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BILAYER TABLET ORAL SOLID DRUG DELIVERY SYSTEM AND CHALLENGES IN THE FORMULATION : A REVIEW

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ABSTRACT
The manufacture of bi-layer tablets, produced by the sequential compaction of loose powder layers has recently become of increased interest within the pharmaceutical industry due to the tailored release profiles of active ingredients that may be obtained. In a bi-layer configuration, the immediate release layer of the bi-layer tablet has worked as the loading dose and the sustained release layer has maintained the therapeutic plasma drug concentration for prolonged time. 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 in producing a quality bi-layer tablet under GMP-conditions, especially when high production output is required.

Key words: *bilayer tablet, layer separation, insufficient hardness, individual layer weight*

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INTRODUCTION

Bilayer tablet oral delivery systems are designed to release a drug at 2 different rates or in 2 different periods of time: they are either quick/slow or slow/quick. A quick/slow release system provides an initial burst of drug release followed by a constant rate (ideally) of release over a defined period of time. This type of system is used primarily when maximum relief needs to be achieved quickly, and it is followed by a sustained release

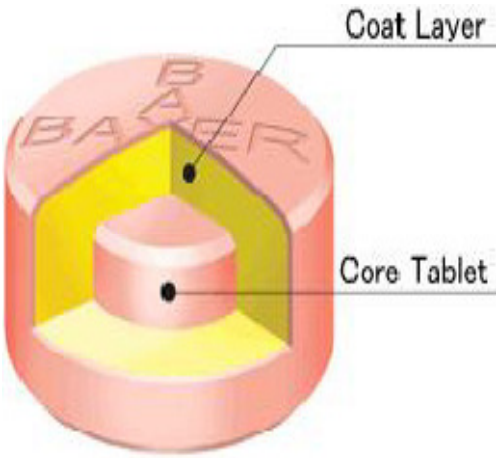
phase to avoid repeated administration. Suitable candidate drugs for this type of administration include non-steroidal anti-inflammatory drugs (NSAIDs) and antihypertensive, antihistaminic, ant-diabetic and anti-allergic agents (1). Developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bilayer tablet) has increased in the pharmaceutical industry. 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 (3, 4). 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.

Types of quick/slow dual-component delivery system:

Compressed Matrix Core Tablet:

A core tablet is a tablet within a tablet. The core is usually for the slow drug release component & the outside shell contains a rapid release dose of drug. Formulation of a core tablet requires two granulations. The core granulation is usually compressed lightly to form a loose core & then transferred to a second die cavity where a second granulation containing additional ingredients is compressed further to form the final tablet (**fig. 1**). Generally, conventional controlled dosage forms delay the release of therapeutic systemic levels and do not provide a rapid onset of action. To modify the release of the drug from these systems, the surface area exposed to a fluid can be restricted by the addition of barrier layers to one or both sides of the tablets. However, most multilayer systems attempt to achieve a constant release rate from a tablet, not a biphasic release of the drug. When a single constant rate for drug release does not entirely satisfy the therapeutic objective, the quick/slow delivery system may be an interesting alternative. This biphasic release system can be achieved by the application of an immediate release layer to the conventional layered matrix tablet. To obtain quick/slow drug release patterns, Uekama *et al* developed a double-layer tablet that prolonged the release of piretanide for 8 hours; β-cyclodextrin was used in the fast releasing layer, and ethylcellulose (EC) and hydroxypropyl methylcellulose (HPMC) were used in the sustained release layer. The quick release layer contained a

super disintegration agent (cross-linked sodium starch glycolate) to increase the drug release rate. The slow release layer consisted of an HPMC matrix tablet. Skye Pharma Co has one quick/slow release formulation on the German market: Diclofenac-Ratiopharm Uno 25 mg Quick + 125 mg Slow, which has been produced using the Geomatrix technology (Jago Pharma AG, Muttenz, Switzerland) for multiple-layer tablets. Recently, Li and Zhu, using combinations of versatile mini tablets (rapid release, sustained release, pulsatile, and delayed onset sustained with various releasing lag times), obtained a multifunctional and multiple-unit oral drug delivery system, including a quick/slow nifedipine release system. Another approach to achieving quick/slow drug release involves the use of a compressed core. The core consists of a sustained release tablet, which is coated by compression over the whole surface with a fast-disintegrating formulation. Both the core tablet and the outer powder layer contain a drug. From the viewpoint of manufacturing, this technology is an attractive alternative to the production of multilayer dosage forms, because getting additional layers to adhere to the pre-compressed layers during the double-layer or multilayer tableting process can be difficult. Furthermore, because this system uses conventional manufacturing methods, it is more acceptable to the industry (3).



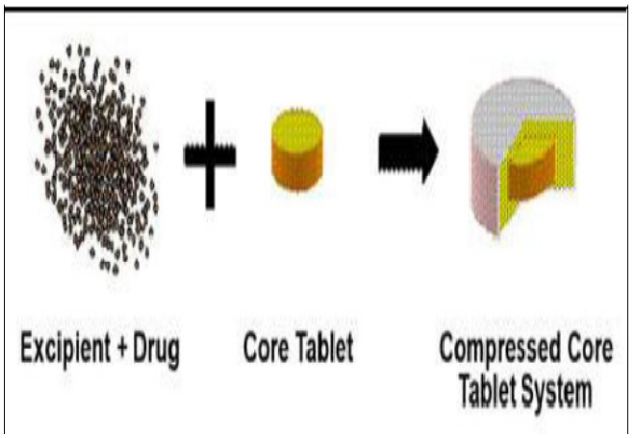


FIG. 1: COMPRESSED CORE TABLET SYSTEM AS BIPHASIC DELIVERY SYSTEM (3)

An Overview of Bi-Layer Tablets: Preferably, the combination of an immediate release layer and sustained release layer will be in the form of a bi- or multi-layer tablet. In a bilayer configuration, one portion of the tablet contains the vinpocetine in the required dose along with appropriate excipients, agents to aid dissolution, lubricants, fillers, etc. The second portion of the tablet will contain the vinpocetine, in the required dose along with other excipients, dissolution agents, lubricants, fillers, etc.(1)

Manufacturing aspect of Bi-Layer Tablets:

The manufacture of bi-layer tablets, produced by the sequential compaction of loose powder layers has recently become of increased interest within the pharmaceutical industry due to the tailored release profiles of active ingredients that may be obtained (4, 5). An observed disadvantage of the formulation however, is the predilection of the assemblies to fail at the interfacial boundary zone between the two adjacent layers.

In an earlier publication (6, 7), the relative interfacial strength of bilayer compacts of the commonly utilized excipient microcrystalline cellulose (MCC) was shown to be a function of both the ultimate applied initial layer and final layer compaction stress: the magnitude of which governs the degree of deformation endured by the particle assembly. MCC is well known to deform in a predominantly plastic manner which is a direct result of the presence of slip planes or dislocations and is thought to be an important factor affecting the compressibility of MCC. Under a relatively large

compressive load the intimate contact area between the particles increases which allows for a greater number of strength increasing junctions or bonds to be formed. The overall tensile strength of the compact will therefore be a function of the number and geometry of these junctions that are present. Thus a naive, yet logical, postulation may be that the predilection of MCC to deform predominately by plastic flow is the governing property of the interfacial strength of the more complex bilayer formulation. Indeed, a rise in the applied final compaction stress will result in the cohesive and interfacial strength of the compacted tablets increasing (6, 7, 8). Paradoxically, the material response (primarily ductile) of the constrained MCC particles to an applied load within the initial compaction layer, defined later, has shown to have a detrimental effect on the resistance to fracture of a bilayer tablet (6, 7). This indicates that the sequential compaction of two layers of the same material cannot be considered comparable in nature and in strength to the cohesion that occurs within a single compacted matrix manufactured of the same material (**fig. 2**).

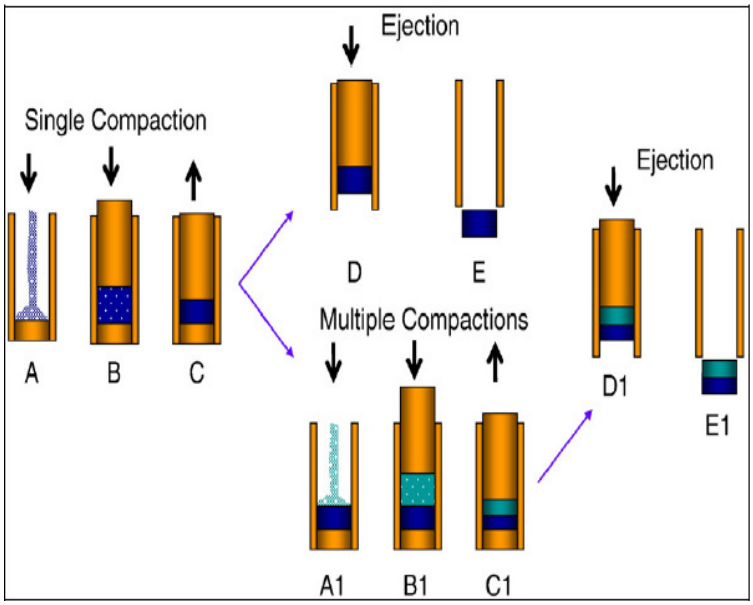


FIG. 2: SCHEMATIC DIAGRAM SHOWING THE MANUFACTURE OF SINGLE AND BILAYER TABLETS UTILIZING UNIAXIAL COMPACTION. A- DIE FILLING, B- COMPRESSION, C- DECOMPRESSION, D- LOWER PUNCH REMOVAL AND REAPPLICATION OF LOAD TO THE UPPER PUNCH, E-TABLET FULLY EJECTED. 1 REFERS TO THE FINAL COMPACTION CONDITIONS

Knowledge of the morphology and surface properties of pharmaceutical particles commonly utilized in tableting applications, in a free or a consolidated state, can assist with the characterization of a materials mechanical response to an applied load. For example the hollow microfibrillar structure of microcrystalline cellulose (MCC) (8) is considered to be responsible for MCC having a high fraction of elastic recovery relative to other commonly used pharmaceutical excipients (9). The determination of the inherent structure of single particles obviously requires a topographical methodology which can accurately operate at relatively small length scales, such as atomic force microscopy. At larger operating length scales, as commonly employed with an optical profilometer, the 'waviness' or form and roughness of a surface can be determined. It is the form of a surface which may provide information regarding the elastic recovery of a compacted material (10). Previous applications of optical profilometers to investigate the properties of compacted materials have involved the generation of both 2D and 3D profiles of surfaces to be analyzed. 3D profiles are usually conducted over relatively small sample areas of a few mm square (11) for an isotropic

Gaussian surface it has been shown that the root mean squared roughness value is the same for a 2D and a 3D profile (12).

Generally for tablet analysis where the samples are relatively large and are considered isotropic a repeatable line profile provides an adequate analysis (13). The determination of surface parameters of pharmaceutical compacts through the application of optical profilometry has been achieved by many authors. Peltonen *et al.,* determined that the roughness parameters obtained using a confocal laser scanning microscope could be correlated with the addition of lubricant to pharmaceutical compacts: as the lubrication was increased the surface roughness became 'smoother'. Rowe (13) utilized the Ra value (introduced later) of coated tablets to determine the effect of process formulation on the surface roughness of coated tablets (14) used optical profiling to determine topographic changes of tablet surfaces with coating time, however, no significant correlation could be made. P. Narayan, B.C. Hancock (14) correlated the determined roughness parameters of compacts of several pharmaceutical excipients with their mechanical strength properties. They found there to be a clear distinction between the compacts classified as brittle: displaying low values of Ra and Rs with high variability and negative skewness, and materials which deformed in a more ductile manner: displaying higher values of Ra and Rs. This result has been confirmed by a complementary analysis of the surface profiles using fractal parameters; however it was highlighted that fractal parameters are inherently scale sensitive (15). Narayan and Hancock extended on this study by investigating the effect of particle size on the obtained roughness parameters for compacts with a predilection to deform in either a predominantly plastic or brittle manner (15). They concluded that the relationship was complex in nature and the roughness was influenced by several factors including the yield stress, ductile/brittle transition particle diameter, the compaction stress and the mean particle diameter, hence further studies were required to obtain conclusive correlations (**fig. 3**).

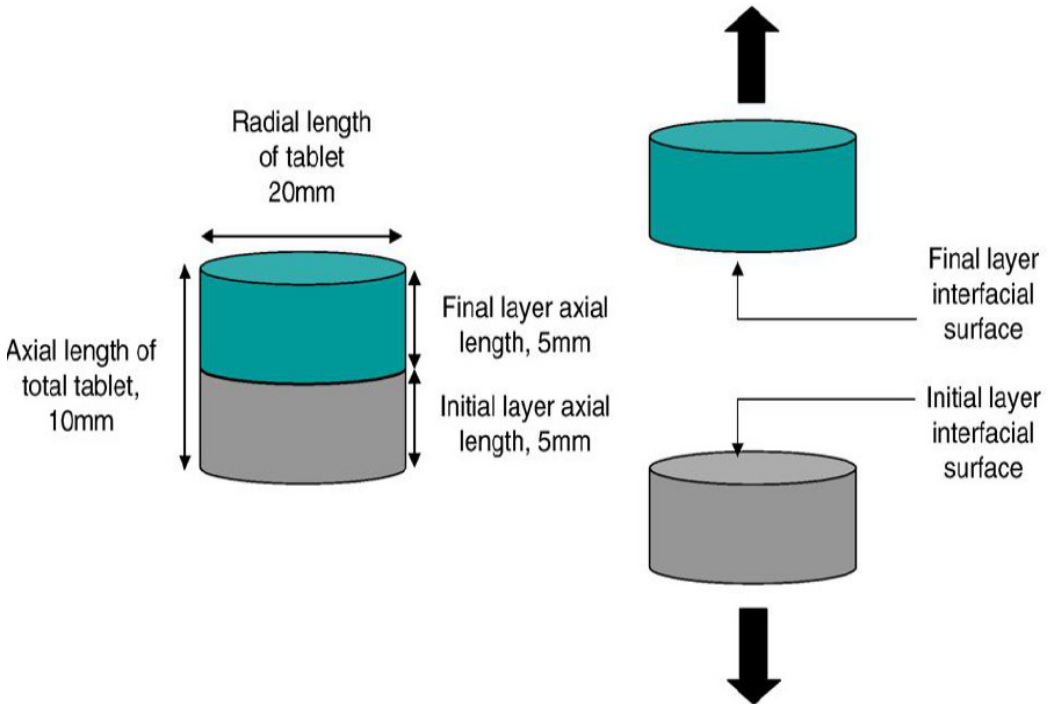


FIG. 3: DIAGRAM SHOWING THE DEFINITIONS OF THE AXIAL LENGTHS, RADIAL LENGTH AND INTERFACIAL FRACTURE SURFACES

Bi-layer tablets : Quality and GMP-requirements:

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

2. Preventing capping and separation of the two individual layers that constitute the bi-layer tablet

3. Providing sufficient tablet hardness

4. Preventing cross-contamination between the two layers

5. Producing a clear visual separation between the two layers

6. High yield

7. Accurate and individual weight control of the two layers is not so easily accomplished as this article aims to demonstrate.

The goal in designing delayed release sustained or controlled delivery system is to (fig. 5):

Reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery.

It would be a single dose for the duration of treatment whether it is for days or weeks, as with infection, or for the life time of the patient, as in hypertension or diabetes.

It should deliver the active entity directly to the site of action, minimizing or eliminating side effects.

This may necessitate delivery to specific receptors or to localization to cells or to specific areas of the body (20).

The safety margin of high potency drug can be increase and the incidence of both local and systemic adverse side effects can be reduced in sensitive patient (21).

Benefits of Modified Drug Delivery System (21):

Decreased in dosing frequency

Reduced peak to trough ratio of drug in systemic circulation.

Reduced rate of rise of drug concentration in blood.

Sustained & Consistent blood level with in the therapeutic window.

Enhanced bioavailability

Customized delivery profiles

Reduced side effects

Improved patient compliance

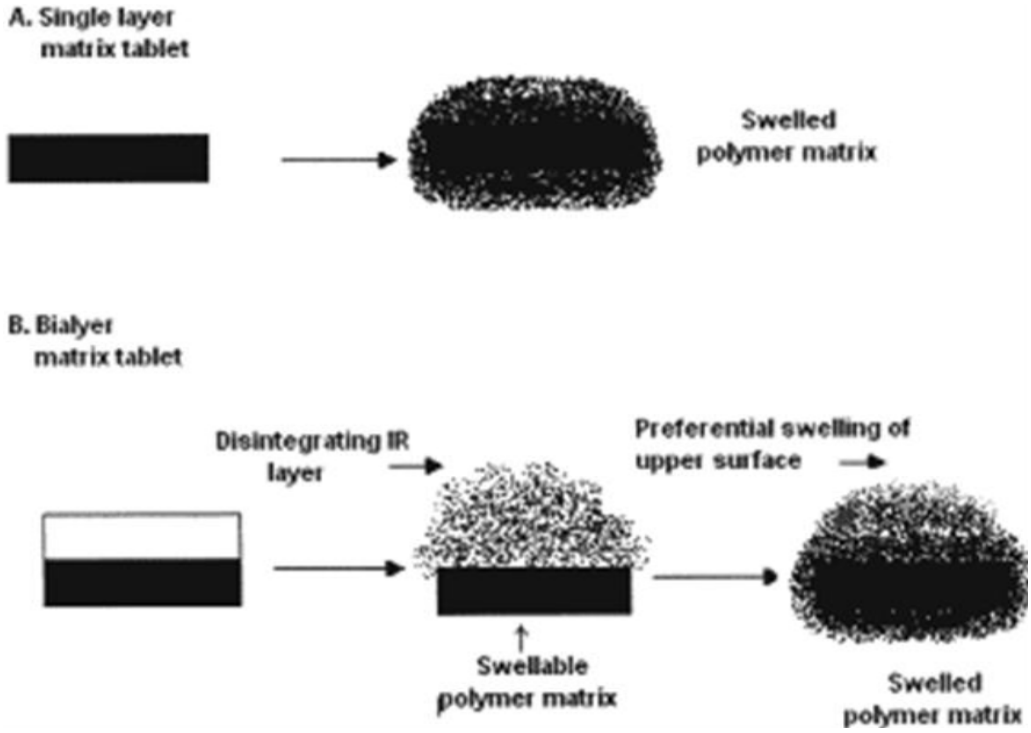


FIG. 5: DRUG RELEASE MECHANISM FORMS A BILAYERED TABLET COMPRISING AN IMMEDIATE RELEASE & A SUSTAINED RELEASE LAYER

Matrix Tablet containing SR Granules & IR Granules : The use of polymeric material in prolonging the release rate of drug has received increased attention. The most important characteristics of this type of this type of preparation is that the prolong release may last days & weeks rather than for a shorter duration (as with other techniques). The first example of an oral polymeric matrix tablet is Gradumet (Abbott Laboratories), which is marketed as an iron preparation. The plastic matrix provides a rigid geometric matrix surface for drug diffusion so that a relatively constant rate of drug release is obtained (**fig. 6**). There may be an attempt to prepare a matrix tablet containing sustained release granules & immediate release granules in order to produce a biphasic system.

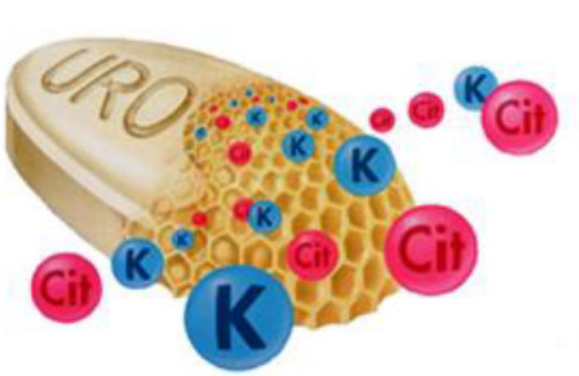


FIG. 6: MATRIX TABLET

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 5: • 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.

LIMITATIONS

Limitation in 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. 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 6:

• No weight monitoring/control of the individual layers

• No distinct visual separation between the two layers

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 preand main-compression station. Very often the pre compression 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, 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.

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" (1,2,8).

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 graphic 1. 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 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 1:

'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

RECOMMENDED WAYS TO OVERCOME THE LIMITATION

Displacement-monitoring/control system for bi-layer compression

Tablet weight control using 'displacement' is based on the measurement of thickness
variations under constant force and is measured at pre-compression. This measurement is possible when using the so-called 'pneumatic compensator'. The displacement-tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system's sensitivity does not depend on the operating point on the graph (i.e. it does not depend on the tablet weight) but depends on the applied precompression force. In fact, the lower the pre compression force, the more sensitive the monitoring/ control system and this is ideal for good interlayer bonding of the bilayer tablet, as explained above. As indicated in the above drawing, the upper pre-compression roller is attached to an air piston, which can move up/down in an air-cylinder. The air pressure [p] in the cylinder is set as a product parameter at initial product set-up and is kept at a constant value by the machine's control system. This pressure [p] multiplied by the piston surface [Spiston] is the constant force at which the piston – and consequently the roller – is pushed downwards against a fixed stop. The lower precompression roller is mounted on a yoke and its vertical position can be adjusted through the control system by means of a servomotor. The position of the lower pre-compression roller determines the pre compression height. At every pre compression, the upper punch hits the upper roller and is initially pushed
downwards into the die. As the lower punch is pushed upwards by the lower roller, the powder is being compressed, while the exerted compression force increases. At a certain point (depending on set air pressure, precompression height and powder characteristics) the reaction force exerted by the powder on the upper punch equals the force exerted by the air pressure on the piston. The punch has to continue its way under the roller, because the turret is spinning. As the piston/roller precompression assembly cannot exert a force above **Fmax = p x Spiston (1)** No further compression of powder is possible. The upper punch will push the upper pre compression roller assembly up and continue its way under the roller. In fact, the top punch, powder slug between punches and bottom punch will move together, **The 'pneumatic compensator'** following the bottom pre-compression roller. During this movement, there is no further compression and the top pre-compression roller will move up and back down. During the time the upper roller makes this up/down movement, the compression force on the punch – and therefore on the powder – remains constant and is equal to Fmax. An LVDT position sensor accurately measures the movement of the upper roller assembly. This vertical movement will reach its maximum value when the punch is right under the centre of the roller. This maximum value is registered by the control system and is called the "displacement". The displacement is measured and recorded at both precompression sections of the Courtoy-R292F, resulting in a displacement value per pre compressed (first) layer or bi-layer tablet.

It is easy to understand that

W = ρ x S x [height of the pre-compressed powder slug] (2) = ρ x S x [PCH + (2 x EqAr) + d] (3)

- W is the weight of the pre-compressed powder slug, and therefore also the first
layer/final tablet weight
- ρ is the density of the pre-compressed powder slug (i.e. not the powder bulk density
nor the final tablet density, but the density of the slug after precompression and prior to main compression)
- S is the surface area of the die opening
- PCH is the "Pre-compression height"

measured as the distance between the 2 extreme tips of upper and lower punch when the punches are right under the centre of the rollers and the upper-roller is in its lowest position

• EqAr is the "equivalent arrow", a correction factor taking into account the concave part of the punch tips

• d is the displacement. This can be reformulated as follows:

• **W = ρ x S x [PCH + (2 x EqAr)] + ρ x S x d (4)**

where the following conditions apply:

• ρ is constant from tablet to tablet as the pre compression force on each slug is the same: Fmax. All powder slugs are pre- Compressed to the same density, thanks to the use of the air compensator.

• S is constant, depending only on tablet size

• The pre-compression height PCH is constant as long as the lower pre-compression roller is not moved

• EqAr is constant as it depends only on the punch tip shape resulting in

W = A + B x d (5) with A = ρ x S x [PCH + (2 x EqAr)]=Constant (6)and B = ρ x S = Constant (7)

The relation between what is measured (the displacement) and what needs to be controlled (tablet weight) is a linear relationship. This linear relationship makes the control algorithm very simple. Yet at the same time very accurate. Graphic 2 clearly shows the relationship between W and d, but also clearly indicates the influence of the other parameters ρ, S, PCH and EqAr. One of the important advantages of the 'displacement control' system is the automatic calculation of the tolerance. If the allowable tolerance on the weight is for example 3%, it will correspond to an allowable displacement tolerance of 3% on [PCH + (2 x EqAr) + d], according to formula (3). As PCH and EqAr are known at any moment, the tolerance on d can easily be calculated. Important to note is that the tolerance on the measured signal (being the displacement d) is independent from the operating point on the weight versus displacement graph. This is not the case with a 'compression force'-controlled system, where the tolerance on the force varies with the working point on the graph. Moreover the upper and lower force tolerances are different, as can be seen from graphic 3. Another important advantage of the 'displacement' control system is its independence from the machine's stiffness. As the displacement is measured at pre compression under relatively low compression forces (typically between 1 and 3 kN), the deformation of the press is negligible.

This is entirely different in case of a 'compression force' control system, which measures the actual compression force at main compression, where forces can go up to 100 kN. As no 2 compression machines have the same stiffness (stiffness of individual parts and stiffness of joints can never be exactly the same), variations in the force-versus weight characteristic of any 2 machines – even of the same model – are inevitable. Graphic 4 illustrates that with the same compression force set point and same set distance between compression rollers, the weaker machine exhibits more deformation, resulting in a thicker (i.e. heavier) tablet. This means that for the same tablet weight and final compression height, the weaker machine will have to run at a lower compression force set point, resulting in tablets with lower hardness. (9).

The 'pneumatic compensator': extended dwell time

The use of an air compensator has the additional and important advantage of an increased and controlled dwell time during precompression of the first layer and final bi-layer tablet. In fact, during the up and downward movement of the upper pre-compression roller, the compression force remains constant. As the dwell time is defined as the time during which compression force is above 90% of its peak value, the dwell time will be extended by the longer flat part in the compression profile shown in graphic 5 1,10. If the pre-compression height PCH is reduced by raising the lower compression roller, the point of initial contact and the point at which the upper roller starts moving up, will move to the left. This results in an increase in displacement, but also in a longer dwell time. A longer dwell time in turn improves the deaeration of the powder and

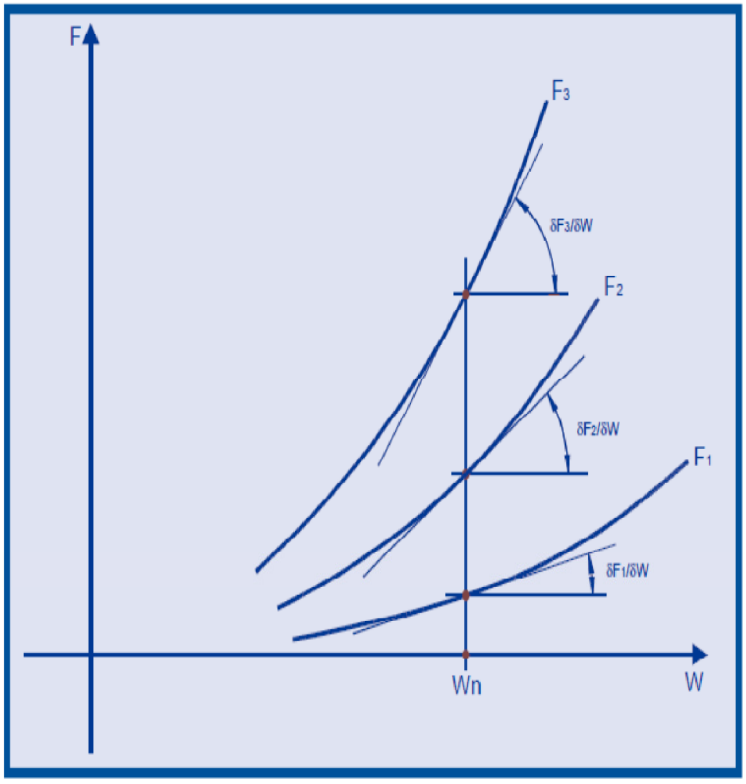
the rearrangement of the granules in the die prior to the final compression. These two factors increase the hardness of the tablets considerably and prevent potential capping problems.

'Displacement' control and first- layer compression

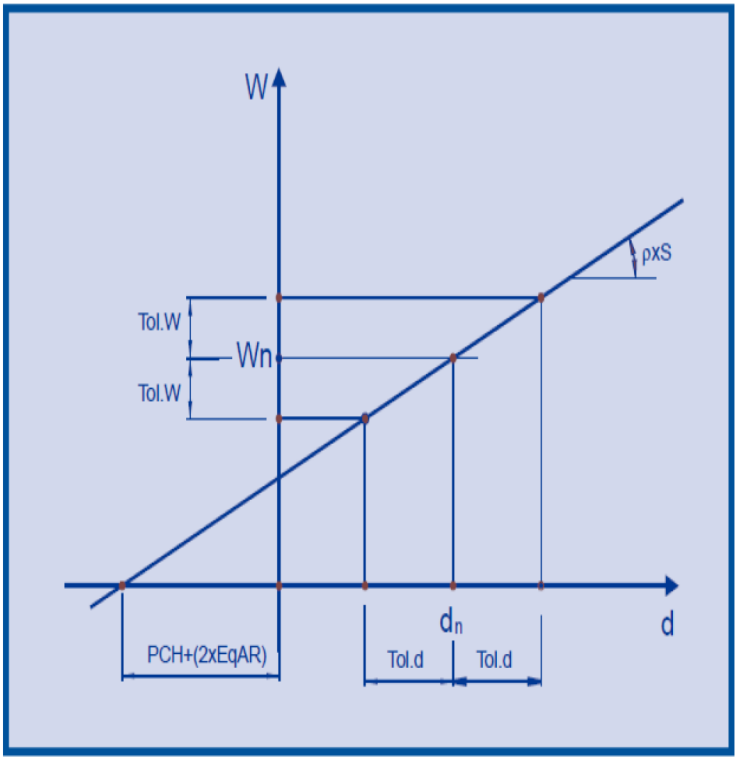
The main problem of a compression force-controlled press for first-layer compression, is its sensitivity δF/δW decreasing with decreasing force, resulting in the need to exert a compression force often above what is allowed to have good interlayer bonding. This problem does not occur in case of a 'displacement'- controlled system. The sensitivity of such a system is δd **/δW = 1 / (ρ x S) (8)** First of all, this 'displacement'-sensitivity is independent from the operating point (i.e. it does not depend on the actual values of W and d). Moreover, the sensitivity increases with decreasing density of the pre-compressed slug. This means that the sensitivity increases with decreasing pre-compression force. This is one of the most important advantages of a bilayer press using 'air compensation' on precompression and based on 'displacement' control: the first layer pre-compression force can be set to a known, constant and importantly a very low compression force (as low as 50 da N). At this low force, the interlayer bonding is optimal, while the control system's sensitivity is maximal. Moreover, displacement tolerance is calculated automatically based on the first-layer weight tolerance, making the system very easy to set up. The displacement signal of first-layer pre-compression is used to adjust the first-layer fill depth in case the displacement is outside the correction tolerance limits. In case the displacement is outside the rejection tolerance limits, the final bi-layer tablet will be rejected at the moment of ejection from the die. After firstlayer pre-compression (and weight control), the first-layer powder slug has a height varying in linear relationship to its weight. In order to achieve the required overfill depth for the second layer powder, it is necessary to push down the first layer slug in the die to this specific depth.

GRAPHICS AND FIGURES:

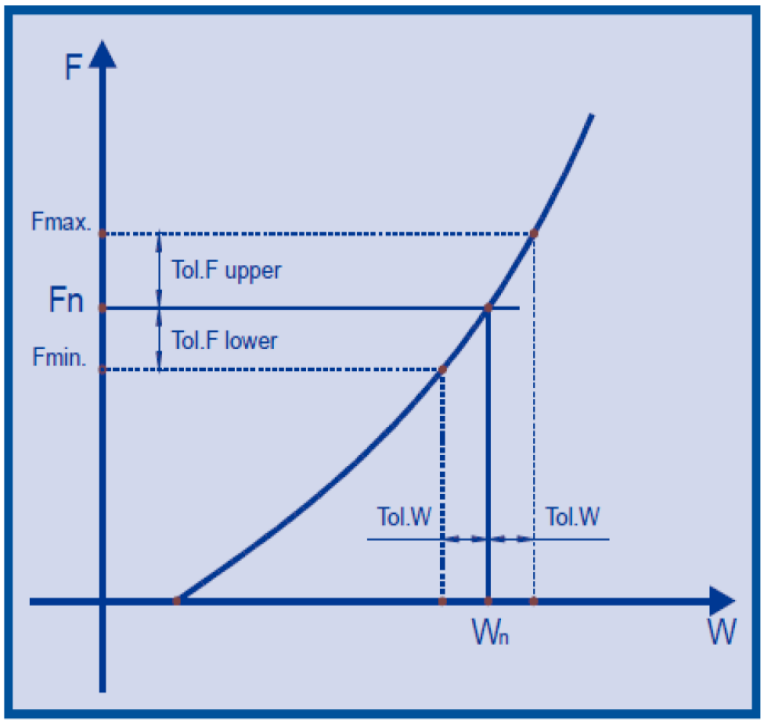
Graphic 1: Force versus weight sensitivity at different comp ression force levels



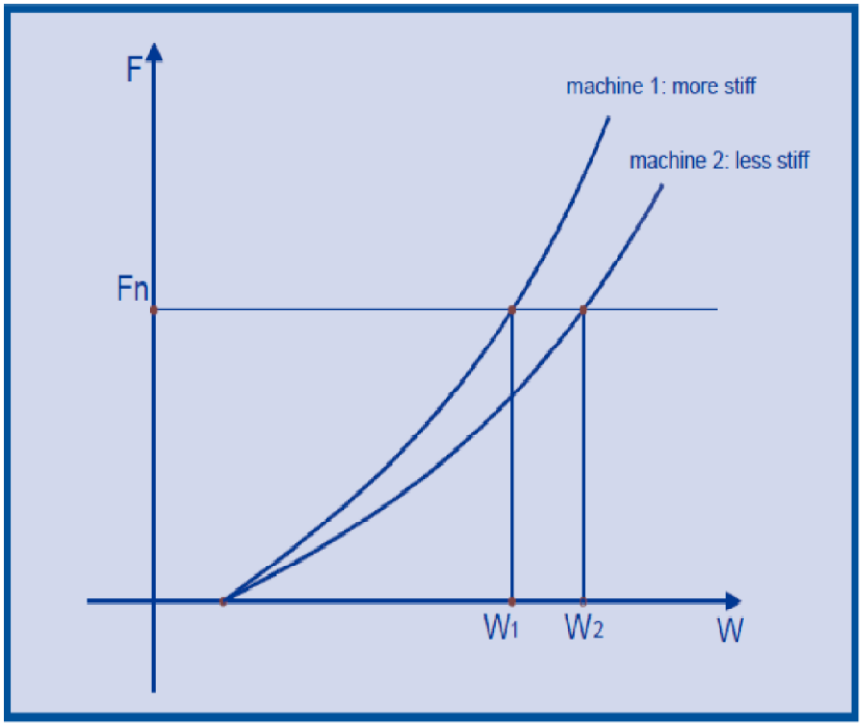
Graphic 2: Weight versus displacement relationship



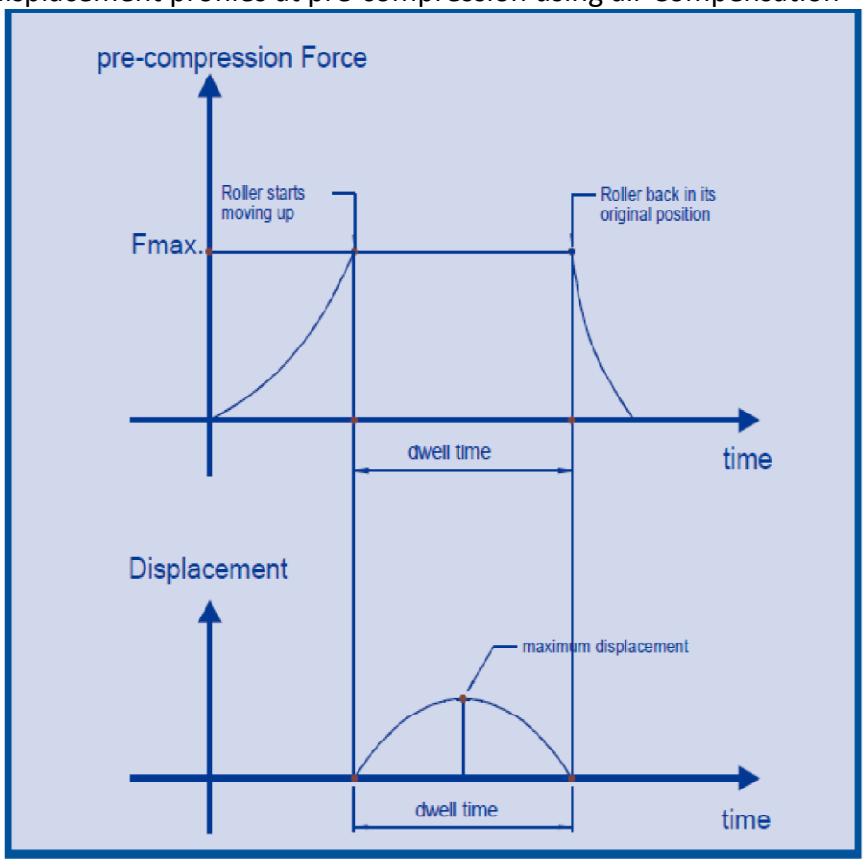
Graphics 3: Force tolerance as a function of weight tolerance



Graphic 4: Influence of machine rigidity on force-weight relation

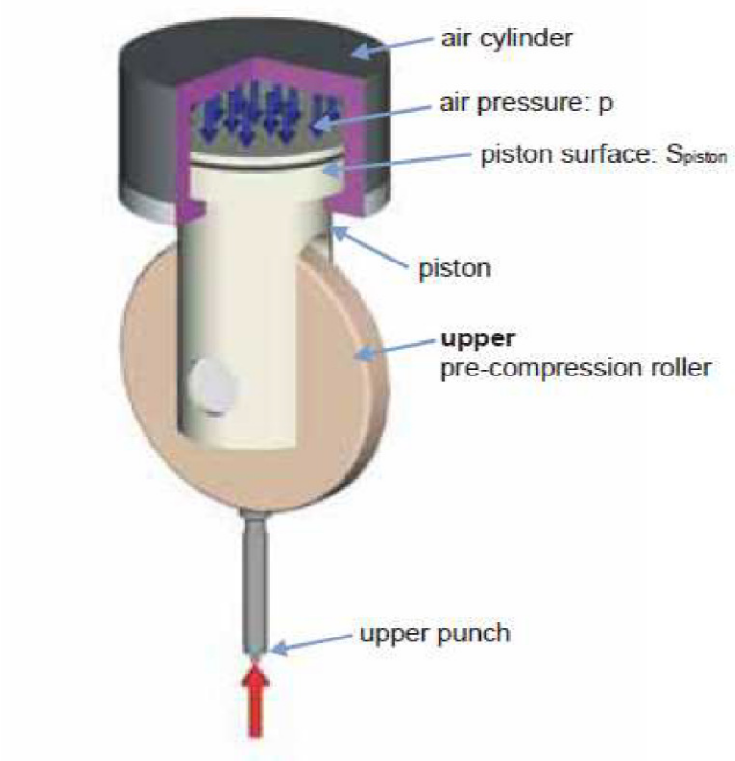


Graphis 5: Force and displacement profiles at pre-compression using air Compensation



FIGURES

Figure 7: Pneumatic compensator



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(16, 17) 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

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