Review Article **Novel drug delivery system**

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AN OVERVIEW ON BILAYERED TABLET TECHNOLOGY

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ABSTRACT

Bi-layer tablet is a new era for successful development of controlled release formulation along with various features to provide successful drug delivery. Bilayer tablet is suitable for combination of separate two incompatible drug substances, also for sustained release tablet in which one layer is for immediate release as loading dose and second layer is maintenance dose. So use of bilayer tablet is a very different aspect for anti-hypertensive, anti-diabetic, anti-inflammatory and analgesic drug where combination therapy is often used. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. This article explains fundamentals of bilayer tablet system which include advantages, disadvantages, GMP requirements, various types of techniques and bilayer tablet press currently available in the market, manufacturing process, and tablet surface characterization by various imaging techniques, challenges in bilayer manufacturing, characterization as well as evaluation of the bilayer tablet system.

KEYWORDS: **Bilayer tablet, DUREDAS Technology, Tablet presses, Surface imaging techniques.**

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INTRODUCTION

Tablet are the most common form of oral solid dosage form in pharmaceutical industries and have been used for many decades to delivered active pharmaceutical ingredient (API), but there remain several challenges to consistent high quality manufacture of this solid dosage form. One well-known difficulty is to attain the desired disintegration rate combined with sufficient physical strength in the same tablet. 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. [2]. One of the major challenges is lack of sufficient bonding and adhesion at the interface between the adjacent compacted layers which is finite distance within the tablet and leads to delamination (layer-separation) which may not always be apparent immediately after compaction.(E.g. during storage, packing, 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 sequence, layer weight ratio, elastic mismatch of the adjacent layers, first layer tamping force, and cross contamination between layers[3.4]

ADVANTAGES[5]

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. Greatest chemical and microbial stability over all oral dosage form.
3. Bi-layer execution with optional single-layer conversion kit.
4. Cost is lower compared to all other oral dosage form.
5. Patient compliance is enhanced leading to improved drug regimen efficacy.
6. Patient convenience is improved because fewer daily doses are required compared to traditional delivery system.
7. Objectionable odour and bitter taste can be masked by coating technique.
8. Easy to swallowing with least tendency for hang-up.

DISADVANTAGES

1. Insufficient hardness, layer separation, reduced yield.
2. Inaccurate individual layer weight control.
3. Bitter tasting drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.
4. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
5. Difficult to swallow in case of children and unconscious patients.
6. 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.
7. It must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

QUALITY AND GMP-REQUIREMENTS[6]

To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the selected press is capable of following points.

1. Preventing capping and separation of the two individual layers that constitute the bi-layer tablet.
2. Providing sufficient tablet hardness.
3. Preventing cross-contamination between the two layers.
4. Producing a clear visual separation between the two layers.
5. High yield accurate and individual weight control of the two layers.

Various Techniques for Bilayer Tablet[7, 8]

1) 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.

2) L-OROS tm technology

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 then a semi permeable membrane, drilled with an exit orifice.

3) 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.

4) DUREDAS™ Technology

It 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 tabletting 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.

Benefits offered by the DUREDAS™ technology include:

a) Bilayer tableting technology.
b) Tailored release rate of two drug components.
c) Capability of two different CR formulations combined.
d) Capability for immediate release and modified release components in one tablet.
e) Unit dose tablet presentation.

DUROS technology

The system consists of an outer cylindrical titanium alloy reservoir.This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the miniature drug dispensing system that operates like a miniature syringe and releases minute quantity of concentrated form in continues and consistent from over months or year.

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

1. To control the delivery rate of either single[9] or two different active pharmaceutical ingredients[10, 11].
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[12, 13].
4. To administer fixed dose combinations of different APIs[14], prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device[15], buccal/ mucoadhesive delivery systems, and floating tablets for gastro-retentive drug delivery[16].

Multi-layer compression basics[17]

Presses can be designed specifically for multi-layer compression or a standard double-sided press can be converted for multi-layers:

The multilayer tablets concept has been long utilized to develop sustained release formulation. Such a tablet has a fast releasing layer and may contain bilayer or triple layers to sustain the drug release.

The pharmacokinetic advantage relies on the fact that drug release from fast releasing granules leads to a sudden rise in blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustained granules.

Various steps of bi-layer tablet formulation as per figure: 1

- Filling of first layer
- Compression of first layer
- Ejection of upper punch
- Filling of second layer
- Compression of both layer together
- Ejection of bi-layer tablet

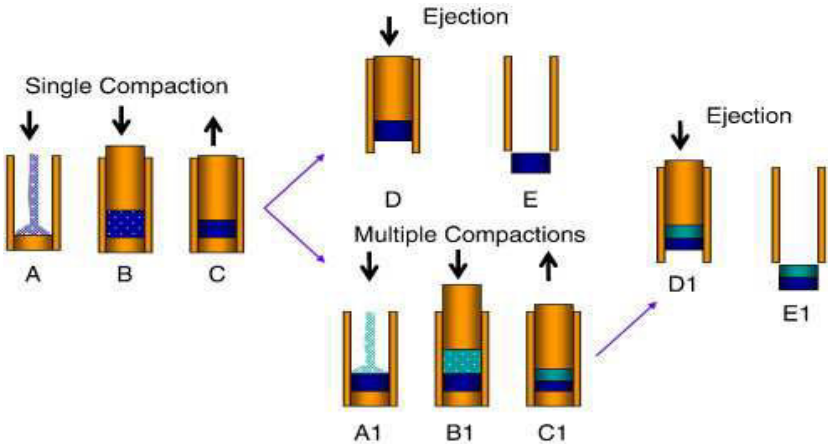


Figure 1
Compression cycle of bilayer tablet

Various types of bilayer tablet press[18, 19]
A. Single sided tablet press.
B. Double sided tablet press.
C. Bilayer tablet press with displacement monitoring.

A. Single sided tablet press
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 powers, thus producing the two individual layers of the tablets. When the die passes under the feeder, it is at first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps.

i. Limitations of single sided press
- No weight monitoring / control of the individual layers.
- No distinct visual separation between the two layers.
- Very short first layer dwell time due to the small compression roller, possibly resulting in poor 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.

ii. Dwell time
Dwell time is defined as the time during which compression force is above 90% of its peak v a l u e. Longerdwell times are a major factor in producing a quality tablet, especially when compressing a difficult formulation.

iii. Compression force
Many bilayer formulations requires a first layer compression force of less than 100 daN in order to retain the ability to bond with the second layer. If force above 100 daN separation of two layer is occurs.

B. Double sided tablet press
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 the main compression of the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance tablets and correct the die fill depth when required.

C. Bilayer tablet press with displacement monitoring
The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied pre-compression force.

Advantages
Weight monitoring / control for accurate an 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. Independence from the machine stiffness 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 Clear visual separation between the two layers and maximized yield.

The Courtoy R292F: "Bilayer" tablet press with 'Displacement monitoring' [20]

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

1. 'Displacement' weight monitoring/control for accurate and independent weight control of the individual layers exerted on each individual tablet or layer
2. Low compression force exerted on the first layer to avoid capping and separation of the two individual layers.
3. Increased dwell time at precompression of both first and second layer to provide sufficient hardness at maximum turret speed.
4. Maximum prevention of cross-contamination between the two layers.
5. A clear visual separation between the two layers.
6. Maximised yield 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] as indicated in Figure 2.

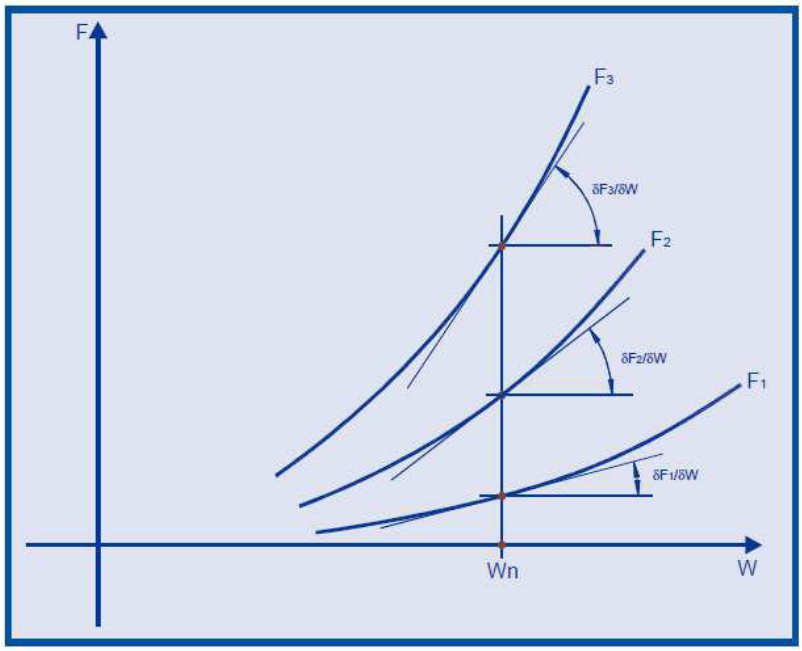


Figure 2

FORCE VERSUS WEIGHT SENSITIVITY AT DIFFERENT COMPRESSION FORCE LEVELS

Above graph show relation between force and weight sensitivity. This sensitivity decreases with decrease in compression force. This is the very reason why a compression force control system is always based on measurement of compression force at main-compression and not at pre-compression 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.

Additional important features: The Courtoy-R292F

The R292F can be used for both single-layer double output production and bi-layer single-output tableting. The press is equipped with 'air compensation' on both pre-compression stations for 'displacement'- based tablet weight control as described above. However, the R292F has several extra features specifically designed for the production of bi-layer tablets:

The R292F has a pneumatically driven ejection cam, allowing the sampling of first-layer tablets for in-line process control and automatic weight recalibration. The required time to sample is extremely short to minimise powder loss. The time delay between sampling and re-calibration is also very short to minimise the length of the control loop.

- Powder is always re-circulated around the die table using a standard feeder with recuperation of re-circulated powder, while the other feeder is a closed type feeder. This closed type feeder is provided with a suitable wear plate to maximise its life expectancy.
- The R292F is equipped with several blow and suction nozzles, located at carefully determined points around the die table. The combined action of blowing and extracting air allows for very specific powder removal, which is vital to the elimination of cross-contamination. At the same time, powder loss is reduced to a minimum.

BI-LAYER TABLET PRESS[21, 22]

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, 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 layer Tablet Press is a small-scale press which is ideal for product development scale-up, clinical trials and mid-range 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.

Properties

✓Free format graphic and statistical analysis to allow the export of many data formats.

✓Reports can be automatically generated in a variety of data formats with and without an electronic signature.

✓Charts can be dimensioned, comments added, formatted and exported before being processed in the MS Office world.

✓Finger print recording during production. Overlay Technology allows safe and quick recognition of subsequent waveforms.

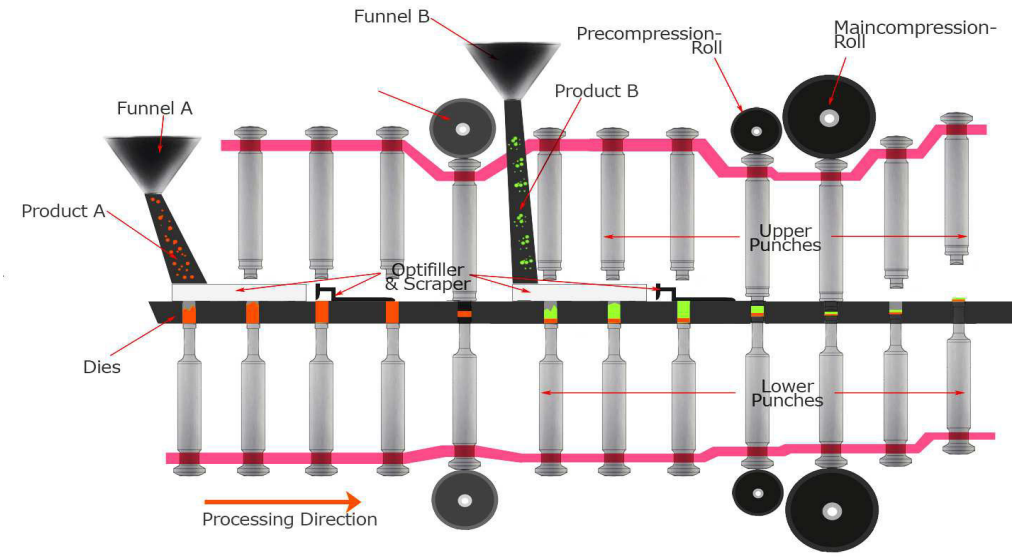
✓Correlation Analysis to establish a "Knowledge Database" that serves to easily compare the properties of known and unknown ingredients. The database enables the user to correlate measuring values from the tableting process and derived and externally recorded quantities (e.g. tablet hardness, density, etc.).

✓Compaction Analysis allows evaluations e.g. Heckel plot, energy, work of compression, contact time, compressibility.

✓"Built-in" PAT function, i.e. the database is automatically filled with process data thereby helping to define and complete PAT requirement for Knowledge Space and Design Space.

RoTab Bilayer press[23]

Figure 3
RoTab Bilayer scheme



Basic technique
Automatically dosing Regulation by compression force and adjustment to die table and Optifiller speed. Optional independent hardness regulation available.

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" touchscreen display. Punch tightness control can be selected as an additional alarm function. Upgrade to R&D Plus is possible at any time.

R&D Plus
Contains all functions of Basic and R&D plus the possibility to evaluate and visualize the 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.

Manufacturing Process[24-38]
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.

1. Skipping first layer compression
As described earlier, the number of compressions in manufacturing of multi-layer tablets is equal to the number of layers in the multi-layer tablet. If the first layer is not compressed before addition of second layer, there is a possibility of uncontrolled mixing of granules of first layer into second layer at the interface. In addition, if the first layer is not compressed before addition of second layer, due to the centrifugal force during the rotation of the turret, the granules of first layer may

shift toward the outer periphery of the die cavity resulting in an angled (skewed) interface. A clear demarcation between the two layers is desirable since it is not only appealing and but also visually assures that there is no cross-contamination.

2. Tablet breaking force

According to the current USP, tablet breaking force is the force required to cause the tablets to break in a specific plane. The tablets are generally placed between two platens, one of which moves to apply sufficient force to the tablet to cause fracture. For conventional, round (circular cross-section) tablets, loading occurs across their diameter (sometimes referred to as diametrical loading), and fracture occurs in that plane. Tensile strength provides a more fundamental measure of the mechanical strength of the tablet and it considers geometry of the tablet. Tensile strength is calculated by the following.

Tensile strength = $2F/\pi Dh$

Where, F is the load required breaking the tablet diametrically (as opposed to de-laminating or capping), “D” and “h” are tablet diameter and thickness, respectively. Thus, tensile strength estimates force per unit area of the tablet at breakage. This equation is applicable only for the tablets that have flat surface. For tablets that do not have flat surface, curvature needs to be considered while calculating the surface area. It is well documented that the mechanical strength of a tablet can be generally characterized by measuring the tensile strength using the compression test. In case of a matrix tablet, the impact of components properties, such as particle size and shape, effective contact surface area and tablet porosity on the tensile strength is well documented. To simplify the process, alternate approaches of determining adhesion strength as a measure of binary tablet performance have been developed and reported in the literature. An apparatus to measure the shear forces needed to separate the layers in the radial direction and relate these forces as a measure of adhesion strength was reported. Although measurement of tensile strength is appropriate for assessing the tablet strength; pharmaceutical firms tend to measure the tablet breaking force, which is essentially the load to break the tablet. Another measure for mechanical strength is the crushing strength-friability ratio (CSFR).

3. Effect of lubrication

Since the first layer surface is uniform and perhaps relatively less rough due to the first layer compression, the interfacial interactions between the first layer and the second layer may be impacted by the level of lubricant. The tablet surface smoothness increases as the level of lubricant, such as magnesium stearate is increased. For example, to achieve a better interfacial interaction between the layers, relatively low lubricant concentration (practically possible) and low compression forces are required for first layer tableting. However, the level of lubricant needed for avoiding picking and sticking of the first layer must be assessed as part of the product development. The blended lubricant in the granules bulk distributes throughout the mixture, or “coats” on the surface of the granules and this provides lubrication and reduces the friction when the granules come in contact with dies and punches during compression. However, the lubrication can also reduce the extent of inter-granular adhesion and potentially affects the critical quality attributes such as tablet breaking force and dissolution. Thus, adding lubricant to the dies and punches, instead of adding directly to the granules, has been investigated to understand the impact of lubricant on the critical quality attributes of the tablet.

4. Coating

Often multi-layered tablets are coated to improve elegance, to protect the cores from ambient conditions or to control the release profile. In either case, exposure of the multi-layered tablets to solvents, high temperatures and effect of loads must be considered in the product development. To avoid layer-separation during the coating process it is important to know the coefficients of thermal expansion of the tablet layers and the impact of this difference on the tablet integrity, have explained that during the coating process of bi-layered tablets, cracks appeared on the surface of only one layer within few minutes of the coating process, leaving the other layer intact. Upon testing, it was found that the thermal expansion coefficient of two different

layers of the tablet were significantly different. When control coating was run, the individual layers separately at 40-55 °C, and no evidence of cracking was found. To alleviate the cracking, the product was reformulated with each layer having almost the same coefficient of thermal expansion. Thus, multi-layer drug products that are intended to undergo coating process require additional scrutiny that may not be needed for drug products that do not require coating. Though cracking is reported for bi-layer tablets that undergo coating, it is possible that the cracking and/or separation of layers could also occur upon extended storage of the drug product. Thus, it is imperative that the excipients are not only screened for their physical properties such as particle size and compressibility during the pharmaceutical development stage, but also, tested to ensure the individual layers are similar in terms of their thermal expansion coefficient.

5. Stability

In the stability studies, drug products need to be observed closely and tested periodically to ensure that their integrity is preserved throughout their shelf life and they perform in a predictable manner. Bi-layer tablets prepared with the combination of two therapeutic agents are certainly convenient, and thus simplify the treatment regimen. The use of a combination of two APIs or the same API with different release rate to optimize therapy and to improve patient compliance has increased steadily over the years. To achieve this objective it is imperative that the quality and the performance of the bi-layer tablets be maintained over the expiration period. The stability studies must be performed under conditions as per ICH guidelines and the supportive stability data generated during the product development phase and on the exhibit (clinical) batches to demonstrate the product quality and performance must be included in the filing. It is recommended that the sponsor perform the drug-drug, drug-excipients interaction, studies the impact of manufacturing process and the impact of heat and humidity on the integrity of the bi-layer and drug release over the expiration period. The selection of the container/closure system must be based on the ability of the system to protect the drug product and maintain the integrity of the bi-layer under use condition over the shelf life. A significant decrease (more than 5%) in the assay was observed in the other drug component. In such scenarios, if alternate approaches are used to improve the product stability of the layered tablets they must be adequately supported by the stability studies.

6. In vitro performance

The *in vitro* dissolution testing requirement of the bi-layer tablets will vary based on the intended dosage design and the physico-chemical characteristics of the drug in each layer. This variability poses special challenges in the development of a meaningful dissolution procedure for bi- layer drug products, especially if drugs with different water solubility are incorporated in the bi-layer tablets. In general, attributes such as rate of swelling and rate of water uptake need to be assessed for the bi-layer tablets. For example, if the goal of bi-layer immediate tablet is to deliver two incompatible API, then the separation of these layers in the dissolution media may be of no significance as this would not have any impact on the product performance (*in vivo*). However, if the bi-layer tablet is a modified release product, with the design feature to control the release rate of the API layer by compacting with placebo layer, the integrity of the layers in the dissolution media is critical to the performance of the drug product (*in vivo*). In the case of bi-layer drug products, a bio-relevant dissolution test conditions would be more meaningful in evaluating product quality and product performance. For example, in vitro dissolution testing of bi-layer tablet made with water insoluble APIs need extensive use of simulated fluids on both fresh tablets and the long-term stability samples. Having a sensitive, reliable and discriminating *in vitro* dissolution procedure to determine the product quality and to predict bioavailability is of primary interest to the agency. It is recommended that all studies done for the development of the dissolution method must be included in the filing to support the final method that will be used for release and stability of the drug product.

Tablet surface characterisation by various imaging techniques[39, 40]

Experimental methodologies to determine surface parametersof materials include optical microscopy, scanning electrical microscopy (SEM), laser profilometry and atomic force microscopy (AFM). It has been shown that although providing useful information about surface quality optical microscopy and SEM are unable to produce quantitative comparable data. AFM and laser profilometry are able to provide a quantitative analysis of the surface but operate on different scales. Laser profilometry is able to provide data covering an area of millimetres whereas AFM provides much more detailed information over areas typically in the micron range making laser profilometry a better choice for relatively large scale geometric analysis. Tomography is a non-destructive method which uses radiographic images taken from multiple angles, by sample rotation, to obtain a full three-dimensional image of the sample. The X-ray tomography imaging process is based on the attenuation of X-rays through matter. The way an X-ray will be attenuated will depend on the density and atomic number of the material being sampled. The use of X-ray tomography to determine density distributions in compacts has recently become appropriate due to the evolutionary progress in the focus size of X-rays increasing the resolution of these instruments from 1 mm in the early 1990s up to approximately 5–10 microns. It should be noted however that for large objects the resolution is determined by the number of pixels in the CCD camera and not the focus of the X-ray tubes. The main disadvantage of X-ray systems is the undesirable presence of artefacts seen in the reconstructed image: the most troubling of these resulting from beam hardening. A direct result of having polychromatic X-ray tubes is that the X-rays emitted will contain a spectrum of different energies. As the X-rays traverse through the sample the lower energy rays will be preferentially absorbed. As the higher energy X-rays pass through the sample the beam becomes ‘harder’. As harder beams are less likely to attenuate the total attenuation, given by the logarithm of the ratio of the incoming and the attenuated X-ray beam is not strictly proportional to the sample thickness.

I. Terahertz Pulsed Imaging(TPI)[41, 42, 43]

The terahertz region of the electromagnetic spectrum spans the frequency range between the mid-infrared (IR) and the millimetre/ microwave. The centre portion of the terahertz region (0.1–4 THz, 3.3–133 cm−1) has a unique combination of properties in that many amorphous pharmaceutical excipients are transparent or semi-transparent to terahertz radiation whilst many crystalline materials have characteristic spectral features in terahertz region. Absorption features within the mid-IR region are dominated by intra-molecular vibrations of sample molecules thus mid-IR spectral features are “molecule fingerprints”. In contrast, absorption features in terahertz region are dominated by intermolecular vibrations, corresponding to motions associated with coherent, delocalized movements of large numbers of atoms and molecules.

Recent pharmaceutical applications of terahertz pulsed spectroscopy and imaging. The following application areas are highlighted[44]

(a) Discrimination and quantification of polymorphs/hydrates,

(b) Analysis of solid form transformation dynamics,

(c) Quantitative characterisation of tablet coatings: off-line and on-line,

(d) Tablet coating and dissolution,

(e) Spectroscopic imaging and chemical mapping.

II. *SEM(Scanning Electron Microscopy)*[45]

It gives an accurate image of the surface but they do not produce quantitative information about surface roughness. It visually detect defect in tablet but data insufficient in in process control testing.

III. Laser Profilometry[46]

It use in pharmaceutical compact and pellets as means of evaluating differences in roughness.

IV. Atomic Force Microscopy(AFM)[47]

AFM also has very good resolution in organic crystal samples compared to SEM and the optical microscope. The disadvantages of AFMare the small measurement area, slow speed and the need for flat samples.

Table 1
Advantages and limitations of techniques for layer separation risk assessment

Techniques	Advantages	Limitations
Tensile strength	A traditional technique, Easy to test	Poor correlation to layer separation risk
Friability testing	A convenient method for rough estimation	Detection of only actual layer separation rather than its risk
SEM	High spatial resolution, Visual identification of defect within sample	Qualitative analysis (cannot predict the magnitude of the layer separation risk)
TPI	Quantitative analysis (can predict the magnitude the risk), Non-destructive 3D imaging, Faster data acquisition and processing time	Lower spatial resolution
XRCT	High spatial resolution, Non-destructive 3D imaging, Visual identification of defect within sample	Qualitative analysis (can predict the magnitude of the risk), Longer data acquisition and processing time

CHALLENGES IN BILAYER MANUFACTURING[48]

Conceptually, bilayer tablets can be seen as two single-layer tablets compressed into one. In Practice, there are some manufacturing challenges.

Delamination: Tablet falls apart when the two halves of the tablet do not bond completely. The two granulations should adhere when compressed.

Cross-contamination: When the granulation of the first layer intermingles with the granulation of the second layer or vice versa, cross-contamination occurs. It may conquer the very purpose of the bilayer tablet. Proper dust collection goes a long way toward preventing cross contamination.

Production yields: To prevent cross contamination, dust collection is required which leads to losses. Thus, bilayer tablets have lower yields than single-layertablets.

***Cost*:** Bilayer tableting is more expensive than single layer tableting for several reasons. First, the tablet press costs more. Second, the press generally runs more slowly in bilayer mode. Third, development of two compatible granulations is must, which means more time spent on formulation development, analysis and validation. These factors, if not well controlled/optimized, in one way or another will impact the bilayer compression per se 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.

Characterization of bilayer tablet[49, 50]

- ***Particle size distribution:*** The particle size distribution was measured using sieving method.
- ***Photo-microscope study:*** Photo-microscope image of TGG and GG taken (X450 magnifications) from Photomicroscope.
- ***Angle of repose:*** The diameter of the powder cone was measured and the angle of repose was calculated using the following equation.

Tan ø=h/r

Where,

h = Height

r = Radius of the powder cone.

- ***Moisture sorption capacity:*** All disintegrates have capacity to absorb moisture from atmosphere which affects moisture sensitive drugs. Moisture sorption capacity was performed by taking 1 g of disintegrate uniformly distributed in petri-dish and kept in stability chamber at 37±1°c and 100% relative Humidity for 2days and investigated for the amount of

moisture uptake by difference between weights.

- ***Density:*** The loose bulk density (LBD) and tapped bulk density (TBD) were determined and calculated using the following formulas:
  LBD ¼ weight of the powder=volume of the packing ð2þ
  TBD ¼ weight of the powder=tapped volume of the packing ð3þ

- ***Compressibility:*** The compressibility index of the disintegrate was determined by Carr's compressibility index.
  C = 100 x (1-þb/þt)

Evaluation of Bilayer Tablets[51-55]

1) ***General Appearance:*** The general appearance of a tablet, its visual identity and overall "elegance" is essential for consumer acceptance. Includes in aretablet's size, shape, colour, presence or absence of anodour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.
2) ***Size and Shape:*** The size and shape of the tablet canbe 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 design to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It isusually 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 orsmashed tablets are not picked up. Normally, when capping occurs, friability values are not calculated. Athick 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 isthe measure of friability and is expressed in percentage as: % Friability = 1- (loss in weight / Initial weight) X 100
6) ***Hardness (Crushing strength)****:* The resistance of tablets to capping**,** abrasion or breakage underconditions 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-1930. 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 coilspring is applied diametrally 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. Hardness 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 with stand the handling during subsequent processing such as coating or packaging and shipping operations. The force required breaking 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 ahardness 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 -20kg). Tablet hardness have been associated with other tablet properties such as density and porosity. Hardness generally increases with normal storage of tablets anddepends 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 guide lines for accelerated studies. The tablets were withdrawn after a period of 15 days and analysed 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.

Table 2
Stability condition as per ICH guideline Study

Study	Storage Condition	Minimum timeperiod
Long term	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH± 5% RH	12 months
Intermediate	30°C ± 2°C/65% RH± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

8) Uniformity of weight

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

9) Dissolution Studies

Bilayer tablets were subjected to in vitro drug release studies in simulated gastric and intestinal fluids to assess their ability in providing the desired controlled drug delivery. Drug release studies were carried out using USP dissolution test apparatus I at 100 rpm, 37±0.5°C, and pH 1.2 buffer (900 ml) (i.e.0.1 N HCl) for 2 hours, since the average gastric emptying time is about 2 hours. The dissolution medium was replaced with pH 6.8 phosphate buffer (900ml) and experiment continued for another 10hours. At different time intervals, 5ml of the samples werewithdrawn and replaced with 5ml of drug-free dissolution medium.The samples withdrawn were analysed by UV spectrophotometer using multi component mode of analysis.

CONCLUSION

The objective of the dosage form is to ensure that the drugs available to its citizen are not only safe and effective, but are also properly manufactured and packaged to meet the established quality target product profile over it shelf life. A well-developed product will effectively address these issues by including appropriate control strategies and establishing the functional relationships of the material attributes and process parameters critical to the bi-layer tablet quality as discussed in the article. Low pre-compression forces are necessary to secure interlayer bonding. The sensitivity of the displacement-based control system increases as pre-compression force decreases, resulting in a higher accuracy. Accurate individual layer weight monitoring/control at high speed and in combination with reduced layer-separation risk can be achieved with the Courtoy-R292F. Also by using new tablet surface characterization techniques such as TPI quantitative analysis of tablet is done.

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