

Review Article



A Review on Novel Approach – Bilayer Tablet Technology

Shila V. Devtalu^{*1}, Ashwini E. Patil¹, Manoj M. Bari¹, Dr. Shashikant D. Barhate¹

¹Department of Pharmaceutics, Shree Sureshdada Jain Institute of Pharmaceutical Education and Research, Jamner, Jalgaon Dist, Maharashtra, India.

^{*}Corresponding author's E-mail: shiladevtalu@gmail.com

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ABSTRACT

In modern era bi-layer tablet is for successful development of immediate and modified drug delivery system for various diseases and disorders. Bi-layer tablets have been developed to achieve modified release of drug. The primary objective of bi-layer tablet is to avoid chemical incompatibilities between APIs by physical separation and to develop different drug release profiles (immediate release and modified release). In bi-layer tablet the immediate release layer act as the loading dose and modified release layer act as the maintenance dose. To produce a good quality bi-layer tablet, the machinery should be constructed as per GMP. Various machineries are available to overcome common bi-layer problems, such as layer separation, insufficient hardness, inaccurate individual weight control, cross contamination between the layers etc. In this review we focus on the different types of press, techniques, how to solve problems of bi-layer tablet, marketed products etc.

Keywords: Approaches, Bi-layer tablet, Marketed products, Press, Techniques, Trouble shooting.

INTRODUCTION

Day-by-day's various developed and developing countries are moving towards combination therapy for treatment of various diseases and disorders requiring long term therapy such as hypertension and diabetes. The problem of dose dependent side effects is minimized by combination therapies and is advantageous over monotherapy.¹⁻⁵ From last few years, interest in developing a combination of two or more active pharmaceutical ingredients in a single dosage form has increased in pharmaceutical industry. Bi-layer tablets can be a primary option to avoid chemical incompatibilities between APIs by physical separation.^{6,7,8} Bi-layer tablet is 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 as initial dose and second layer is maintenance dose.^{9,10}

Bi-layer tablets are prepared with one layer of drug for immediate release with second layer design to release drug later as second dose or in an extended release or for both immediate release. Bi-layer tablets are tablet, made by compressing two different granulations fed into a die succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet press can be set up for two layers. More layers are possible but the design becomes very special. Bi-layer tablets are composed of two layers of granulation compressed together. They have the appearance of a sandwich because the edges of each layer are exposed.⁵ General concept of bi-layer tablet is shown in figure 1.

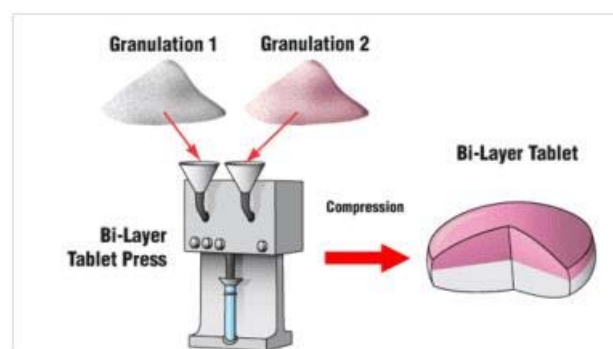


Figure 1: General concept of Bi-layer tablet

However, these drug delivery devices are mechanically complicated to design/manufacture and harder to predict their long term mechanical properties due to the poor mechanical and compression characteristics of the constituent materials in the compacted adjacent layers, elastic mismatch of the layers, insufficient hardness, inaccurate individual mass control, cross contamination between the layers, reduced yield, and their tendency to delaminate at the interface between the adjacent compacted layers during and after the various stages of production downstream of the compaction process.¹⁴

Rationale behind formulation of bi-layer tablet^{4,12}

1. Controlling the delivery rate of either single or two different APIs.
2. To separate incompatible API's with each other, to control the release of one layer by utilizing the functional property of the other layer (such as osmotic property).
3. To adapt the total surface area available for API layer either by sandwiching with one or two



inactive layers in order to achieve swellable/erodible barriers for controlled release.

Applications⁹

1. Bi-layer tablets are mainly used in combination therapy.
2. Bi-layer tablets are used to deliver the loading dose and maintenance dose of the same or different drug.
3. Bi-layer tablets are used for bi-layer floating tablets in which one layer is floating layer another one is immediate release layer of the drug.
4. Bi-layer tablets are used to deliver the two different drugs having different release profile.

GMP-requirements of quality bi-layer tablet¹³

To produce a quality bi-layered tablet, in a validated and GMP way, it is important to select a bi-layer tablet press capable of:

1. Preventing capping and separation of the two individual layers that constitute the bi-layer tablet.
2. Providing sufficient tablet hardness.
3. Preventing cross-contamination between the two layers.
4. Producing a clear visual separation between the two layers.
5. Accurate and individual weight control of the two layers.
6. High yield.

Advantages of bi-layer tablet over the conventional oral solid dosage forms⁴

1. Low cost compared to other dosage forms.
2. Fit for large scale production.
3. Bi-layer tablet is suitable for preventing direct contact of two drugs and thus to maximize the efficacy of combination of two drugs.
4. Expansion of a conventional technology.
5. Separation of incompatible components.
6. Patient compliance is improved leading to improve drug regimen efficiency.
7. Fewer daily doses are required compared to traditional delivery system.
8. Product identification is easy.

Disadvantages of bi-layer tablet^{4, 12, 14}

1. Difficult to swallow in case of children and unconscious patients.
2. Add complexity and bi-layer tablet presses are expensive.
3. Insufficient hardness, layer separation, reduced yield.
4. Inaccurate individual layer weight control.
5. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.

Various techniques of bi-layer tablet^{34, 12, 15}

1. Oros® push pull technology

This system consist of mainly two or three layer among which the one or more layer are necessary for the drug and other layer are consist of push layer. The drug layer mainly consists of drug along with two or more different agents. So this drug layer comprise of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core.

2. L-Oros™ technology

This system used for the solubility concern Alza developed the L-OROS system where a lipid soft gel product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, then osmotic push layer and then a semi permeable membrane, drilled with an exit orifice.

3. DUROS technology

DUROS (Alza Corporation) is based on implant technology, which provides an alternative of a wide range of therapeutic compounds, includes peptides, proteins and other bioactive macromolecules. These implants are miniature titanium cylinders designed to provide continuous osmotically driven delivery of drugs within the body for up to one year.

4. EN SO TROL technology

Solubility enhancement of an order of magnitude or to create optimized dosage form Shire laboratory used an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies.

Compression cycle for bi-layer tablet¹⁶

Bi-layer tablets are made by compressing two different granulations fed into a die succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet press can be set up for two or three layers. More are possible but the design becomes very special. Mechanism of compression of bi-layer tablet is shown in figure 2.

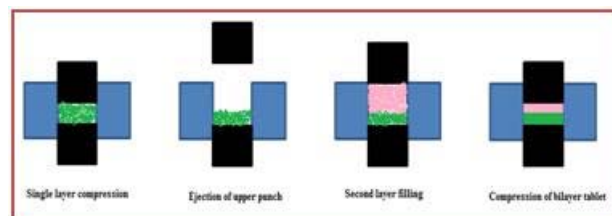


Figure 2: Compression cycle of bi-layer tablet

Various approaches used in bi-layer tablet

A. Floating drug delivery system^{12, 16, 17}

They are designed to have a low density and thus float on the 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 bi-layer tablet is designed in such way that, one layer gives immediate dosing of the drug which gives faster onset of action while other layer is designed as a floating layer which forms a gastro retentive system. Release pattern of floating bi-layer tablet is shown in figure 3.

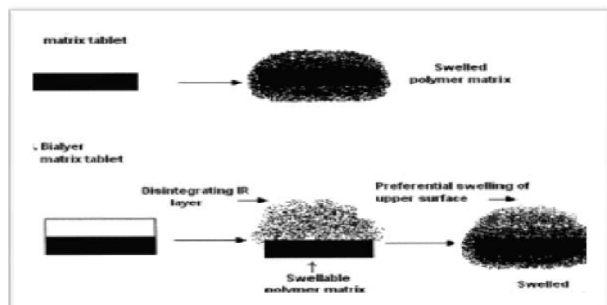


Figure 3: Release pattern of bi-layer floating tablet

B. Polymeric bioadhesive system^{11, 18}

These are designed to imbibe fluid flowing administration such that the outer layer becomes a 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 a one layer with immediate dosing and other layer with bioadhesive property.

C. Swelling system^{12, 19}

These are designed to be sufficiently small on administration so as not to make ingestion of the dosage form difficult (e.g., less than approximately 23 mm long and less than 11 mm wide for an oval or capsule-shaped tablet whereas 10-12 mm in diameter for round tablets). 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. The simple bi-layer tablet may contain an immediate release layer with the other layer as extended release or conventional release or both as controlled release layer. Such systems are shown in figure 4 and figure 5.

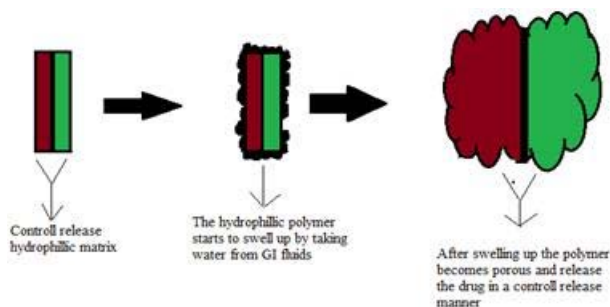


Figure 4: Bi-layer tablet consist of two controlled release layer

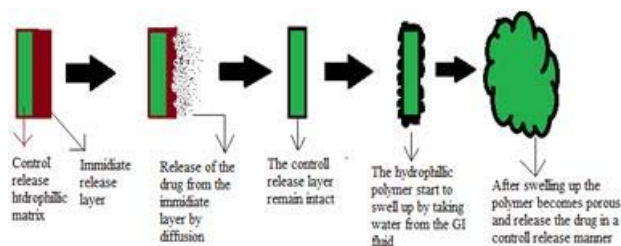


Figure 5: Bi-layer tablet consist of immediate release and controlled release layer

Types of bi-layer tablet press

1. Single sided tablet press⁴

The simplest design is the single sided press with both chambers of the double feeder separation from each other. Each chamber is gravity or fed with different powder, thus producing the two individual layers of the tablets. When the die passes under the feeder, it is first loaded with the first-layer powder followed by the second layer powder. Then the tablet is compressed in one or two steps. Various bi-layer tablet press are enlisted in table no. 1. Single Sided 16 to 23 stations bi-layer tablet press is as shown in figure 6.

1.1 Single Sided 16 to 23 stations (JS) Standard & GMP Heavy Duty Machine³⁴

- Suitable for veterinary, herbal, chemicals, minerals, confectionary, metal.
- Pharmaceuticals and nutraceuticals
- R & D / Pilot scale model
- Machines with pre-compression
- PLC & computer interfaced controls
- 23- Station machine is with B-Tooling



Figure 6: Single Sided Bi-layer Press

2. Double sided tablet press⁴

A double sided press offers an individual fill station, pre-compression and main compression for each layer. In fact bi-layer tablet will go through four compression stages before being ejected from the press. Most double sided tablet press with automated production control use compression force to monitor and control

tablet weight. ADEPT double sided tablet press is as shown in figure 7.

2.1 ADEPT double sided tablet press³²

Offers significant technical advantages that permit higher output and increased efficiency in production. Special emphasis has been given on durability while designing so that the machine can be used in a 24/7 production environment. The higher load bearing capacity of Adept tablet press makes it suitable for bigger tablets. The machine also offers flexibility to produce both single-layer and bi-layer tablets on the same platform.



Figure 7: ADEPT Double Sided Tablet Press

3. *Bi-layer tablet press with displacement monitoring*^{4, 30}

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 Courtoy R292F: "bi-layer" tablet press with 'displacement monitoring' is as shown in figure 8.

3.1 The Courtoy R292F: "bi-layer" tablet press with 'displacement monitoring'³⁰

This double-sided tablet press has been specifically designed and developed for the production of quality bi-layer 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 8: Courtoy R292F bi-layer press

Table 1: Bi-layer tablet press available in the market²⁹⁻³⁷

Bi-layer Tablet Press	Make
Expert 1 bi-layer tablet press for R& D	Kambert
Modul™ P with bi-layer ECM	GEA Courtesy
XM 12 small scale bi-layer tablet press	Korsch
OYSTAR Manesty Xpress® 700 Tablet Press	Thomasnet
ADEPT double sided tablet press	Adept
Piccola-bi-layer tablet press	Smtmc
Double sided bi-layer tablet press	Jaguar
Bi-layer tablet press	Aayush Techno Pvt. Ltd.
Double tablet press	Kambert Engineering Ltd.
Double rotary double layer tablet press	Karnavati Engineering Ltd.

Troubleshooting of processing problems in bi-layer tablet compression^{13, 20}

Various problems are arises in the process of compression of bi-layer tablet, these are summarized in table 2.

Evaluation of bi-layer tablet^{9, 18, 21, 22, 23}

General Appearance

The general appearance of a tablet, its visual identity and overall "elegance" is essential for consumer acceptance. Includes tablet size, shape, color, presence or absence of an odor, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

Size and Shape

The size and shape of the tablet can be dimensionally described, monitored and controlled.

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. Thickness of tablet should be recorded by using digital vernier caliper. It is expressed in mm.

Hardness (Crushing strength)

Hardness indicates the ability of the tablet to withstand mechanical shocks while handling. Hardness of the tablet recorded by Monsanto hardness tester. It is expressed in kg/cm².

Table 2: Troubleshooting of processing problems in bi-layer tablet compression

Trouble	Possible cause	Remedies
Tablet weight variation	- Poor flow characteristics of material - Dies not filling - Material loss or gain after proper die fill	- Wrong setting of hopper. - Material bridging in hopper - Too much recirculation - Press running too fast - wrong feeder paddle speed or shape - Recirculation band leaking - Excessive vacuum or nozzle improperly located
Product yield	- Incorrect feeder fit to die table - Incorrect action on recirculation band - Die table scraper action insufficient - Loss at compression point	- Feeder bases incorrectly set (too high or not level) - Gap between bottom edge and die table - Binding in mounting screw - Too little hold down spring pressure - Scraper blade worn or binding - Outboard edge permitting material to escape - Compressing too high in the die - Excessive or misdirected suction on exhaust nozzle
Low hardness	- Factors related to machine - Lubricant level	- Tablet press having pre-compression and main compression facilities - Press speed is reduced to increase total compression time - Over mixing can reduce tablet hardness
Capping and lamination	- Non-optimized formulation - High compression force - Ratio of pre-compression to main compression is insufficient - Curled or damaged punches	- Incorporate plastically deforming matrix - Reduced compression force - Reduced press speed - Pre-compression force high can be harmful - Use large compression roller diameter - Tools should be rewashed or replaced
Picking and sticking	- Excessive heat generation during compression - Fouling the punch faces	- Use of cooling system for the compression section - Lower mechanism section may be helpful - Startup should always be close to optimum conditions
Separation of two individual layers	Insufficient bonding between the two layers during final compression of bi-layer tablet	First layer should be compressed at a low compression force so that this layer can still interact with second layer during final compression of the tablet
Mottling	- Improper setting of both feed frame - Due to weak suction	- Both feed frame should set properly. - Suction capacity should be such that, all waste material is sucked.

Friability

The ability of the tablet to withstand abrasion in packaging, handling and shipping. Friability is determined 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. Friability is expressed in percentage as:

$$\% \text{ Friability} = 1 - (\text{loss in weight} / \text{Initial weight}) \times 100$$

Drug content and release

To evaluate tablets potential for efficacy, the amount of drug per tablet needs to be monitored from tablet to tablet and batch to batch, and a measure of the tablet's ability to release the drug needs to be ascertained.



Weight variation

Twenty tablets are selected randomly from each batch and weighed individually to check weight variation. Calculate average weight and comparing the individual tablet weights the average. The tablet meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. A little variation is allowed in weight of a tablet according to U. S. Pharmacopoeia. The following percentage deviation shown in table no. 3 in weight variation is allowed.

Table 3: Weight variation parameters

Average weight of tablet	Percentage deviation
130 mg or less	±10
>130 mg and <324 mg	±7.5
324 mg or more	±5

In-vitro dissolution study⁴

Dissolution study is done in simulated gastric and intestinal fluids to assess their ability in providing the desired controlled drug delivery. In- vitro drug release studies are carried out using USP dissolution test apparatus at 37°C temperature at specific RPM or as mentioned in monograph.

Marketed bi-layer tablets

Various researcher works on bi-layer tablet, which are shown in table no. 4. Commercially available bi-layer tablets are enlisted in table 5.

CONCLUSION

Bi-layer tablet is suitable for sequential release of two drugs in combination, and also for sustained release tablet in which one layer is immediate release as an initial dose and second layer is maintenance dose. By using bi-layer tablet technology we can administer incompatible drugs in combination as well as same drug with different release rate. This technology avoids frequent administration of dosage form. Now a day such technology is used for administration of drugs like anti-diabetic, anti-hypertensive, anti-inflammatory, anti-pyretic, anti-asthmatic to the patients. Conventional solid oral dosage forms are a traditional, but bi-layer tablet is a novel approach. This novel approach requires new machinery for manufacturing. This article explains different types of presses used to produce bi-layer tablet ranging from simple single sided machines to highly sophisticated machines. For good quality bi-layer tablet the machines should be inherently built as per GMP. This technique is cost effective, safe and reproducible.

Table 4: Previous study done on bi-layer tablet

Drugs		Super disintegrant used in Immediate release layer	Polymer used in Sustained release layer	References
First layer	Second layer			
Glimepride	Metformin HCL	Sodium starch glycolate	HPMC K4M, sodium carboxy methyl cellulose	19
Paracetamol	Acetaminophen	Microparticles by ethylcellulose	Microparticles by ethylcellulose	24
Tramadol HCL	Acetaminophen	Sodium starch glycolate as superdisintegrant	Sodium starch glycolate as superdisintegrant	25
Valsartan	Metformin HCL	Crospovidone	HPMC K100M, sodium CMC, PVP K90	26
Glipizide	Glipizide	Starch	HPMC, xanthan gum, guar gum, karaya gum,	27
Zolpidem tartrate	Zolpidem tartrate	Sodium crosscarmellose	HPMC K100M	28
Ranitidine	Ranitidine	Starch	Carbopol, HPMC	17

Table 5: Marketed bi-layer tablet: 2, 3, 36, 37

Product Name	Active Pharmaceutical Ingredients (API)	Manufacturer
Pioglu	Pioglitazone, Metformin hydrochloride	Emcure Pharmaceutical Ltd.
Xilla M- Forte	Glimepride, Metformin hydrochloride	Emcure Pharmaceutical Ltd.
Gluconorm	Glimepride, Metformin hydrochloride	Lupin Pharmaceuticals
Volise-M	Voglibose, Metformin hydrochloride	Ranbaxy Laboratories Ltd.
Glimeto- MP	Glimepride, Pioglitazone	RPG Life Sciences Ltd.
Istamet	Sitagliptin, Metformin hydrochloride	Ranbaxy Laboratories Ltd.
Glyrep	Glyclizide, Metformin hydrochloride	Emcure Pharmaceutical Ltd.
Unistar	Rosuvastatin, Aspirin	Unichem Laboratories Ltd.

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