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BI-LAYER TABLETS- AN EMERGING TREND: A REVIEW

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ABSTRACT

Keywords:

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Layer separation,
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Bi-layer tablets have been developed to achieve controlled delivery of different drugs with pre-defined release profiles. In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bilayer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance. 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. Bilayer tablets offer definite advantages over conventional release formulation of the same drug. 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 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. Using a modified tablet press may therefore not be your best approach to producing a quality bi-layer tablet under GMP-conditions. Especially when in addition high production output is required.

INTRODUCTION: Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease of administration. It is well known that modified release dosage forms may offer one or more advantages over immediate release formulations of the same drug. There are many ways to design modified release dosage forms for oral administration; from film coated pellets, tablets or capsules to more sophisticated and complicated

delivery systems such as osmotically driven systems, systems controlled by ion exchange mechanism, systems using three dimensional printing technology and systems using electrostatic deposition technology. The design of modified release drug product is usually intended to optimize a therapeutic regimen by providing slow and continuous delivery of drug over the entire dosing interval whilst also providing greater patient compliance and convenience¹⁻³. The most

common controlled delivery system has been the matrix type such as tablets and granules where the drug is uniformly dissolved or dispersed throughout the polymer, because of its effectiveness, low cost, ease of manufacturing and prolonged delivery time period^{4,5}.

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.

However, these drug delivery devices are mechanically complicated to design/manufacture and harder to predict their long term mechanical properties due to the poor mechanical and compression characteristics of the constituent materials in the compacted adjacent layers, elastic mismatch of the layers, insufficient hardness, inaccurate individual mass control, cross contamination between the layers, reduced yield, and their tendency to delaminate at the interface between the adjacent compacted layers during and after the various stages of production downstream of the compaction process. Therefore, the major problem, that has to be overcome, is to understand in detail the sources of these problems in micro- and macro-scales and to develop remedies to solve them during solid dosage delivery design.

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^{6,7}. Since the adjacent compacted layers of a bilayer tablet are bonded together by mechanical means, understanding what influences the stress state, the mechanical properties of each layer and the resultant bilayer tablet, and compression parameters along with specialized techniques to predict failure as a function of layer properties and compression conditions are primordial to successfully developing bilayer tablets.

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

1. To control the delivery rate of either single⁸ or two different active pharmaceutical ingredient(s)^{9,10}.
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^{11,12}.
4. To administer fixed dose combinations of different APIs¹³, prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device¹⁴, buccal/mucoadhesive delivery systems¹⁵, and floating tablets for gastro-retentive drug delivery¹⁶.

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

1. They are unit dosage form and offer the greatest capabilities of all oral dosage form for the

- greatest dose precision and the least content variability.
2. Cost is lower compared to all other oral dosage form.
 3. Lighter and compact.
 4. Easiest and cheapest to package and strip.
 5. Easy to swallowing with least tendency for hang-up.
 6. Objectionable odour and bitter taste can be masked by coating technique.
 7. Suitable for large scale production.
 8. Greatest chemical and microbial stability over all oral dosage form.
 9. Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.

Disadvantages of Bi-Layer Tablet Dosage Form are:

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

General properties of Bi-Layer Tablet Dosage Forms:

1. A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration, and contamination.
2. Should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.

3. Should have the chemical and physical stability to maintain its physical attributes over time. The bi-layer tablet must be able to release the medicinal agents in a predictable and reproducible manner.
4. Must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

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 in 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 tablet¹⁷. 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 layers¹⁸.

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 following¹⁹.

$$\text{Tensile strength} = 2F/\pi Dh$$

Where, F is the load required to break 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 introduced by Fell and Newton (1970). 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 documented²⁰⁻²².

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 reported²³. 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). Regardless of how the tablet is evaluated for its strength, a measure to assess this critical attribute must be fully evaluated and the choice of the test method must be supported by the formulation and the manufacturing process. The integrity of the tablet needs to be assessed during the stability studies to confirm that aging and environment have not negatively influenced the adhesion of the layers.

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 increased²⁴. For example, Dietrich *et al.*, (2000) have concluded that in order 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. This process is referred to as external lubrication in the literature. In external lubrication, the lubricant is

sprayed onto the die and punches for each compression cycle instead of adding it to the bulk powder mixture²⁵, have shown that the external lubrication can increase crushing strength by 40% without prolonging the tablet disintegration. It is confirmed by observing a layer of magnesium stearate on the tablet through scanning electron microscope. Though this new technology appears advantageous for the mono-layer tablets, it can potentially be used to better understand the impact of lubricant on the quality attributes of bilayer tablets.

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 affect 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 integrity²⁶, 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 years²⁷.

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 and/or BA/BE) 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. The study done, demonstrated that the bi-layer tablets prepared with amlodipine besylate and atenolol had a better stability profile than the mono-layer matrix tablets consisting both the APIs²⁸. This strategy, although improving the stability of one drug component, did not completely prevent the interaction. 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 agency²⁹. 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. In general, development of a meaningful dissolution procedure for APIs with limited water solubility is more challenging than for the drug product with a high water solubility API. Having both classes of drugs in the same unit presents additional challenges to both the pharmaceutical industry and the regulatory agency. To measure the *in vitro* drug release performance of the bi-layer drug product, well established techniques can be used to achieve adequate

dissolution by understanding the solubility differences of the APIs (where applicable), use of relevant and appropriate amount of surfactants³⁰, composition and volume of dissolution test medium, pH, type of apparatus and rate of agitation³¹.

Evaluation of Bilayer Tablets:

1. **General Appearance:** The general appearance of a tablet, its visual identity and overall “elegance” is essential for consumer acceptance. Includes in are tablet’s size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.
2. **Size and Shape:** The size and shape of the tablet can be dimensionally described, monitored and controlled.
3. **Tablet thickness:** Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.
4. **Weight variation**³²: Standard procedures are followed as described in the official books.
5. **Friability**³²: Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator. A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed

tablets are not picked up. Normally, when capping occurs, friability values are not calculated. A thick tablet may have less tendency to cap whereas thin tablets of large diameter often show extensive capping, thus indicating that tablets with greater thickness have reduced internal stress the loss in the weight of tablet is the measure of friability and is expressed in percentage as:

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

6. **Hardness (Crushing strength)**³³: The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The small and portable hardness tester was manufactured and introduced by Monsanto in the Mid 1930s. It is now designated as either the Monsanto or Stokes hardness tester. The instrument measures the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet. The Strong-Cobb Pfizer and Schleuniger apparatus which were later introduced measures the diametrically applied force required to break the tablet.

Hardness, which is now more appropriately called crushing strength determinations are made during

tablet production and are used to determine the need for pressure adjustment on tablet machine. If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specifications; if it is too soft, it may not be able to withstand the handling during subsequent processing such as coating or packaging and shipping operations. The force required to break the tablet is measured in kilograms and a crushing strength of 4 Kg is usually considered to be the minimum for satisfactory tablets.

Oral tablets normally have a hardness of 4 to 10 kg; however, hypodermic and chewable tablets are usually much softer (3 kg) and some sustained release tablets are much harder (10 -20 kg). Tablet hardness have been associated with other tablet properties such as density and porosity. Hardness generally increases with normal storage of tablets and depends on the shape, chemical properties, binding agent and pressure applied during compression.

7. **Stability Study (Temperature dependent)**: The bilayer tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

TABLE 1: RECOMMENDED LONG-TERM AND ACCELERATED STORAGE CONDITIONS

Study	Storage condition	Minimum time period covered by data at submission
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

*It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH. **If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability and Dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25°C.

Quality and Good manufacturing practice (GMP) requirements of bi-layer tablets³⁴: To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the selected press is capable of:

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

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

Bilayer Tablets:

Limitations of the Single Sided Press³⁴: 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. The limitations of such single-sided press are:

- No weight monitoring/control of the individual layers.
- No distinct visual separation between the two layers.

The fact that it is not possible to monitor and control the weight of the individual layers raises the question whether we can consider this production GMP? Individual layer-weight control on a single-sided press requires some form of measurement of the first layer and of the total tablet. The first control loop indirectly monitors weight and controls the fill depth of the first layer. The second loop indirectly monitors the total tablet weight, but adjust only second-layer fill depth. In general, compression force is used to monitor tablet- or layer-weight.

But to do so it is necessary to apply a compression force to the first layer before adding the second layer-powder. To apply a compression force to the first layer prior to adding the second layer, it is necessary to use two separate powder feeders with a compression station in-between. This can be achieved on a single-sided press by installing an additional feeder between the pre- and main-compression station. Very often the precompression roller must be reduced to a much smaller size in order to create the space required for the second feeder. Additional limitations of such single sided press are:

- Very short first layer-dwell time (*) due to the small compression roller, possibly resulting in poor de-aeration, causes 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.

(*) dwell time is defined as the time during which compression force is above 90% of its peak value. Longer dwell times are a major factor in producing a quality tablet, especially when compressing a difficult formulation.

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, precompression and main compression for each layer. In fact, the bi-layer tablet will go through 4 compression stages before being ejected from the press.

Bi-layer tablets:

Limitations of “compression force” - controlled tablet presses³⁴: 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”. 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] as indicated in **Figure 1**.

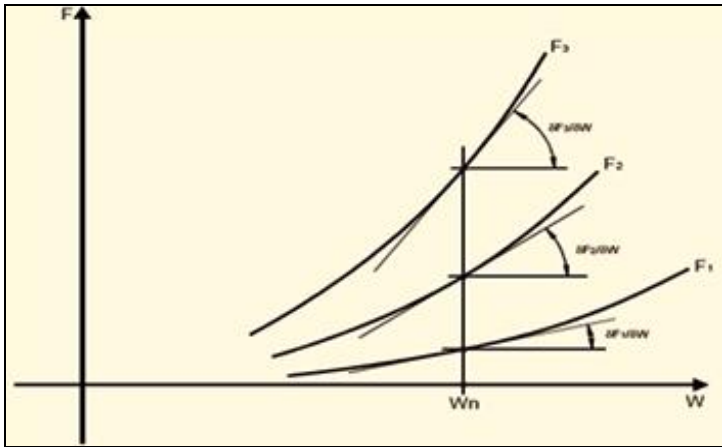


FIG. 1: FORCE VERSUS WEIGHT SENSITIVITY AT DIFFERENT COMPRESSION FORCE LEVELS

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 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.

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.

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.
- One 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.

CONCLUSION: Bi-layer tablets provide one of the important design approaches where incompatible drugs, with different indication, and same drug with different release rate (e.g. IR and ER) can be incorporated in a single unit. To develop a robust bi-layer tablet a complete mechanistic understanding must be developed through the application of scientific and quality risk management tools: Pharmaceutical development and quality risk management. 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 its 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. 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 pre-compression 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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