

Bi-layer tablets: why special technology is required.
The Courtoy™ R292F and MODUL™ D tablet presses,
designed for quality bi-layer tablets.

Several pharmaceutical companies are currently developing bi-layer tablets, for a variety of reasons: patent extension, new therapeutic developments and marketing to name but 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 the best approach to producing a quality bi-layer tablet under GMP conditions, especially when high production output is also required.

Bi-layer tablets: 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:

- 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.

Bi-layer tablets: limitations of the single-sided press.

Various types of bi-layer presses have been designed over the years. The simplest design is a single-sided press with both chambers of the double feeder separated from each other. Each chamber is gravity- or forced-fed with a different powder, thus producing the two individual layers of the tablet. 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 bi-layer 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 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 tablets sampling and sample-transport to a test unit for in-line quality control and weight re-calibration.

() 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.*

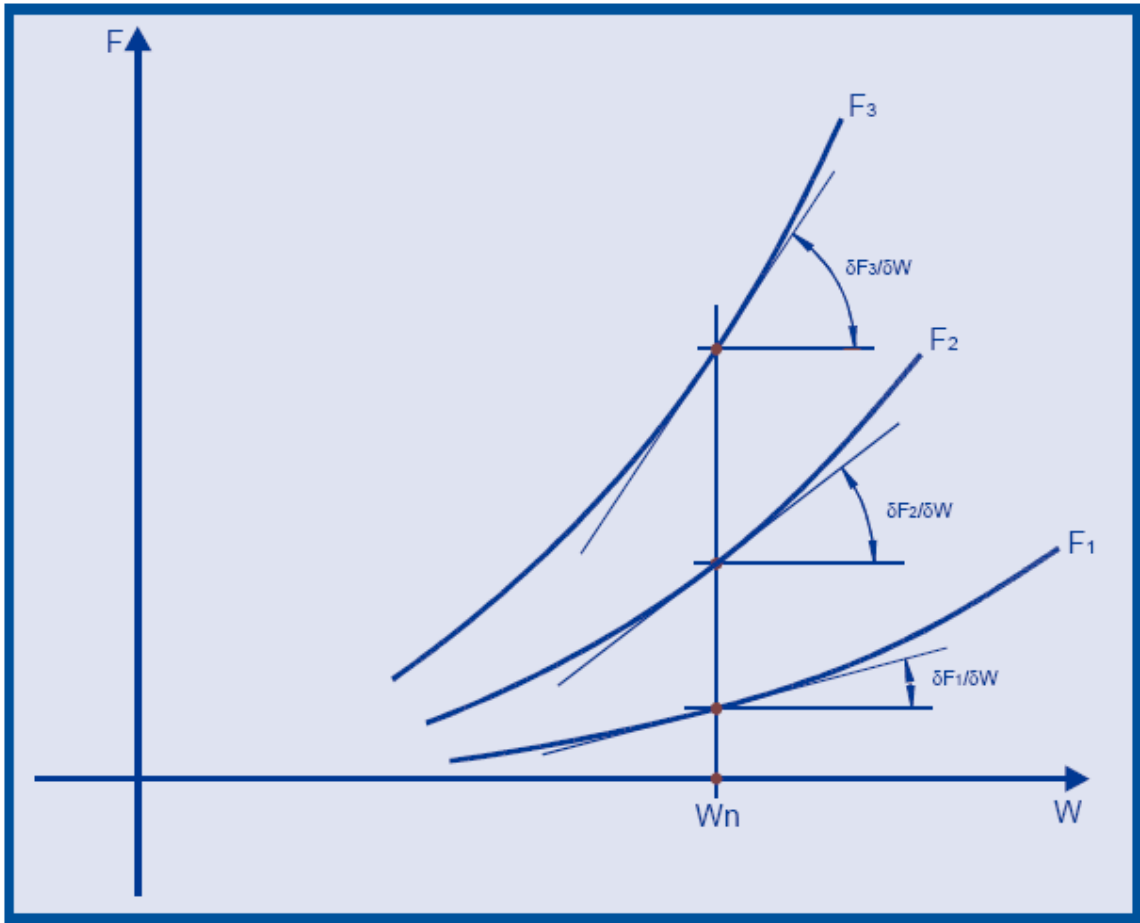
To eliminate these limitations, a double-sided tablet press is preferred over a single-sided press. A double-sided press offers an individual fill station, pre-compression and main-compression for each layer. In fact, the bi-layer tablet will go through 4 compression stages before being ejected from the press.

Bi-layer tablets: 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”.

The overall majority of 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.

Graphic 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'** (see below). "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 and MODUL™ D "bi-layer" tablet presses with 'displacement monitoring'.

Courtoy™'s double-sided tablet presses have been specifically designed and developed for the production of quality bi-layer tablets and provide:

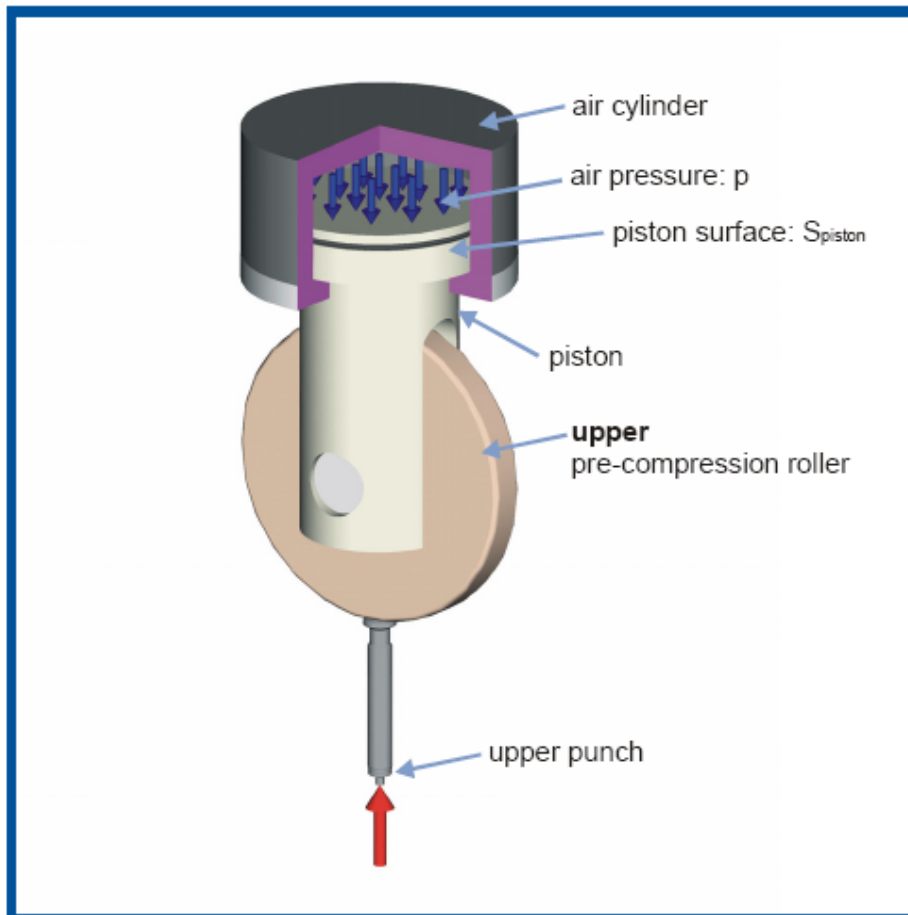
- 'displacement' weight monitoring/control for accurate and independent weight control of the individual layers
- low compression force exerted on the first layer to avoid capping and separation of the two individual layers
- increased dwell time at pre-compression of both first and second layer to provide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

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 pre-compression 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 bi-layer tablet, as explained above.

The 'pneumatic compensator'



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 [S_{piston}] is the constant force at which the piston – and consequently the roller – is pushed downwards against a fixed stop. The lower pre-compression 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, pre-compression 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 pre-compression assembly cannot exert a force above

$$F_{\max} = p \times S_{\text{piston}} \quad (1)$$

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, 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 F_{\max} . 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 pre-compression sections of the Courtoy™ R292F and MODUL™ D, resulting in a displacement value per pre-compressed (first) layer or bi-layer tablet.

It is easy to understand that

$$W = \rho \times S \times [\text{height of the pre-compressed powder slug}] \quad (2)$$

$$= \rho \times S \times [\text{PCH} + (2 \times \text{EqAr}) + d] \quad (3)$$

- 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 and not the final tablet density, but the density of the slug after pre-compression 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 re-formulated as follows:

$$W = \rho \times S \times [\text{PCH} + (2 \times \text{EqAr})] + \rho \times S \times d \quad (4)$$

where the following conditions apply:

- ρ is constant from tablet to tablet as the pre-compression force on each slug is the same: F_{\max} . 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

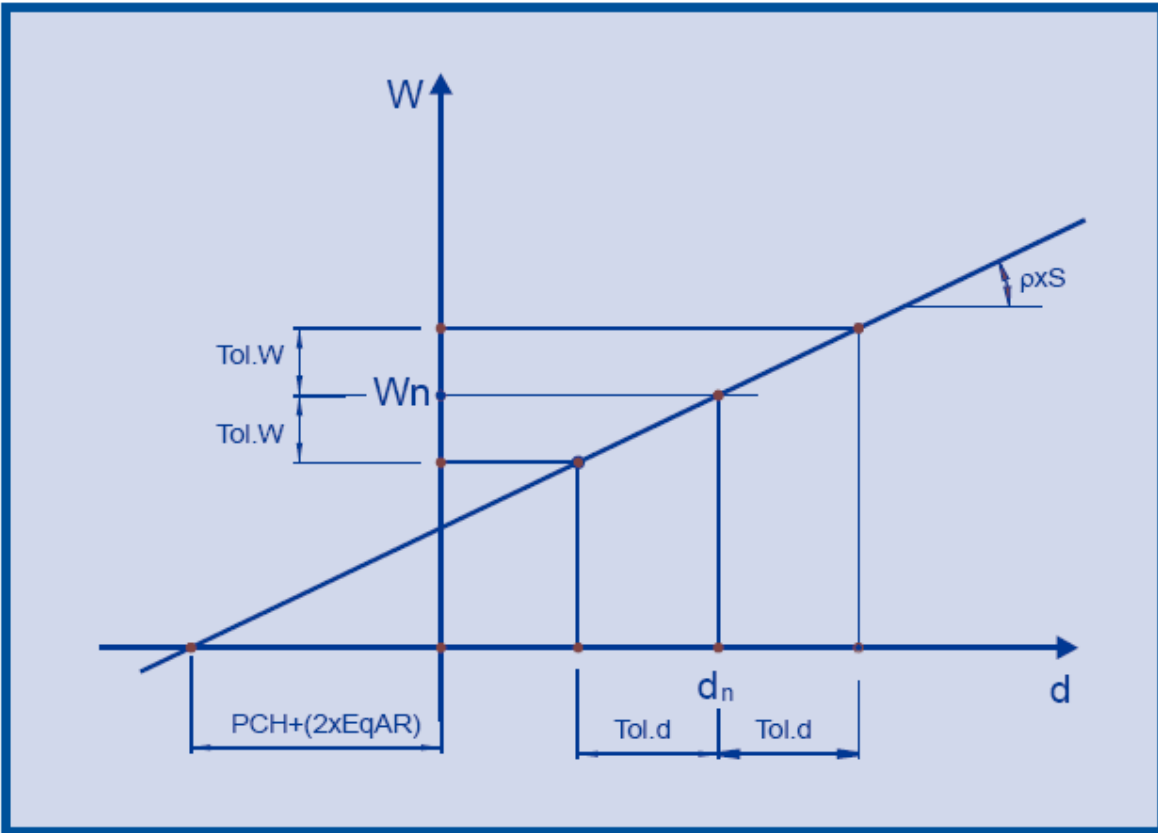
$$W = A + B \times d \tag{5}$$

$$\text{with } A = \rho \times S \times [PCH + (2 \times EqAr)] = \text{Constant} \tag{6}$$

$$\text{and } B = \rho \times S = \text{Constant} \tag{7}$$

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.

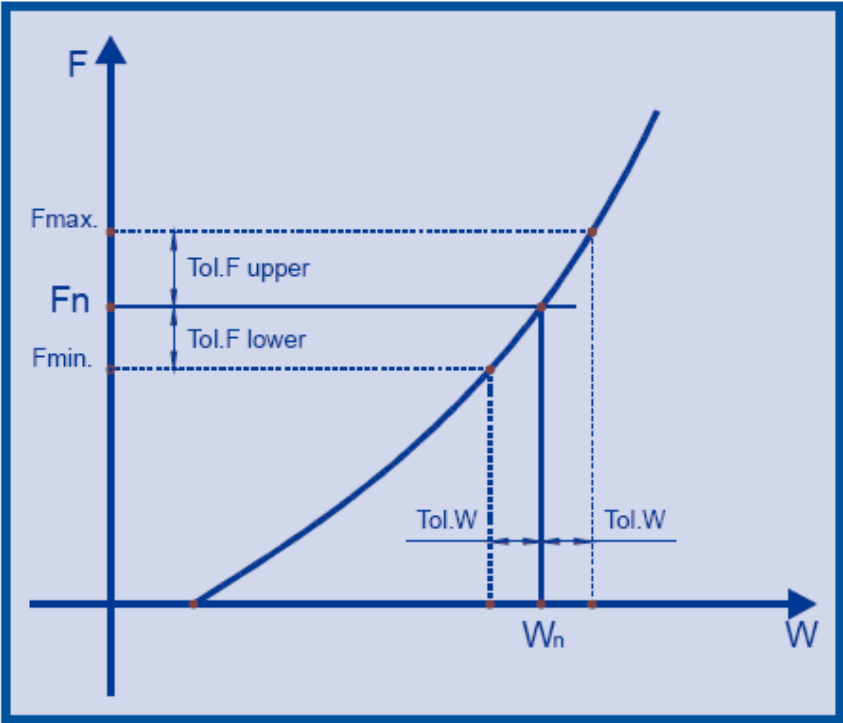
Graphic 2 - Weight versus displacement relationship



The above 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 $[PCH + (2 \times EqAr) + d]$, 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

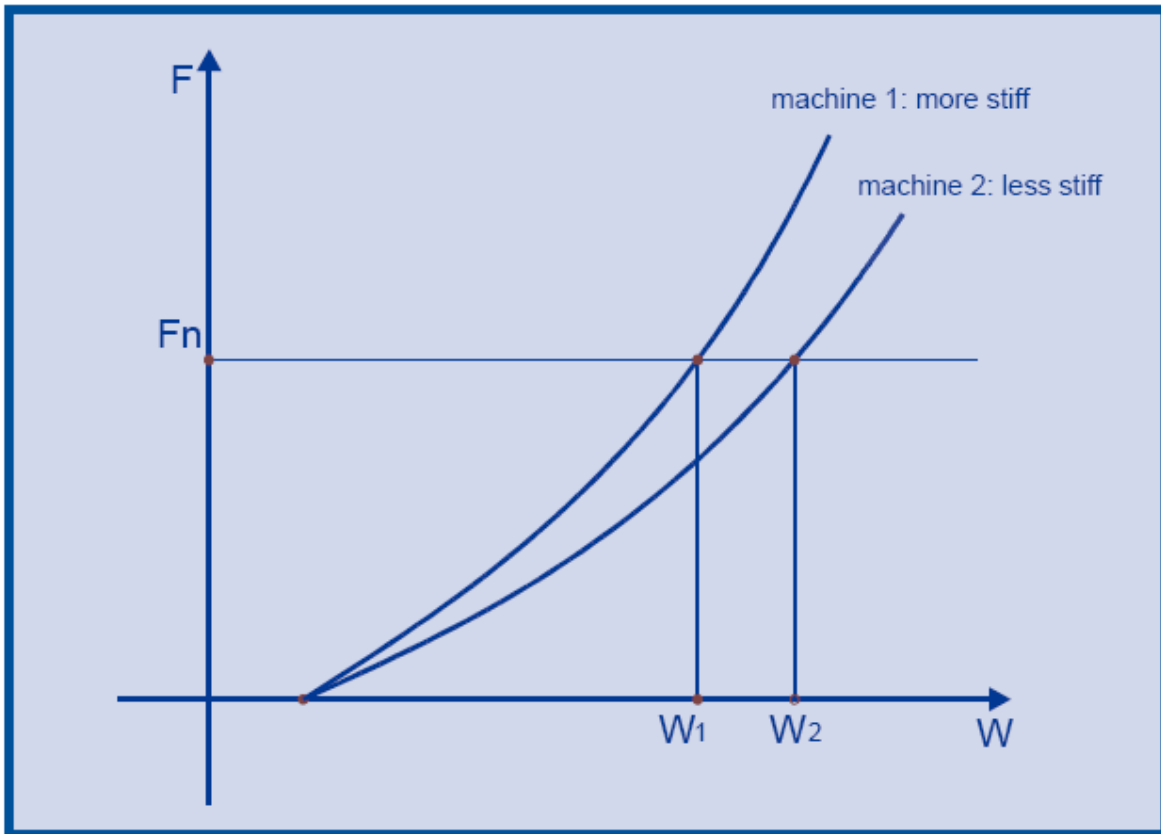
weight-versus-displacement graph. This is not the case with a ‘compression force’-controlled system, where the tolerance on the force varies with the working point on the graph. Moreover the upper and lower force tolerances are different, as can be seen from graphic 3.

Graphic 3 - Force tolerance as a function of Weight tolerance



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. Moreover, the variation in force / tablet weight varies with the rigidity of the complete system (i.e. tablet + tablet press), resulting in different force tolerance limits between various machines for the same tablet weight tolerance. It is clear that, in case of compression force control, simple transfer of force set point, force tolerance limits and compression height (i.e. distance between main compression rollers) is impossible, requiring parameter set-up per product and per machine.

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

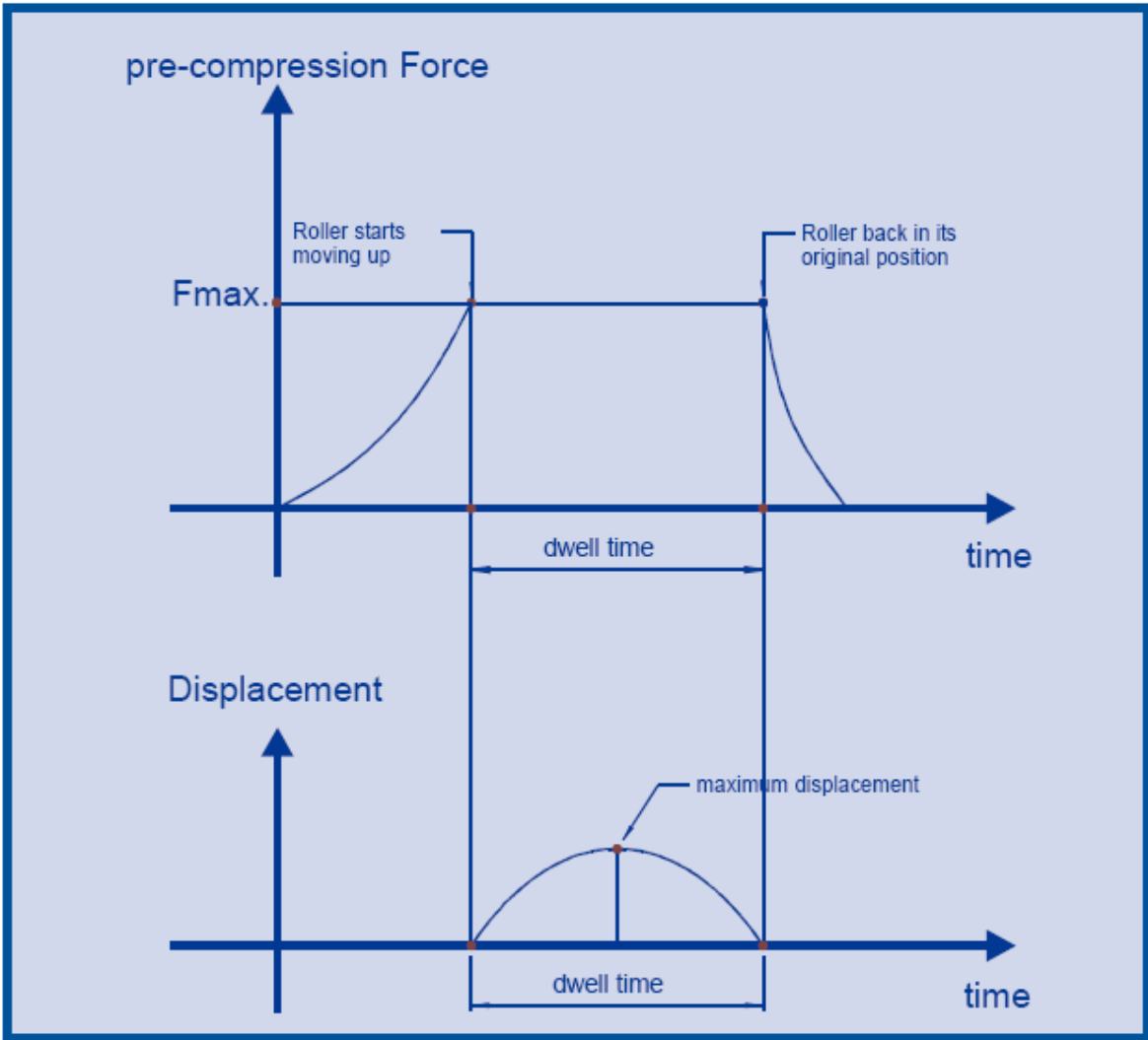


The stiffness-independence of the 'displacement' control system makes production exchange between displacement-controlled presses much easier, allows for more straightforward product scale-up, more flexible production, easier production transfer between different sites in case of a multinational pharmaceutical company.

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 pre-compression 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.

Graphic 5 - Force and Displacement profiles at pre-compression using air compensation



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 de-aeration of the powder and the re-arrangement 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. The PCH and pre-compression force can be set up so as to offer optimal dwell time. Once fixed, the control system automatically calculates and sets the tolerance on the displacement as a function of weight tolerance.

‘Displacement’ control and first- layer compression.

The main problem of a compression force-controlled press for first-layer compression, is its sensitivity $\delta F/\delta W$ 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

$$\delta d/\delta W = 1 / (\rho \times S) \quad (8)$$

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 bi-layer press using ‘air compensation’ on pre-compression 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 daN). 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 first-layer 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. The required level is set at the first-layer main compression station: the upper punch penetration in the die determines the overfill depth for the second layer. The position of the lower main compression roller determines the exerted compression force. This force should also be kept very low, in order not to affect interlayer bonding. Typically, the compression force in this first-layer main-compression station is only a few daN more than that of the first-layer pre-compression. Its sole purpose is to bring all first-layer slugs to the same thickness and the same depth in the die. The slug is then ready to receive the second layer.

After feeding the second layer into the die, the final tablet is pre-compressed and compressed to form the final bi-layer tablet. As the first-layer weight is already checked, the indirect measurement system in the second compression cycle is meant to control only the weight of the second layer.

The exerted compression force, once more appears to be of the utmost importance. As weight variations need to be monitored for the second layer only, the indirect measurement should be carried out under a pre-compression force, which is LOWER than the force under which the indirect measurement of first layer was carried out. If this is not the case, the first layer will be further compressed together with the second layer, and its weight will influence the measured signal. In this case, the measured signal will reflect the weight variation of the sum of both layers, instead of that of the second layer only. The correct way to solve this problem is once again to use an air compensator and to measure ‘displacement’ under constant force. This constant force being lower than the one used in the first pre-compression station.

The ‘displacement’ measured in this case, reflects weight variations of the second layer only, and is used to adjust the fill depth of the second layer and/or reject the final tablet if the rejection limits are exceeded.

An example of a real life situation will make this clear:

- pre-compression force Side A: 80 daN, i.e. low in order to avoid separation of the individual layers
- main-compression force Side A: 100 daN: i.e. only a few daN more, just to compress all 1st layer slugs to the same thickness
- pre-compression force Side B: 70 daN, i.e. lower than the 80 daN on side A
- main-compression force Side B: whatever force is required to make the final bi-layer tablet at the correct thickness and hardness.

The above explanation suggests what is crucial with regard to individual layer weight control on a bi-layer press. Whether the press is a single or a double-sided press, the final compression force exerted on the final bi-layer tablet is always higher than the compression force on first layer only. Otherwise both layers would not bond together. In the case of a compression force-control system, the force signal measured in this final station reflects not only variations in weight of the second layer, but also of the first layer as this first layer is further compressed in the final compression station. The use of the air compensator avoids this problem as this system measures displacement on pre-compression, where the air pressure on side B can be set at a lower level than the air pressure in the first pre-compression station (side A).

The Courtoy™ R292F and MODUL™ D - additional important features:

The R292F and MODUL™ D can be used for both single-layer double-output production and bi-layer single-output tableting. The presses are equipped with 'air compensation' on both pre-compression stations for 'displacement'-based tablet weight control as described above. However, Courtoy™'s double-sided presses have several extra features, specifically designed for the production of bi-layer tablets:

- a pneumatically driven ejection cam, allowing the sampling of first- layer tablets for in-line process control and automatic weight re-calibration. 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.
- several blow and suction nozzles are 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 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 and MODUL™ D. 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 in combination with reduced risk layer-separation risk can be achieved with the Courtoy™ R292F and MODUL™ D, especially appreciated when the weight of one of the layers is low compared to the weight of the other. 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 and MODUL™ D excellent bi-layer tablet presses.

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