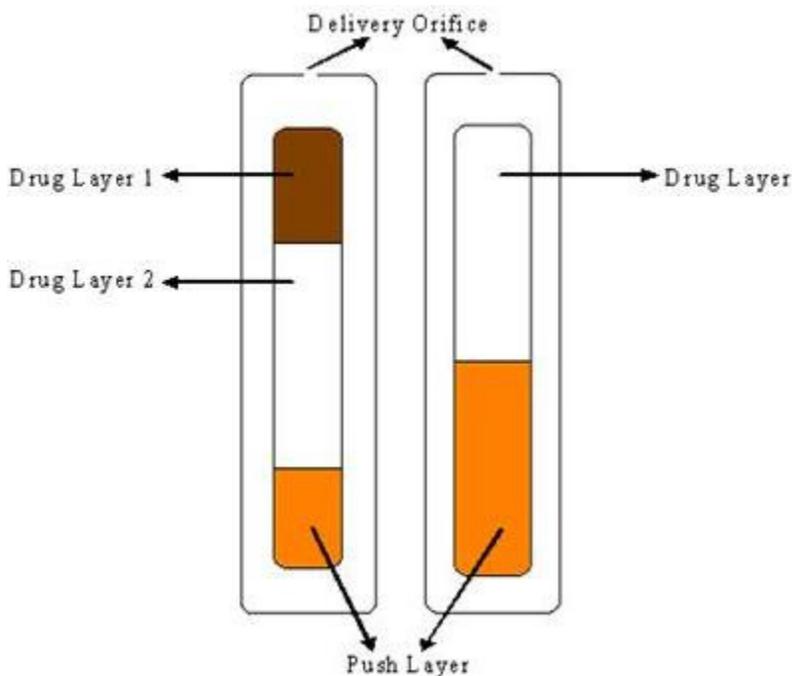


Fig. 1: Bilayer and trilayer OROS push pull technology

B) 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, than osmotic push layer and than a semi permeable membrane, drilled with an exit orifice^[14](Figure 2).

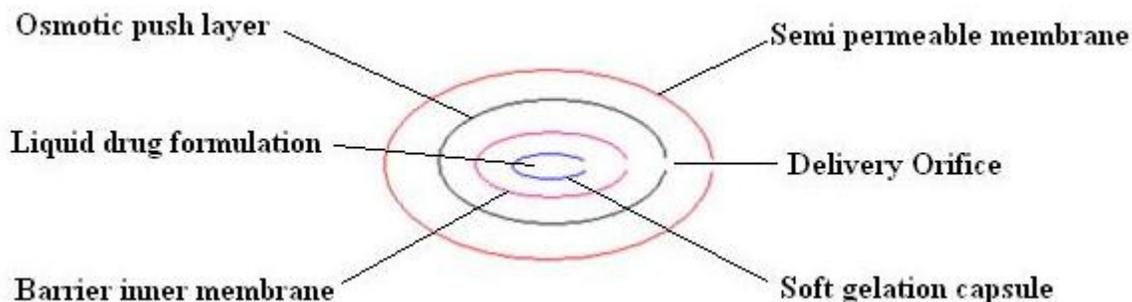


Fig. 2: L – OROS™ Technology

C) 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^[14](Figure 3).

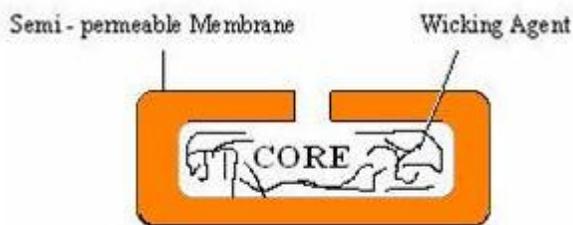


Fig. 3: EN SO TROL Technology

D) DUREDAS™ Technology

This system is also known as Elan drug technologies' Dual release drug delivery system. DUREDAS™ Technology is a bilayer tablet which can provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form. The tableting process can provide an immediate release granulate and a modified-release hydrophilic matrix complex as separate layers within the one tablet. The modified-release properties of the dosage form are

provided by a combination of hydrophilic polymers^[14].

E) DUROS technology

The system consists from an outer cylindrical titanium alloy reservoir. This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the miniature drug dispensing system that opposes like a miniature syringe and release minute quantity of concentrated form in continues and consistent from over months or year^[14](Figure 4).

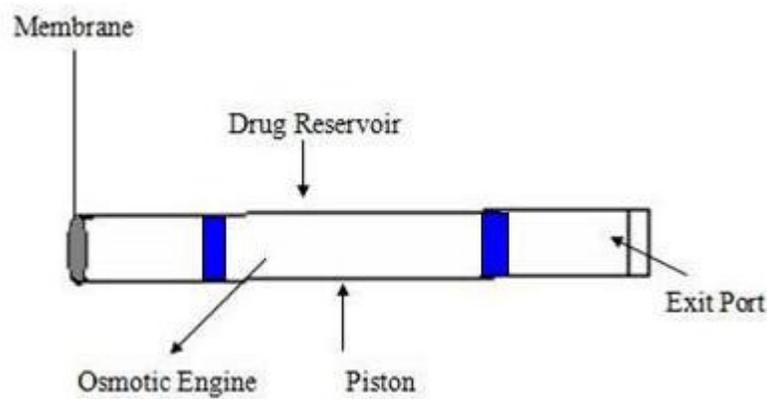


Fig. 4: DUROS Technology

LIMITATIONS

A) Limitations of the single sided press:

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^[15,16]. 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^[17,18]. 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 four compression stages before being ejected from the press^[19,20].

B) Limitations of “compression force” -controlled tablet presses

Separation of the two individual layers is the consequence of insufficient bonding between the two layers during final compression of the 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 of the tablet. Bonding is severely restricted if the first layer is compressed at a too-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”^[21].

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 that layer. There exist a typical exponential relationship between the measured peak compression force [F] and layer or tablet weight [W].

This measured peak compression force [F] (under constant thickness) is the signal used by the control system to reject out-of-tolerance tablets and correct the die fill depth when required. The above graph indicates that the sensitivity $\delta F / \delta W$ decreases with decreasing compression force (i.e. when the distance between the compression rollers is made greater). This decreasing sensitivity is inherent to an exponential relationship and therefore inherent to the compression force-controlled system. The rate at which the sensitivity decreases depends on the formulation or powder characteristics. This is the reason why a compression force control system is always based on measurement of compression force at main-compression and not at precompression since a higher compression force is required to obtain sufficient sensitivity, thus allowing a more accurate control. A weight control system based on compression force monitoring is not the best solution for first layer weight control in a bi-layer

tableting process. A compression force-controlled system requires a minimal compression force of several hundreds of daN. However, many bi-layer formulations require a first layer compression force of less than 100 daN in order to retain the ability to bond with the second layer. Above 100 daN, this ability may be lost, bonding between both layers may not be sufficient, resulting in low hardness of the bi-layer tablet and separation of the two layers. This basic problem, inherent to the principle of compression force monitoring is overcome by using a different weight monitoring system based upon ‘displacement’.

“Displacement measurement” as the alternative to “compression force measurement” has the advantage that accuracy increases with reduced compression force. At higher production speed, the risk of separation and capping increases but can be reduced by sufficient dwell time at all four compression stages. Weight monitoring based upon ‘displacement’ also provides increased dwell time in addition to good bonding between the two layers, with improved and accurate weight monitoring/control of the first layer. A double sided tablet press with “displacement measurement” is thus the preferred press to produce bi-layer tablets.

The Courtoy R292F: “Bilayer” tablet press with ‘displacement monitoring’

This double-sided tablet press has been specifically designed and developed for the production of quality bi-layer tablets and provides:

- ‘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 precompression 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

VARIOUS ASPECTS OF BILAYER TABLET

Floating Drug Delivery Systems (FDDS)

From the formulation and technological point of view, the floating drug delivery systems are considerably easy and logical approach in the development of Gastro retentive dosage forms (GRDFs)^[22].

Approaches to design Floating Drug Delivery System

The following approaches have been used for the design of floating dosage forms of single- and multiple-unit systems.

Intra gastric bilayered floating tablets

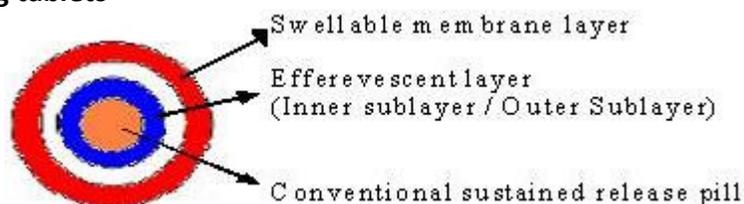


Fig. 5: Multiple units of oral FDDS

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:^[23-25]

- 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.
- Providing high yield.
- Providing accurate and individual weight control of the two layers.

EVALUATION OF SUSTAIN RELEASE BILAYER TABLET

1) Tablet Thickness and Size

Thickness and diameter of tablets are important for uniformity of tablet size. Thickness and diameter is measured using venire calliper^[26,27].

2) Tablet Hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and

These are also compressed tablet as shown in figure and contain two layers i.e.

- Immediate release layer
- Sustained release layer.

Multiple unit type floating pill

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. (Figure 5)

handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester^[26,27]. The hardness was measured in kg/cm².

3) Friability

Friability is the measure of tablet strength. Friabilator is used for testing the friability using the procedure: Twenty tablets are weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed and the percentage loss in tablet weight is determined^[26,27].

$$\% \text{ loss} = \frac{\text{Initial weight of tablets} - \text{Final weight of tablets}}{\text{Initial weight of tablets}} \times 100$$

4) Uniformity of weight

Twenty tablets are selected at random and the average weight is calculated. Weight Variation is calculated and is compared with I. P. standards.

CHARACTERIZATION OF BILAYER TABLET

1) Particle size distribution

The particle size distribution is measured using sieve shaker.

2) Photo-microscope Study

3) Photo-microscope images are taken (450X magnifications) by photomicroscope

4) Angle of Repose

The diameter of the powder cone is measured and the angle of repose is calculated using the following equation.

$$\tan \phi = h/r$$

Where, h and r are the height and radius of the powder cone.

5) Moisture Sorption Capacity

All disintegrates have capacity to absorb moisture from atmosphere which affects moisture sensitive drugs. Moisture sorption capacity is performed by taking 1 g of disintegrate uniformly distributed in

petri-dish and kept in stability chamber at $37 \pm 1^\circ\text{C}$ and 100% relative humidity for 2 days and investigated for the amount of moisture uptake by difference between weights.

6) Compressibility

The compressibility index of the disintegrate is determined by Carr's compressibility index.

$$\% \text{compressibility} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

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 (Table 1).

Table 1: Recommended long-term and accelerated storage conditions

Study	Storage condition ($^\circ\text{C}/\% \text{RH}$)	Minimum time period covered by data at submission (Months)
Long term*	$25 \pm 2/60 \pm 5$ or $30 \pm 2/65 \pm 5$	12
Intermediate**	$30 \pm 2/65 \pm 5$	6
Accelerated	$40 \pm 2/75 \pm 5$	6

*It is up to the applicant to decide whether long term stability studies are performed at $25 \pm 2^\circ\text{C}/60\% \text{RH} \pm 5\% \text{RH}$ or $30^\circ\text{C} \pm 2^\circ\text{C}/65\% \text{RH} \pm 5\% \text{RH}$.

**If $30^\circ\text{C} \pm 2^\circ\text{C}/65\% \text{RH} \pm 5\% \text{RH}$ is the long-term condition, there is no intermediate condition.

The tablets are 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 plotted according Arrhenius equation to determine the shelf life at 25°C .

CONCLUSION

Bi-layer 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. Compression Force-controlled presses are clearly limited when a quality bi-layer tablet needs to be produced in conjunction with accurate

weight control of both layers. Low precompression forces are necessary to secure interlayer bonding. But at low forces, the compression force control system is not sufficiently sensitive and therefore lacks in accuracy. The use of higher compression forces may rapidly result in separation and hardness problems when compressing bi-layer tablets.

Such problems become even more apparent when the tableting speed is high or increased. Whenever high-quality bi-layer 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. The sensitivity of the displacement-based control system increases as pre-compression force decreases, resulting in a higher accuracy. As explained, this is particularly important with regard to bi-layer compression.

Accurate individual layer weight monitoring/control at high speed and in combination with reduced layer separation risk can be achieved with the Courtoy-R292F. In addition, the increased dwell time provided by the 'pneumatic compensator' and the special attention to reduced interlayer cross-contamination risk make the Courtoy- R292F an excellent bi-layer tablet press.

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