BILAYER TABLET: A PROMISING DOSAGE FORM WITH DESIGNING CHALLENGES

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ABSTRACT

Bilayer tablet is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. Bilayer tablet is improved beneficial technology to overcome short coming of single layer tablet. Bilayer (and multilayer) tablets are gaining more acceptances among brand and generic products due to advanced delivery strategies, patient compliance and combination therapy. Bilayer tablet is also suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release and other is sustained release. In this article we review the state-of-the-art of bilayer tablet technology, highlighting the main advantages of bilayered oral dosage forms while incorporating current challenges and advances encountered during manufacturing. The available manufacturing equipment for bilayer tablet production is also described briefly.

KEYWORDS: Tablet technology, bilayer tablets, compaction pressure.

INTRODUCTION

Despite major developments in drug delivery, oral route still remains most preferred route for drug administration among patients and clinicians. Among the dosage forms administered orally, tablets and capsules, currently account for well over two third of the total number and cost of medicines produced all over the world.[1,2] In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form has increased in the pharmaceutical industry, promoting patient convenience and
compliance. But conventional dosage form are accused of repetitive dosing and unpredictable absorption window that cause wide range of fluctuation in drug concentration in the blood stream and tissues with subsequent undesirable toxicity and poor therapeutic efficiency. Hence multi-layer tablet dosage forms/ bilayered were designed for variety of reasons; to control the delivery rate of either single or two different active pharmaceutical ingredient(s) (API), to separate incompatible APIs from each other, to control the release of API from one layer by utilizing the functional property of the other layer (such as, osmotic property), to modify the total surface area available for API layer either by sandwiching with one or two inactive layer for modified release, to administer fixed dose combinations of different APIs, prolong the drug product life cycle, buccal/mucoadhesive delivery systems, and floating tablets for gastro-retentive drug delivery.

Bi-layer tablets require fewer materials than compression coated tablets weigh less and may be thinner. 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.

ADVANTAGES OF THE BILAYER TABLET DOSAGE FORM

1. They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and least content variability.
2. Patient compliance is improved due reduced frequency and lesser number of dosage unit to be taken.
3. Economical, versatile and flexible.
4. Bilayer tablets can be designed in various modified / novel drug delivery systems like mucoadhesive, floating, chronotherapeutic and combined dosage form for extended and immediate release.
5. Objectionable odour and bitter taste can be masked by coating technique.
6. Suitable for large scale production.
7. Chemical and microbial stability of overall oral dosage form with greatest precision and least variation in content uniformity.
8. Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.
9. Easiest and cheapest to package and strip.
10. Separation of incompatible components is possible.

**DISADVANTAGES OF BILAYER TABLET DOSAGE FORM**\(^{[5,11]}\)

1. Adds complexity and bilayer rotary presses are expensive.
2. Lower production yields than single layer tablets.
3. Imprecise individual layer weight control, Insufficient hardness, layer separation.
4. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
5. Cross contamination between the layers.
6. Difficult to swallow in case of children and unconscious patients.

**Types of Bilayer Tablets**\(^{[4,10]}\)

**Homogenous Type**

Bilayer tablets are preferred when the release profiles of the drugs are different from one another. It allows designing and modulating the dissolution and release characteristics. This are prepared with one layer being immediate release and other layer is designed to give second dose or extended release.

**Heterogenous Type** Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances.

**Principles and considerations of bi-layer formulation**\(^{[12]}\)

The better flowing formulation is generally selected as the first layer, because the fill of the first layer will determine the weight and fill control of the second or subsequent layers.

Optimization of the first layer tamping force, main compaction force and lubrication: The first layer tamping force should be just sufficient for some densification or to make space for the second layer filling. The amount of elastic and plastic deformation, caused by first layer compaction force has a significant effect on the strength of the interface. The strength of the interface decreases with the increase in the first layer compaction force. Since the first layer formulation is subjected to double compression in bi-layer tableting, typically the more compactable material is chosen to be the first layer. In addition to considerations of tablet formulations like selection of plastic, brittle, and other desirable components, it is preferable to formulate layers with similar properties and compactibility to increase success in compression and layer adhesion. Process-related factors like compaction pressure and
Tableting speed can influence dwell time and strength of the interface adhesion. The balance between efficiency of high speeds and yield of good tablets can be achieved with reasonable compression dwell times. Lubricant concentration in the formulation can also influence the adhesion strength of the layers.

**Compression cycle**

The production of a bi-layer tablet involves double compression cycle:
- the first layer powder is fed into the die, the quantity of powder is determined by the position of the lower punch inside the die by using a dosing cam.
- precompression is applied to the first layer.
- the second layer powder is then fed to the die, the quantity of powder is determined by the position of the first layer inside the die.
- precompression and final compression are applied and the final tablet is thus produced
- the bi-layer tablet is ejected.

A compression cycle for a bi-layer tableting operation is given in Figure 1.

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**Fig 1:** Schematic diagram of tablets manufacture based on 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.

**FEATURES OF A WELL DESIGNED BILAYERED TABLET**\(^{[14]}\)

- It should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
- It should have the chemical and physical stability to maintain its physical attributes over time.
- The bi-layer tablet must be able to release the medicinal agents in a predictable and reproducible manner.
- It must have a chemical stability throughout shelf-life, so there is no alteration of the medicinal agents.
- A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration and contamination.

**Types of Bilayer Tablet Presses**[^4^,^10^,^11^]

Various types of bilayer tablet press had been designed over the years are.

**Single Sided Tablet 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 single or double (pre and main-compression) steps. The two layers in the die mix slightly at the interface and bond sufficiently so that no separation occurs during compression load recovery.

![Fig. 2: Single sided tablet press.](image)

**Limitations**[^15^,^16^]

- There no weight monitoring or control on the individual layers.
- Distinct visual separation between the two layers is absent.
- Very short first layer-dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping and hardness problems.
- First-layer tablet sampling and sample transport to a test unit for in-line quality control and weight recalibration is very difficult.
Double Sided Tablet Press\textsuperscript{[10]}

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. 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 the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance tablet and correct the die fill depth when mandatory.

![Double sided tablet press](image)

**Fig. 3: Double sided tablet press.**

**Limitations**

Separation of the two individual layers is due to insufficient bonding between the two layers during final compression of bi-layer tablet.

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”.

**Bilayer Tablet Press With Displacement\textsuperscript{[17]}**

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 operation point. But depends on the applied pre-compression force. In fact the lower the pre- compression force, the more accurate the monitoring control system and this ideal for good interlayer bonding of the bi- layer tablet.
Fig. 4: GE double sided tablet press with displacement.

ADVANTAGES

- ‘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.

Quality and GMP requirements for Bilayer tablet\(^\text{[18]}\)

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

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

Various patented techniques for bilayer tablets\(^\text{[19,20]}\)

**OROS® Push Pull Technology**

(Ormosic [Controlled] Release Oral [Delivery] System) is a controlled release oral drug delivery system in the form of a tablet. It consist of mainly two or three layer among which the one or more layer are essential of the drug and other layer are consist of push layer. The pull layer mainly consists of drug along with two or more different agents. There is further
addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core.

![Diagram of drug delivery system](image)

**L-OROS™ Technology**

Liquid OROS system was used for the solubility issue ALZA developed the system where a lipid soft gel product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, than osmotic push layer and than a semi permeable membrane, drilled with an exit orifice.

![Diagram of OROS system](image)

**EN SO TROL Technology**

SHIRE laboratory developed an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies.
DUROS TECHNOLOGY
The system consists from an outer cylindrical titanium alloy reservoir. This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the miniature drug dispensing system that operates like a miniature syringe and release minute quantity of concentrated form in continues and consistent from over months or year.

ELAN DRUG TECHNOLOGIES’ DUAL RELEASE DRUG DELIVERY SYSTEM
DUREDAS™ technology can provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form (bilayer tablet). The tabletting process can provide an immediate release granulate and a modified-release hydrophilic matrix complex as separate layers within the one tablet. The DUREDAS™ system can also be manipulated to incorporate two controlled release formulations within the bi-layer. Two different release rates can be achieved from each side. Thus greater prolongation of sustained release can be achieved. Typically an immediate release granulate is compressed first followed by the addition of a controlled release element to be compressed onto the initial tablet. This gives the characteristic bi-layer effect to the final dosage form.

CHALLENGES IN BILAYER MANUFACTURING[21]
Conceptually, bilayered tablets are two single layer tablets compressed as one so, there are some manufacturing challenges in the manufacturing.

- **Delamination**: Tablets falls apart when the two hales of the tablet do not bond completely.
Cross-contamination: When the granulation of the first layer intermingles with the granulation of the second layer or vice versa, cross-contamination occurs. Proper dust collection goes a long way toward preventing cross contamination.

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

- Cost: Bilayered tablet is more expensive than single layer tableting because; Tablet press costs more because of complex design.
- The press generally runs more slowly in bilayer mode.
- Development of two compatible granulation is must, which means more time spent on formulation development, analysis and validation.
Table I: List of Commercially Marketed Bilayer Tablet.

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Chemical Name</th>
<th>Developer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tribet -1</td>
<td>Glimepiride, Metformin hydrochloride, Pioglitazone</td>
<td>Abbot Health Care Pvt. Ltd.</td>
</tr>
<tr>
<td>Alprax Plus</td>
<td>Sertraline, Alprazolam</td>
<td>Torrent Pharmaceuticals Ltd.</td>
</tr>
<tr>
<td>Glycomet®-GP2Forte</td>
<td>Metformin hydrochloride, Glimepiride</td>
<td>USV Limited</td>
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<tr>
<td>Newcold Plus</td>
<td>Levocetirizine hydrochloride, Phenylpropanolamine, Paracetamol</td>
<td>Piramol Healthcare Ltd.</td>
</tr>
<tr>
<td>DIAMICRON®XRME500</td>
<td>Gliclazide, Metformin hydrochloride</td>
<td>Sedia® Pharmaceuticals (India) Pvt. Ltd.</td>
</tr>
<tr>
<td>DIUCONTIN-K®20/250</td>
<td>Furosemide, Potassium chloride</td>
<td>T.C. Health Care Pvt. Ltd.</td>
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<tr>
<td>TRIOMUNE 30</td>
<td>Nevirapine, Lamivudine, Stavudine</td>
<td>Cipla Ltd.</td>
</tr>
<tr>
<td>PIOKIND®-M15</td>
<td>Pioglitazone, metformin hydrochloride</td>
<td>Psychotropics India Ltd.</td>
</tr>
<tr>
<td>Revelol®-Am 25/5</td>
<td>Metoprolol succinate, Amlodipine besilate</td>
<td>Ipcal Laboratories Ltd.</td>
</tr>
<tr>
<td>Clarinex – D</td>
<td>Desloratadine / Pseudoephedrine Sulphate</td>
<td>Merck &amp; Co.</td>
</tr>
<tr>
<td>Ditropan XL</td>
<td>Oxybytynin Chloride</td>
<td>Alza Corporation</td>
</tr>
<tr>
<td>Augmentin</td>
<td>Amoxicillin / Clavulanate</td>
<td>Janssen Pharmaceuticals</td>
</tr>
<tr>
<td>Zyrtec – D</td>
<td>Cetirizine HCL / Pseudoephedrine HCL</td>
<td>Dr. Reddy’s Labs</td>
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<td>Istamet</td>
<td>Sitagliptin, Metformin Hydrochloride</td>
<td>Ranbaxy Laboratories Ltd.</td>
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<td>Volise – M</td>
<td>Voglibose, Metformin Hydrochloride</td>
<td>Ranbaxy Laboratories Ltd.</td>
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<td>Gluconorm</td>
<td>Glimepride, Metformin Hydrochloride</td>
<td>Lupin Pharmaceuticals</td>
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<td>Pioglu</td>
<td>Pioglitazone, Metformin Hydrochloride</td>
<td>Emcure Pharmaceutical Ltd.</td>
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Table II: List of Patents recently filed for Bilayer tablets.

<table>
<thead>
<tr>
<th>Patent no.</th>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Company</th>
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<tr>
<td>20150238421</td>
<td>Metformin XR</td>
<td>SGIT2 inhibitor</td>
<td>AstraZeneca UK Ltd</td>
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<td>201500037410</td>
<td>Ranolazine</td>
<td>Dronedarone</td>
<td>Gilead Sci Inc.</td>
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<td>20150018421</td>
<td>Ibuprofen</td>
<td>Diphenhydramine</td>
<td>Wyeth Lic</td>
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<td>20150017242</td>
<td>Dronedarone</td>
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<td>Lupin Ltd</td>
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<td>20140377350</td>
<td>flurbiprofen</td>
<td>glucosamine</td>
<td>Sanovellac Sanayi</td>
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<td>20140255484</td>
<td>Dexlansoprazole</td>
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<td>Sanovellac Sanayi</td>
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<td>20130309307</td>
<td>Telmisartan</td>
<td>Hydrochlorothiazide</td>
<td>Boehringer ingelhamPharmGmbh</td>
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</table>
EVALUATION OF BILAYERED TABLETS

For the evaluation of bilayered tablets various evaluation parameters are to be checked which are as follows.

1. **Dwell Time:** The Contact between punch head and compression roller is dwell time. Shorter the first layer dwell time it creates pours, aeration, capping and hardness problems. It may be removed by reducing turret- rotation speed or increasing the dwell time.

2. **Risk of separation and capping:** It can be done by forming correct bonding which can be attain by formation of first layer at low compression force. Therefore first layer can interact with the second layer during final compression of tablet.

3. **Tamping force:** It is applied on the first layer of bilayer tablet to minimize capping and separation of two individual layers. When dwell time is increase at pre-compression of both first and second layer, it will provide sufficient hardness and low pre-compression force, which requires to secure interlayer bonding.

4. **Cross-contamination:** Multilayer tablet forming machines are functioned with suction nozzles or dust extractor to remove fine particles and granules to eliminate the cross-contamination between the two layers and getting clear visual separation of both layers.

5. **Deaeration:** If dwell time increases, it promotes deaeration of powder and rearrangement of granules in die.

6. **Weight variation:** It occurs some time due to non-uniform flow of granules, incomplete die filling and lower punch sticking due to excessive fine particles in final blend and thus these parameters should be controlled carefully during tableting.

7. **Layer weight ratio:** Generally layer weight ratios are 50:50, 60:40 and 25:75 used for formulation of such tablets, provided that granules having good binding properties.

8. **Hardness and thickness:** These parameters tightly controlled during final compression because it directly affect the release of the API. Many times due to high hardness disintegration matrix takes more time to the set limit.

9. **Segregation:** Sometimes it occurs in out coming granules in most machines and therefor it is better blend granules before loading into hopper for reuse to minimize the content uniformity in finished products.

CONCLUSION

Over the years, advancements in technology and innovation have brought about increasing interest within the pharmaceutical industry in developing tablets containing two or more
Active Pharmaceutical Ingredients (API) in a single dosage form, promoting customer convenience, compliance, and marketing. Bilayer tablets offer several advantages over conventional single layer tablets in that respect and also offer an excellent opportunity for manufactures to separate themselves from their competitors, improve their product efficacy, and protect against impersonator products. However, the manufacturing of bilayer tablets has great number of challenges due to insufficient bonding strength and process control. In the pharmaceutical industry the process of bilayer design has been heavily dependent on the trial-and-error approach during the formulation and process development stages. To overcome this hurdle a complete mechanistic understanding must be developed through the application of scientific and quality risk management tools: Pharmaceutical development and quality risk management.

REFERENCES


25. WIPO Patent WO2007132281A1


28. US patent 4874388
