AN UPDATED REVIEW: MULTILAYERED TABLET

Nirmal Shah*, Jainam Shah, Punit Hadiya

Rofel Shri G. M. Bilakhia College of Pharmacy, Namdha road, Vapi- 396191.

ABSTRACT

The Multilayer system is a unique drug delivery device; the system usually provides nonlinear release profile. The multi-layered matrix system overcomes inherent disadvantages of non-linearity associated with diffusion controlled matrix devices by providing additional release surface with time to compensate for the decreasing release rate. Multilayer tabletting is getting increasing attention from a variety of industries 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. While general tablet manufacturing principles remain the same, there is much more to consider because making multi-layer tablets involves multiple-often incompatible products, additional equipment and many formulation and operation challenges. An attempt has been made in this review article to introduce the readers to the various aspects of multi-layered tablet technology and various applications in current research.

Key words: Multilayered tablet, bi layer tablet, tablet press, GMP requirements.

INTRODUCTION

➤ Pharmacological therapies either require or benefit from the administration of drugs in a sequential manner. This can be done by a regimen in which the patient follows a prescribed time schedule. The patient noncompliance and scrupulous adherence to a schedule requires the assistance of a medical professional. Solid oral multiple drug formulations have therefore been developed. These combined formulations function from a single dosage form, which simplifies the therapy and reduces or eliminates the chances of improper administration.

➤ For chronic diseases controlled drug delivery system have been available separately, a system that can deliver drug at a prolonged rate may ensure improved patient compliance and reduce the problems associated with multi-drug therapy. In addition to improved patient compliance, as a once a day, it improves the safety profile and activity of drugs exhibiting short biological half-life [1, 2].

➤ Multilayered systems (bilayered, triple-layered, quadruple-layered, etc.) are becoming increasingly recognized as controlled-release drug delivery systems.
Multilayered tablets have demonstrated promise, possessing various benefits, namely the ability to prevent interactions between drugs and excipients; and by providing an array of release profiles in one delivery system of either the same or different drugs, treatment for conditions that require a regimen of more than one drug, immediate drug release using a disintegrating monolithic matrix in order to achieve an initial peak in plasma drug level, delayed drug release using an eroding monolithic matrix which may deliver another active drug to a different part of the gastrointestinal tract, providing controlled drug release instituting a swellable monolithic matrix and better control and regulation of release profiles by retarding initial burst release and achieving zero-order kinetics \(^ {[3, 4]}\).

**Multilayer tablet dosage forms are designed for variety of reasons:**

1. To modify the total surface area for active pharmaceutical ingredient layer to achieve modified release.

2. To separate incompatible active drug from each other, to control the release of each drug layer \(^ {5, 6} \).

3. To overcome multiple disease condition by incorporating more than one active drug in separate layer in appropriate dose.

4. To administer fixed dose combinations of different active drugs, for novel drug delivery system, prolong the drug product life cycle and other drug delivery system such as mucoadhesive delivery system and floating delivery system \(^ {7-10} \).

**Advantages:**

1. They are unit dosage form so they offer greatest dose precision and least content variability.

2. Easiest and cheapest for packaging.

3. Cost is lower compare to other oral dosage form.

4. Product identification is easy.

5. Suitable for large scale production.

6. Objectionable odour and bitter taste can be masked by coating techniques.

7. Greatest chemical and microbial stability compare to all oral dosage form.

**Disadvantages:**

1. Manufacturing steps are increased.
2. Difficult to swallow in case of children and unconscious patients.
3. Some drugs resist compression into dense compacts, owing to amorphous nature and low density character.
4. Difficult to formulate by direct compression technique when the dose of drug is high.

Figure 1: It shows simple tablet

Figure 2: It shows Bilayer tablet

Figure 3: It shows Trilayer tablet

**Multilayer tablet:**

- Multi-layered systems consist of a hydrophilic matrix layer containing either or only one active ingredient and one or more impermeable or semi permeable layers with other drug/s incorporation.
- The presence of the barrier layers modifies hydration, swelling rate, lag time for diffusion, dissolution, etc.
- By varying the number of layers and geometry of devices provide different drug release.
These multilayered formulations may swell, gel or erode to modulate drug release.

- The controlling effect of a polymer material on drug release depends on its physico-chemical properties and the embedding procedure during the preparation of the system, which may be due to the polymers, its molecular weight, nature of monomer, type of substitution, degree of substitution and viscosity \[11-16\].

These systems are generally having two approaches,

a. Swellable barrier technique;

b. Erodible barrier technique. (Following figure)

---

**Figure 4: It shows Types of Multi Layered Systems**

- The layering patterns are of various types as shown in following figure, viz. single face coated, double face coated, side coated, face and side coated tablets.

- Layered tablets are used for zero order release; combination therapy as well for multiple rate delivery of the drug from formulation.
Figure 5: It shows Types of layering patterns

Bilayer tablet:

- Bilayer tablets are composed of two layers of granulation compressed together.
- Two-layer tablets require fewer materials than compression coated tablets weigh less and may be thinner.
- Monograms and other distinctive markings may be impressed in the surfaces of the multilayer tablets.
- Coloring the separate layers provides many possibilities for unique tablet identity.
- Separation of the layers prior to assay may simplify the analytical work.
- Since there is no transfer to a second set of punches and dies, as with the dry-coating machine, odd shapes (such as triangles, squares, and ovals) present no operating problems except for those common to keyed tooling [17].
- Several pharmaceutical companies are currently developing bilayer tablets, for a variety of reasons viz. patent extension, therapeutic, marketing to name a few.
- Various problems are associated with the formulation of bilayer tablets, such as layer-separation, insufficient hardness, inaccurate individual layer weight control, cross contamination between the layers, reduced yield etc.
- To overcome these problems, development and production of quality bilayer tablets need to be carried out on purpose built tablet presses [18].

Challenges in bilayer manufacturing [19]:

- Delamination: Tablet falls apart when the two halves of the tablet do not bond completely. The two granulations should adhere when compressed.
Cross-contamination: When the granulation of the first layer intermingles with the granulation of the second layer or vice versa, cross-contamination occurs. It may conquer the very purpose of the bilayer tablet. Proper dust collection goes a long way toward preventing cross contamination.

Cost: Bilayer tableting is more expensive than single-layer tableting for several reasons. First, the tablet press costs more. Second, the press generally runs more slowly in bilayer mode. Third, development of two compatible granulations is must, which means more time spent on formulation development, analysis and validation.

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

These factors, if not well controlled/optimized, in one way or another will impact the bilayer compression and the quality attributes of the bilayer tablets. Therefore, it is critical to obtain an insight into the root causes to enable design of a robust product and process.

Physical parameters of Bi-layered tablets [20]:

1. Size and shape:
   - Size is limited by the capacity of the machine with the total thickness being the same as for a single layer tablet.
   - Many shapes other than round are possible and are limited only by the ingenuity of the die maker.
   - However deep concavities cause distortion of the layers. Therefore standard concave and flat faced bevelled edge make for the best appearance, especially when layers are of different colours.
   - Punches with bevelled edges or concave faces will make the top and bottom layers. Flat faced tooling will produce the equal thickness of the layers, but unfortunately the edges of the tablets tend to clip readily.

2. Layer thickness:
   - This can be varied with a reasonable proportion within the limitations of the tablet press. Thickness depends on the fineness of the granulation.
Figure 6: It shows various types of punches used for multilayered tablet 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 tablet. 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 layers.

**Bilayer tablets: Quality and GMP requirements** \[18\]:

To produce a quality bilayer 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 bilayer tablets.
- Providing sufficient tablet hardness.
- Preventing cross-contamination between the two layers.
- High yield, accurate and individual weight control of the two layers.
- Producing a clear visual separation between the two layers.

**Types of bilayer tablet press** \[23, 24\]:

**A.** Single sided tablet press

**B.** Double sided tablet press

**C.** Bilayer tablet press with displacement monitoring.

**A) Single-sided press:**

- 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 (pre and main-compression) steps.

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.

Limitations of 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 roller, possibly resulting in poor de-aeration, capping and hardness problems.
- Very difficult first-layer tablet sampling and sample transport to a test unit for in-line quality control and weight recalibration.

Dwell time:

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.

B) Double-sided tablet press:

- A double-sided press offers an individual fill station, pre-compression and main compression for each layer.
- 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.
- Measured peak compression force (under constant thickness) is the signal used by the control system to reject out-of-tolerance tablets and correct the die fills depth when required.

Limitations of compression force controlled system:
A compression force-controlled system requires a minimal compression force of several hundreds of daN.

However, many bilayer formulations require less than 100 daN to compress first layer 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 bilayer tablet and separation of the two layers.

At higher production speed, the risk of separation and capping increases but can be reduced by sufficient dwell time at compression stages.

C) Bilayer tablet press with displacement monitoring:

The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied pre compression force. This double-sided tablet press has been specifically designed and developed for the production of quality bilayer 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 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 – maximized yield.
Figure 7: It shows Bilayer tablet manufacturing.
Bi-Layer Application [25]:
The XM 12 features an exchangeable turret capability to permit a single machine to run all press tool sizes to provide maximum flexibility and versatility. An internal lift arm eliminates the cost and space requirement of a large external turret removal device.

- Single layer conversion kit adds yet another dimension of flexibility.
- Single Layer Conversion.
- 30 Minute Conversion Time.
- High Speed Single-Layer Capability (120 RPM).

Advantages:

- Flexible Concept.
- Bi-Layer execution with optional single-layer conversion kit.
- Exchangeable turret.
- Turret sizes for product development, scale-up, and midrange production.
- Full production capability in a scale up machine.
- Self-contained, fully portable design.
- Fast and Easy Changeover.
- Internal turret lift device for extreme simplicity inturret removal and installation.
- Clean compression zone with quick disconnect design.

Applications of Bi-layered tablets [20]:

- Bi-layer tablets are mainly used in the combination therapy.
- These are used to deliver the loading dose and sustained dose of the same or different drugs.
- These are used for bi-layer floating tablets in which one layer is floating layer another one is immediate release layer of the drug. These are used to deliver the two different drugs having different release profiles.

Various aspects used in the bi-layered tablet [26]:

1. Floating drug delivery system-
   These are designed to have a low density and thus float on gastric contents after administration until the system either disintegrates or the device absorbs fluid to the point where its density is such that it loses buoyancy and can pass more easily from the stomach with a wave of motility responsible for gastric emptying.
The bilayer tablet is designed in such a way gives the immediate dosing of the drug which gives faster onset of action while other layer is designed as a floating layer which floats in the stomach.

**Disadvantages:**

- It may not have the controlled loss of density alternatively required for it to eventually exit from the stomach.
- These are not applicable to higher dose levels of highly water soluble drugs where large amounts of polymer is needed to retard the drug release.
- The performance of floating formulation may be posture dependent.

2. **Polymeric Bioadhesive system:**

These are designed to imbibe fluid following administration such that the outer layer becomes viscous, tacky material that adheres to the gastric mucosa/ mucus layer. This should encourage gastric retention until the adhesive forces are weakened. These are prepared as one layer with immediate dosing and other layer with bioadhesive property.

**Disadvantages:**

The success seen in animal models is not translated to human models due to differences in mucous amounts. The mucous layer in humans would appear to slough off readily, carrying any dosage form with it. Therefore, bioadhesive dosage form would not appear to offer a solution for extended drug delivery.

3. **Swelling system:**

These are designed to be sufficiently small on administration so as not to make ingestion of the dosage form difficult. On ingestion they rapidly swell or disintegrate or unfold to a size that precludes passage through the pylorus until after drug release has progressed to a required degree. Gradual erosion of the system or its breakdown into smaller particles enables it to leave stomach.
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[^27]: Standard procedures are followed as described in the official books.

5. Friability[^27]: 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:

\[
\% \text{ Friability} = 1 - \left( \frac{\text{loss in weight}}{\text{Initial weight}} \right) \times 100
\]

6. **Hardness (Crushing strength)** [28]: 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. 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 tablets:

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.

Recent Developments in the Field of Bilayer Tablets:

The introduction of bilayer tablets into the pharmaceutical industry has enabled the development of pre-determined release profiles of active ingredients and incorporation of
incompatible active ingredients into the single unit dosage form. Large number of work has been done in this field.

**Various techniques used for multilayered tablet:**

1. Duredas
2. Geomatrix technologies
3. OROS\textsuperscript{\textregistered} push pull technology
4. L-OROS tm technology
5. EN SO TROL technology
6. Duros
7. Geminex
8. PRODAS
9. Erodible molded multilayer tablet.

**CONCLUSION**

Multilayer tablets offer an excellent opportunity for manufacturers to separate themselves from their competitors, improve their products’ efficacy, and protect against impersonator products. Multilayer tablet quality and GMP requirements can vary widely. This explains why many different types of presses are being used to produce multilayer tablets, ranging from simple single-sided presses to highly sophisticated machines. When a quality bilayer tablet needs to be produced in conjunction with accurate weight control of both layers, compression force-controlled presses are clearly limited because of their insufficient sensitivity and hence lack of accuracy at low compression forces required to secure interlayer bonding. Such problems become even more apparent when the tableting speed is high or increased. Accurate individual layer weight monitoring/control at high speed and in combination with reduced layer separation risk can be achieved with the displacement weight control system based presses.

**REFERENCES**


For Correspondence:
Nirmal Shah
Email: nirmalh_shahvapi@yahoo.com