Abstract: Pharmaceutical companies are currently developing bilayer tablet and studying the process feasibility with a special focus on production of quality bilayer tablets and compression technology 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. and to critically analyze the in-process quality bilayer tablets and compression technology 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. and to critically analyze the in-process parameters.

Key words: Bi-layer tablets, XM-12 bilayer tablet press, press operation, troubleshooting.

Introduction:
It should be realized that tablets rightly regarded as complex drug delivery systems and to trivialize their design, development and manufacture it is certain to invite significant problems at some stage in development or during product life. Some of the advantages of this type of tablet are co-presentation of incompatible medicaments, facilities repeat or prolonged action properties, renders more difficult to copy or counterfeit and gives a distinct appearance. From the manufacturing point of view it is better to use only simple tablet shapes, low compression force and of course must ensure no cross contamination of the layer.

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.

Bi-layer tablets: Limitations of the single sided press:

Various types of bi-layer press have been designed over the years, the simplest design is a double feeder separated from each other. Each chamber is gravity or forced-fed with a different powder, thus producing the two individual layers to 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.
- Very short first layer – dwell time (*) due to the small compression force side A: 80 daN: i.e. low in order to avoid separation of the individual layer.
- Very difficult first-layer tablet sampling and sample transport to a test unit for in-line quality 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 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.

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 layer.
- 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.
Advantages: Flexible concept
- 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 the 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 variation 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 use of courtoy R292F for quality bilayer tablet: The “bi-layer tablet press” with displacement monitoring:

This double sided tablet press has been specifically designed for production quality bilayer tablet and provides displacement weight monitoring/control for accurate and independent weight of the individual layer. Low compression force extended on the first layer to avoid capping and separation of the two individual layers. Increased dwell time at the pre-compression of both first and second layer to provide sufficient hardness at maximum turret speed, maximum prevention of cross contamination between the two layers, clear visual separation between the two layers and maximum yield.


Fig: Pneumatic Compensator

XM-12: A small bilayer press:

**Advantages: Flexible concept**
- Bilayer execution with single layer conversion kit
- Exchangeable turret
- Turret sizes for product development, scale up and mid-range production
- Full production capability in a scale up machine.
- Fast and easy change over
- Internal turret lift device for extreme simplicity in turret removal and installation
- Clean compression zone with quick-disconnect zone.

**Design Advantages**
- Small scale bi-layer capability

**Full instrumentation**
- Touch screen control
  - Integrated control cabinet
  - Press force control and single tablet rejection capability
  - Comprehensive data collection and analysis capability
  - Real time display and batch data documentation
  - Identical control and software concept as in KORCH production machines

The XM 12 bi-layer tablet press features a retractable second layer feeder that permits automated first layer sampling at production speeds. The first layer sampling capability also offers a hardening feature in which the main compression station will automatically compress the first layer tablet for in-process measurement. The two feeders are zero clearance and are configured with an integrated dust extraction manifold, which cleans the die table and completely eliminates any potential for cross-contamination.

**Bi-layer Applications**
- Small scale Bi-layer
- 5 kN first layer tamping force
- 40 kN precompression force
- 80 kN main compression force
- Single layer conversion capability

**Instrumentation:**
- Tamping force
- Precompression force
- Main compression force
- Ejection force

**Single layer applications**

**Single layer conversion:**
- Minute conversion type
- High speed single layer capability (120 rpm)
- 40 kN precompression force
- 80 kN main compression force
- Exchangeable turret
- Mix-turret

**Instrumentation:**
- Precompression force
- Main compression force
- Ejection force

**Operation of compression machine for Bilayer tablets:**

**Removal of near ejection cam**
Take down the lower pressure cam to the maximum possible extent by rotating the thickness adjustment knob in clockwise direction. Separate the lower roller bracket from the thickness adjustment assembly by pushing the roller bracket in the upward direction. Remove the two hexagonal Ellen screws from the ejection cam and pull out the ejection cam.

**Fixing of feed frames**
Use separate feeders, which are designed for bi-layer tablets of feed frame.
Fix one feed frame in the front side such that the first layer powder shall be compressed. Presume that the excess powder from this feed frame shall come out from its slot and shall be collected in a SS powder collection box. Fix the other feed frame on the other side for second layer such that the powder will be re-circulated around the corner of the turret and will again merge with the same blend.

Fixing of vacuum to the feeders & dust collection system
Inter connect the silicon tubes between feeder nozzles and dust collection system. Connect the flexible hosepipes between dust collection unit, which is attached to the machine and the extended suction system. Use the hoppers, which are intended to use for gravity feeders.

Operation of the bi-layer compression machine:
Start the suction system. Load the blend pertaining to the first layer in the front hopper. Start the machine in inch mode and check for any abnormal sound. Keep low RPM and engage the clutch. Adjust the hopper flow such that material is not over flowing from the feed frame. Collect the tablets and Check the weight. Adjust the weight by using the thickness adjustment knob. Keep in pressure in lower limit. Load the blend pertaining to the second layer in another hopper. Adjust the weight of second layer and thickness to the bilayer. Continue the compression after setting the physical parameters. To check the individual weight of two layers lift the layer separating lever to upward direction hold for less than one minute, the two layers will be separated and check the weight of the first layer.

Recent advancement in the design of Tablet Compression:
Recent advances in the design of tablet compression equipment have resulted in higher-efficiency machines designed to optimize compression efficiency, minimize tablet wt. variations and provide greater flexibility, allowing the production of a greater range of products. However, modern machines provide greater accuracy as follows.
- Improved material feed systems
- Improved cam design and material of construction.
- Multistage compression.
- Isolated design for quick cleaning and change over.
- Improved force measurement techniques
- Introduction of electronics to provide force control
- Integration of online weight, thickness and hardness test units providing weight feed back control to the force control units
- High speed single tablet sorting to reject out of specification tablets

Troubleshooting
A proper understanding of material’s compression characteristics combined with knowledge of tablet compression equipment allows efficient troubleshooting of production problems. Although there is no substitute for robust granulation, a product can be optimized by examining all of the different machine factors that can affect performance. By applying a variety of processing problems can be eliminated.

Tablet Weight variation
Excessive tablet weight variation can be caused by a variety of factors. For many granulations, the inherent poor flow characteristics of the material may be the rate-limiting step, and simply slowing down the machine may reduce weight variation. The tightness of hold down cam should be examined to verify that it is not excessively worn and is holding the lower punch tight against the dosing cam. If the previous product resulted in tight lower punches, premature wear may have occurred on this cam, increased wt. variation. The condition of the lower-punch pull down cam is examined to verify it is overly worn and that it does drop the lower punch to pull the material in the die cavity below the die table surface. Both the condition and position of the excess material stripper should be examined to ensure that it sits snug and level in the die table surface for complete scrape-off. Different types of feeder paddles can be to promote flow (e.g. Round feeder paddles are used for material that exhibit bridging), the feeder speed should be optimized to minimize force and weight variation. The best fill cam size is that where the fill depth is centered in its range. A minimum amount of material recirculation is necessary to provide steady flow and fill. Too much recirculation can result in material back up and reduction in the granulation particle size. The recirculation channel must be free of obstructions (i.e. broken tablets). If large tablets are being produced requiring more fill depths, an insertion depth should be used. Otherwise, as the punches pans from a deep fill to a shallow insertion depth, the uncompressed granulation will be pushed from the die cavity resulting in material loss.

Product Yield
Product yield can be affected by a number of factors. Unfortunately, yield problems are not noticed until after the loss occurs. However, by paying attention to the following areas during setup, these problems can be minimized. Excess material loss can be avoided by ensuring that the excess material stripper is flush against the die table. Otherwise the material is rushed into the dust extraction system. The feed frame height should be maintained between 0.05 and 0.1 mm (0.003-0.004 in). For very fine particle granulation, clearance should be reduced to 0.025 to 0.05 mm (0.001-0.002 in) to fill cam size should be reduced to minimize overfilling and material recirculation. Material re circulation channel should be minimal. As more material is re circulated, the likelihood for loss is greater. The piece guiding the material from the re circulation channel to the feeder must be properly positioned. If the insertion depth is too shallow relative to fill depth, material will be pushed out of the die and lost to the dust extraction system. Excessive feeder speeds caused excess material re circulation and increases material loss. It may be necessary to reduce press speed. As the press speed is increased the turret from both the re circulation channel and the die cavity.

Low Hardness
Tablet hardness is affected by many factors. For troubleshooting purposes it should be determined if low hardness is due to capping or of non-compressibility. For formulation that exhibits low hardness without capping, the following guidelines are helpful:
- For multistage compression, a machine should be equipped for both pre compression and main compression with large diameter rollers.
- The ratio of pre compression to main compression should be adjusted. For tablets that exhibit no capping problems, both pre compression and main compression force should be maximized.
- Press speed is reduced in order to increase total compression time.
- Formulation sensitive to lubricant levels may exhibit low hardness due to over mixing in the feeder. If the formulation contains a significant quantity of magnesium stearate or there is a shift in particle size thus extending the lubricant unevenly, over mixing can reduce the tablet hardness. In this case the feeder should be reduced to a minimum.

Capping and Lamination
Tablet capping and Lamination typically create the most difficult problems, due to a variety of causes. Identification of the cause often leads to the solution. The basic concepts to alleviate these problems center or minimizing elastic behavior while promoting plastic deformation. Depending on the exact nature of the problem this can be achieved from a formulation perspective by modifying the formula to incorporate a plastically deforming matrix,
by adding component to enhance level. Alternatively, from a machine perspective, the following guidelines should be followed:

- The rate of force application should be reduced by applying the compression force as gradually as possible. Lowering the press speed or using a machine with a small pitch circle diameter can accomplish this.
- The ratio of pre compression to main compression should be modified and the pre compression is applied as gradually as possible followed by main compression. A pre compression force of high can be harmful.
- The effect of reducing the compression force should be evaluated. In many circumstances, over compression of a granulation will result in failure.
- A machine with large compression roller diameter should be used to minimize the rate of force application.
- Die cavity wear must be investigated and the condition of the die cavities examined. If the dies are much worn, Ship-stick behavior may occur during tablet ejection resulting in tablet failure.
- Curled or damaged punches promote tablet capping. Under these conditions the tools should be rewash or replaced.

### Picking and Sticking
Tablet picking and sticking problems are typically related to formulation issues. However, in small scale manufacturing these problems frequently do not occur. Regardless, once a product is approved, it is difficult to make significant formulation changes. To minimize these problems the following areas should be considered.

### Heat of compression
Excessive heat generation during compression will increase the picking tendency of a low melting material. Use of cooling system for the compression section or lower mechanism section may be helpful.

### Press Speed
Lowering press speed and compression force reduces heat generation. Lower press speeds extend the contact time of the material and the punch face.

### Precompression Force
Elimination of pre compression may prevent picking. For examples, some materials pick if the compression force is too low. Therefore, application of pre compression at low force may result in tablet picking.

### Tool condition
The condition of press tooling should always be evaluated when picking occurs. Polishing the punches and application of various coatings to the tools may help to eliminate picking for certain materials.

### Startup conditions
Startup should always be close to optimum conditions to prevent fouling the punch faces. If maintaining a force above a minimum is necessary to prevent picking, starting up near optimum conditions of compression force prevents initial picking.

### Tablet Stripper
The point of impact of the lower punches should be repositioned to the tablet stripper. Upper many circumstances the stress impact on the stripper can cause failure and sticking in Logos.

### Tablet Jams and chipping
Tablet Jams and chipping at the stripper reduce tablet quality and may contaminate the feeder resulting in weight variation. High-speed machines typically have greater problems than slower machines. Focusing on the tablet stripper and lower punch ejection height solves these problems.

#### Scraping off weight
For many tablet types (e.g., deep conceive tablets) the height of the lower punch at the point of scrape-off must be increased to ensure that the tablet is removed completely from the die when it impacts the tablet stripper.

#### Modified tablet stripper
For shaped tablets, a modified stripper that removes the tablets from the die table quickly prevents tablet back up and breakage.

#### Height of plastic cover
If the tablets exhibit layering or shining the height of the plastic cover should be lowered to just accommodate one tablet between the cover and the die table.

### Tablet stripper and Punces
The impact point of the stripper can cause chipping. Both the height and position the tablet stripper must be checked. Damages punches must be replaced or repaired.

### Air Assist
If tablet jams cannot be eliminated the stripper, an air assist blow-off at the tablet may solve the problem.

### Static Eliminator:
In the production of lighten height tablets in a low humidity environment, static electricity may cause tablet back up. In this case, installation of a static elimination will improve tablet discharge.

## Latest advancement in the field of bilayer tableting technology:

### R292f Bilayer tablet press:
This double –sided rotary tablet press for single and double layer tablets having the following advantages:

- Automatic double layer rotary press for single layer tablet production
- High volume production as single layer/double output
- Medium volume production as double layer/single output
- Extremely fast change over from single layer to double mode
- GMP modular design with isolated compression zone
- Fast change over design
- Cooling unit fitted to bottom module
- Unique air compensator system at pre-compression for extended dwell time
- Constant level powder in feed system
- Double rotary paddle feeder with independent drive for each paddle
- Forged steel, nickel plated turret
- Hard chromium plated die table
- Replaceable punch guide bushings
- ITS or Multi-control 4 control system

### CONCLUSION:
Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablets. 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 results in separation and hardness problems when compressing bilayer tablets. Whenever high quality bilayer tablets need to be produced at high speed, use of an ‘air compensator’ in combination with displacement control appears to be the best solution. It is a new technology of tablet formulation and dosage form and further improvement in this field is appreciable.

REFERENCES
14. www.korch.com
15. www.geapharmasystems.com

Source of support: Nil, Conflict of interest: None Declared