

Bilayer Tablet Technology: A Concept Of Immediate And Controlled Drug Delivery

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Abstract

Combination therapy has more popularity and various merits over monotherapy (conventional dosage forms). Bilayer tablet technology is the best and most recent used example of combination dosage formulation. In the last decade, the single-dose formulation has the combination of two or three active pharmaceutical ingredients (API) increased in pharmaceutical industry. It is known for promoting patient convenience and compliance by reducing the number of dosages and enhancing the bioavailability of dosage forms. Bilayer or multilayer tablets are innovative forms of conventional oral drug delivery systems. Bilayer layer can be the only technology that has been used in different APIs for synergistic effect, to enhance the bioavailability or to avoid the interaction between the incompatible substance by separating them physically, and to enable the development of different drug release profiles (sustained release or controlled release, etc). The goal of this review is to give a general overview of the development and production of bilayer tablet technology and to highlight the issues encountered during the production of bilayer tablets as well as the expected solutions to these problems.

Keywords: Bilayer tablets, synergistic effect, combination therapy, challenges, compliance.

INTRODUCTION

About 90% of the formulations are manufactured today for oral ingestion worldwide. This illustrates that this class of formulation is the most popular among global researchers and their major attention is towards this direction. The bilayer or tri-layer drug delivery is to reduce the frequency of dose intake. The technique of a modified release either controlled, sustained, or immediate release drug is to enhance a therapeutic regimen by providing immediate, continuous, or slow delivery of the API (Active Pharmaceutical Ingredient) over the entire dosing interval providing greater patient convenience and compliance.

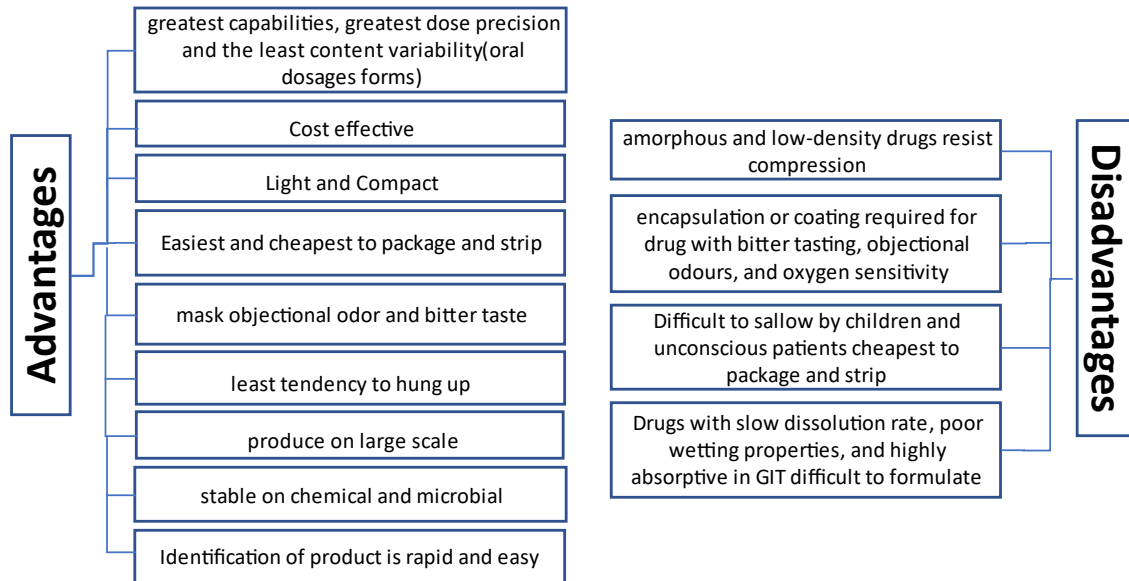
The dual release technique is the easiest way to successfully develop a cost-effective controlled release formulation. Bilayer tablet is more successful than the traditionally used dosage forms due to their suitability for sequential release of drugs in combination and it also has characteristics of separating incompatible substances, the best example is a sustained release tablet or controlled release tablet in which one layer is as initial dose (immediate release) and the second layer is maintenance dose (controlled release). In a few cases, bilayer tablets have two sustained-release layers of different drugs.

The immediate release layer contains super disintegrants which promote drug release rate and attains the onset of action (quick release) as a loading dose whereas the sustained release contain low viscosity polymers (maintenance bioavailability of drug) which help to release the drug in a sustained manner for a prolonged time period.

The biphasic system is used mostly when the onset of action needs to be achieved quickly and it is followed by a sustained release phase. It also avoids repeated administration of drugs. This type of drug delivery is mainly suitable for coronary vasodilators, antihypertensives, antihistaminics, analgesics, antipyretics, and antiallergenic agents.

Certain antidiabetic bilayer tablets have both layers as the sustain release layers. (Sandhyarani et al., n.d.) Advantages (Singh Tomar, Mishra, and Pathak 2015), disadvantages (Singh Tomar, Mishra, and Pathak 2015) and ideal characteristics of bilayer tablet (Pujara, n.d.) are presented in Figure 1 and Figure 2 respectively.

Figure 1. Advantages and Disadvantages of Bilayer Tablets



TYPE OF BILAYER TABLET (Syed et al. 2013)

The term bilayered tablets containing subunits that may be either the same (homogeneous) or different (heterogeneous)5.

Homogenous Type

Bilayer tablets are favored when the release profiles of the drugs had to be dual release or the release pattern of the drug are different from one another. Bilayer tablets allows for designing and modifying the dissolution rate and release characteristics in such a way that immediate release layer act as a loading drug dose while second layer act as to be the second dose, release later, or fallow an extended release.

Heterogeneous Type

Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances. 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: (NIZAMI and MALVIYA 2022)

1. High yield.
2. Preventing capping and separation of the two individual layers that form the bilayer tablet.
3. Preventing cross-contamination between the two layers.
4. Producing a clear visible separation between the two layers.
5. Accurate and individual weight control of the two layers.

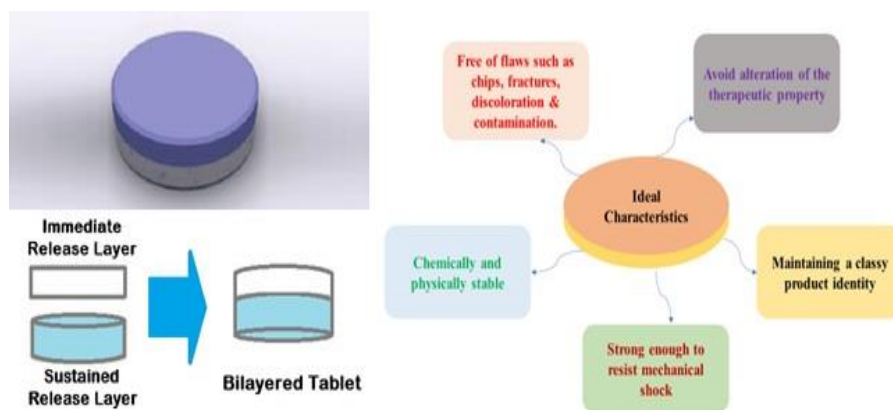


Figure 2. Bilayer Tablet and characteristics

DIFFERENT DRUG DELIVERY SYSTEM USED IN BILAYER TABLET (Santra, Mahanti, and Bera 2021)

a. **Floating drug delivery system:** Floating drug delivery system is a class of gastro retentive drug delivery system. These systems remain in the gastric region for several hours, thus significantly prolonging the gastric residence time of

drugs. This system improves bioavailability. The solubility of drugs which are less soluble in high pH can be improved by such systems. Floating drug delivery systems for bilayer tablets can be of two types:

- Intra-gastric bilayer floating tablet
- Multiple unit type floating tablet

Intra-gastric bilayer floating tablets are compressed bilayer tablets intended to remain in the stomach or gastric region and produce suitable therapeutic effects. On the other hand, Multiple unit type floating tablets are systems which consist of sustained release pills as 'seeds' surrounded by double layers. The outer layer is a swellable membrane while the inner layers have effervescent agents. In the body, they form swollen pills like balloons and float due to low density. It is also known as multi particulate floating reservoir type of delivery system.

b. Polymeric bioadhesive system: Bio-adhesion may be defined as the state in which two materials are held together for extended periods of time by interfacial forces. Polymeric bio-adhesive bilayer tablets can be mucoadhesive or Bucco adhesive. Mucoadhesive bilayer tablets adhere to the stomach mucosa and release active pharmaceutical ingredients gradually or in sustained manner. These tablets can persist in the stomach for several hours and thus extend the gastric residence time of therapeutics. These enhance bioavailability due to extended gastric retention. The potential use for mucoadhesive systems as drug carriers lies in its prolongation of the residence time at the absorption site, allowing intensified contact with the epithelial barrier. However, a disadvantage of such systems is the removal of preparation by mucociliary clearance system which is a natural defence mechanism of the body. But by coupling mucoadhesive properties to bilayer tablets has additional advantages such as high bioavailability, efficient absorption and intimate contact with the mucous layer. Bucco-adhesive bilayer tablets release the drug in the buccal cavity and avert the first pass metabolism which leads to high bioavailability. Bucco-adhesive system is the interaction between a drug carrier polymer along with other excipients and the mucin in the buccal mucosa surface. This system offers various advantages such as bypasses first pass metabolism, allows optimum absorption of APIs as well as self-placement and removal. However, a suitable buccal drug delivery system should have good bio-adhesive properties, so that it can be retained in the oral cavity for desired duration of time.

c. Swelling system: Swelling systems are designed in a way that upon ingestion they swell or rapidly unfold to release drug to a required degree. They are sufficiently small on administration as they swell inside the body. They may contain immediate release layer with the other layer as extended release or immediate release. The system gradually breaks down into smaller particles to leave the stomach

VARIOUS TECHNIQUES FOR FORMULATION OF BILAYER TABLET:

OROS® Push Pull Technology: This system consists of mainly two or three layers among which the one or more layer is essential of 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 comprises of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semipermeable membrane surrounds the tablet core. (Santra, Mahanti, and Bera 2021)

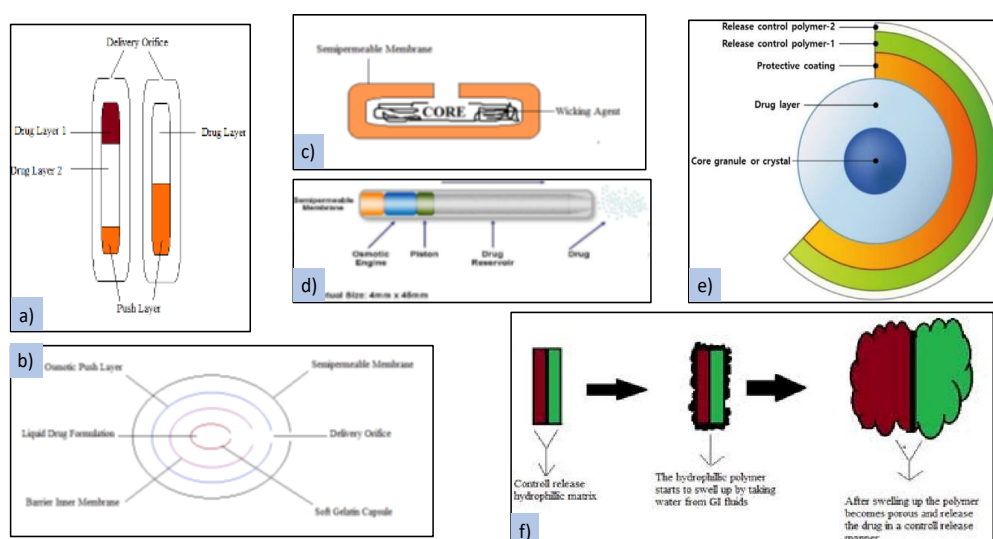


Figure 3. Various Techniques for Formulation of Bilayer Tablet
a) OROS® Push Pull Technology b) L-OROS™ Technology c) EN SO TROL Technology
d) DUROS Technology e) PRODAS technology f) ELAN. Drug Technologies or DUREDAS technology

L-OROS™ Technology: This system used for the solubility issue 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. (Rameshwar, Kishor, and Tushar 2014)

EN SO TROL Technology: Solubility enhancement of an order of magnitude or to create optimized dosage form Shire laboratory uses an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies. (Gaonkar 2021)

DUROS Technology: The system consists of an outer cylindrical titanium alloy reservoir. This reservoir has a high impact strength and protects the drug molecules from enzymes. The DUROS technology is the miniature drug dispensing system that opposes like a miniature syringe and releases minute quantity of concentrated form in continuous and consistent from over months or year.

PRODAS technology (Programmable Oral Drug Absorption System) (Elan Corporation): is a multi-particulate drug delivery technology that is based on encapsulation of controlled release minitables in the size ranging from 1.5 to 4 mm I diameter. This technology is combination of multi-particulate and hydrophilic matrix technology thus shows benefits of both. Minitables with different release rates can be combined and incorporated into single dosage form to present different release rates. These combinations may include immediate release, delayed release and/or controlled release minitables. (Santra, Mahanti, and Bera 2021)

ELAN. Drug Technologies or DUREDAS™ technology (Dual Release Drug Delivery System): DUREDAS™ Technology is used for a bilayer tablet, which can show the immediate or sustained release of two drugs or different release rates of the one drug in a single dosage form. The tableting process can shows both properties like an immediate release granulate and second one modified-release hydrophilic matrix complex as separate layers within the one tablet. The modified-release properties of the dosage form are provided by a combination of hydrophilic polymers. Controlled release matrix remains intact and slowly absorbs fluid from GI tract, which causes matrix to expand and transform hydrophilic matrix into porous, viscous gel which acts as barrier releases drug in controlled manner. (Ghugarkar et al. 2015)

Benefits offered by the DUREDAS™ technology

- 1) Bilayer tableting technology.
- 2) Tailored release rate of two drug components.
- 3) Capability of two different CR formulations combined.
- 4) Capability for immediate release and modified release components in one tablet.
- 5) Unit dose tablet presentation.

Ro Tab Bilayer (Kumar Verma et al. 2017)

a. Software:

It is modular designed software to which additional functions can be added. PC- system with 15” touch- screens is an advanced system which provides fast graphical evaluations with accurate results.

b. Working:

Ro Tab bilayer when using is switched to production mode. Dose and compression force is automatically regulated by adjusting filling speed and die table. Hardness is also regulated when required.

c. R and D modified technique:

R and D modified Ro Tab Bi-layer is featured with measuring points on which there are graphical visualization and evaluation are possible. There is an additional alarm function on which punch tightness is controlled. Anytime up gradation is possible which are R and D Plus.

d. R and D Plus:

R and D Plus provides improved standards in tableting technology with all important functions such as punch tightness control, display of force displacement and tablet scraper force.

Geminex Technology

In this drug delivery system at different time more than one drug can be delivered. This technology basically increases the therapeutic efficacy of the drug by decreasing its side effects. It is useful both to industry as well as patient as in single tablet it provides delivery of drug at different rates. (Kumar Verma et al. 2017)

Erodible molded multilayer tablet (Ghildiyal and Kumar 2018)

Egalet erodible molded tablets in an erosion-based system. It is beneficial in delivering zero order or sustain release with least effect from the gastrointestinal environment. Egalet erodible molded multi-layered tablets are developed by injection moulding egalet technology consists of a coat and a matrix. Drug release is superintended through the gradual erosion of the matrix part. The mode and rate of release are designed and engineered by altering the matrix the coat and the geometry to achieve by altering the matrix the coat, the geometry to attain either a zero-order release or a delayed. For a zero order, a drug is scattered through the matrix. The coat is biodegradable but has low water permeability to prevent its penetration. The matrix tends to erode when in contact with available water. The erosion of the matrix is due to GI fluids and initiated by gut movements in the GI tract. The drug release is mediated almost completely by erosion because the dosage form is

designed to slowdown the water diffusion into the matrix. It is definitely more desirable for drugs with chemical and physical stability issues after contacting with water. Egalet delivery technology is developed based on standard plastic injection moulding to ensure accuracy, reproducibility and low production cost.

CHALLENGES IN BILAYER TABLET MANUFACTURING (Shelke, Pote, and Salunkhe 2020) (Singh et al. 2021) (Abebe et al. 2014)

Challenges during the development of bilayer tablets might include:

- inadequate hardness
- the order of layer sequence
- layer weight ratio
- elastic mismatch of the adjacent layers
- first layer tamping force and cross contamination between layers.
- lamination i.e., layer separation is major problem in production of layered tablets. (Venkatrao Pulgamwar et al. 2015)
- difficult to maintain integrity of final Tablets.
- production yield of Bilayer tablet is very low compared to single layer tablet.
- Bilayer tableting is more expensive than single layer tableting

If these elements are not adequately regulated in some way, they will have an adverse effect on bi-layer compression pressure, as well as qualitative characteristics such as mechanical strength and individual layer weight control. Therefore, care must be taken to enable design of a vigorous product and process.

Bilayer tablets can be thought of as two single-layer tablets compacted into one but in practicality there are several manufacturing problems associated.

Material properties:

Physicochemical properties of API and excipients are crucial for the success of Bilayer tablet manufacturing. The nature of materials plays a key role in the strength of multi-layer tablets and their manner of fracture. Material properties such as:

- plasticity,
- brittleness and
- visco-elasticity

The plasticity deformation and the brittleness of material have significant role in the compression process. This means that the plasticity would not affect the compression process if the elasticity of the plastic material does not go beyond the bond limit. Besides, the particle deterioration in the central area of die is greater in comparison to the outer layer; Hence before using a substance for manufacturing of Bilayer tablets, it's critical to pay attention to its material characteristics. Each layer in multi-layer tablet formulation must exhibit a sufficient volume reduction and ability to form a mechanically strong and coherent solid form. Therefore, they should be characterized by good compressibility (ability of a substance to reduce the volume under pressure) and compatibility (ability of powdered substances to convert into tablets). It is important to optimize the size distribution of the particles, the flow characteristics, and compression ability of material when used in layered tablet manufacturing, to ensure accurate control of each layer weight.

Compression force:

According to the research conducted by the Li et al., the most vital parameter in the production process of multi-layer tablet is the assessment of compression force used for the very first layer, which influences the interfacial strength and adhesion between the two layers, resulting in the mechanical attraction among the layers in the tablet.

Therefore, if the initial layer of the bilayer medication was more elastic, the stress and tension produced in the entire system as a result of it leads the bilayer tablet's strength to deteriorate. This can cause the bond between the two layers at the bilayer tablet's interface to break which directly impact the adherence of layers. The compression pressure and also punch speed significantly affect the compatibility and resistance to compressibility into the die. The job of the initial layer of compression forces (generally in the range of 2-18 KN) is to tamp the powder/granulated substances in order to reduce the volume, smooth the first layer surface and generate a space for depositing the second layer. In general, the application of higher compression force tends to increase tensile strength and decreased surface roughness. Smoothing the surface of the initial layer may augment the delamination by limiting the intermolecular adherence between adjacent layers.

Proper bonding is only obtained when the first layer is compressed at a low compression force so that this layer can still interact with the second layer during final compression of the tablet. Bonding is severely restricted if the first layer is compressed with high compression force.

Lubricant:

The substances which are having greater lubricity will have lower friction between its particles die and punches when it comes into contact because all the matter will be uniformly distributed. Conversely, when it comes to bilayers substances to achieve greater interaction and strength between the two layers' low lubricant level is obligatory. As we know that

lubricant and its levels have a greater impact than brittle substances, this characteristic of the material should be considered while dealing with the development of Bilayer tablet.

The specific quantity of lubricant required to prevent the initial layer from picking up and sticking must be calculated as part of the product development process. The lubricant in blended form, in the granular bulk permeates throughout the mixture or "coats" on the surface of the granules when the granules come into contact with dies and punches during compression, supplying lubrication and lowering friction. It is also effective in lowering inter-granular adhesion, lubrication can also affect other vital quality indicators including tablet breaking force and dissolving. Therefore, rather than adding lubricant directly to the granules, the efficacy of lubricant on the fundamental quality features of the tablet has been investigated by adding it to the dies and punches. External lubrication is the term used in the literature to describe this process.

External lubrication, in which the lubricant is sprayed over the die and punches for each compression cycle rather than being added to the bulk powder combination, has been demonstrated to enhance crushing strength by 40% without extending tablet disintegration time. The presence of a coat of magnesium stearate on the tablet was confirmed using a scanning electron microscope. Though this new technique tends to be beneficial for monolayer tablets, it may be utilized to better understand the influence of lubricant on bilayer tablet quality features.

Layer ratio and layer sequence:

The least amount of study has been done in this section. The weight of the two layers in a bilayer tablet isn't usually the same when it's being designed. In most cases, there will be a substantial variation in the ratio of their weights. However, it has been shown that in most cases, the ratio between the first and second layers might be 1:1, 1:2, or even 1:3 in rare cases. However, it is difficult to keep the weight of the second layer constant with that of the first layer, which is frequently hefty, and this presents a problem for producing bilayer medications.

Environmental condition:

The environment must be taken into consideration when creating the bilayer tablet since factors like humidity and moisture have a big impact on how compact the bilayer tablets are. Although the impact of moisture on the strength of bilayer tablets has only been studied by a small number of authors. Bilayer tablets made of hygroscopic material will respond to the relative humidity of the air around them by allowing moisture to enter or exit their pore structure.

If the compacts contain starches, microcrystalline cellulose, polyvinylpyrrolidone, crospovidone, hydroxypropyl methylcellulose, sodium starch glycolate, and colloidal silicon dioxide, moisture may also be able to permeate the majority of the particles. Layer expansion occurs when porous compacts and/or particles take up moisture. Any modification in layer thickness reduces the bonding between them, which could cause time-dependent delamination. It was advised to pre-condition the materials to ensure that they are in equilibrium with the amount of moisture in the air in the manufacturing area and to package the compacts in airtight, moisture-resistant blisters.

Physical stability of bilayer tablets during storage, in addition to formulation design and manufacturing process considerations, is an important factor to consider during product development because it can affect quality attributes such as tensile strength, layer adhesion, friability, and dissolution.

Upon storage, the potencies of bilayer tablets composed of plastic/brittle, brittle/brittle, and plastic/brittle were compared. During increased humidity and storage duration, the interfacial strength of biphasic tablets made with MCC in the first layer/lactose in the second and lactose in the first layer/MCC in the second decreased, whereas those made with lactose/lactose showed an improvement in tablet strength because solid bridges formed during storage.

Layer weight control:

To make sure the content uniformity of the active pharmaceutical ingredients in the bilayer tablets some precursors play a significant role, such as material flow property, particle size distribution, and the ability of the bilayers to press accurately. Each instrumented bilayer press from different vendors has its own weight control mechanism. The existing development and commercial presses provide the option of monitoring the first layer weight and the second bilayer weight. However, yet there is no commercially accessible bilayer press with a mechanism to sample the second layer weight independently. This generates a huge challenge while manufacturing the bilayer tablets. Therefore, a way should be developed to minimize this effect.

Some precursors, such as material flow characteristics, particle size distribution, and the ability of the bilayers to press precisely, play a significant role in ensuring the content uniformity of the active pharmaceutical ingredients in the bilayer tablets. Every instrumented bilayer press sold by various vendors has a unique weight control system. The second and the first layer weight may both be monitored using the development and commercial presses now in use. However, there is currently no commercially available bilayer press that has a mechanism to separately sample the weight of the second layer. This is a significant challenge in making bilayer tablets. Therefore, a strategy for reducing this impact should be established.

TYPE OF PRESS FOR BILAYER TABLET (Ghugarkar et al. 2015)

1. Single sided tablet press.
2. Double sided tablet press.
3. Bilayer tablet press with displacement monitoring.

Single sided tablet press:

The most basic layout is a single-sided press with the doublet feeder's two chambers kept apart. The two distinct layers of tablets are produced in each chamber using different power sources that are either forced or gravity fed. The first layer of powder and then the second layer of powder are put onto the die as it passes beneath the feeder. The tablet is then compressed completely in one or two stages.



Figure 4. Different Types of Tablet Compression Machines a) Single-sided tablet press
b) Double-sided tablet press c) Bilayer tablet press with displacement monitoring

Limitations of the single sided press.

There is no weight control or monitoring of the individual layers.

- 1) The two levels are not clearly separated visually.
- 2) Due to the small compression roller, the first layer dwell time was extremely brief, perhaps causing issues with capping, hardness, and poor deaeration.
- 3) This can be fixed by slowing down the turret rotation (to increase the dwell time), but the output of tablets will be reduced as a result.

Double sided tablet press: Compression force is used to monitor and regulate tablet weight in the majority of double-sided tablet presses with automated production control. The control system measures, at primary compression of the layer, the effective peak compression force applied to each individual tablet or layer. The signal from this observed peak compression force is what the control system uses to reject out-of-tolerance and adjust the die fill depth as necessary. (Santra, Mahanti, and Bera 2021)

Bilayer tablet press with displacement monitoring:

The press's design is based on displacement monitoring and it works on a principle that is fundamentally different from the principle based on compression force. The press design is sensitive when measuring displacement and it depends on the applied pre-compressed force unless the tablet weight.

QUALITY AND GMP REQUIREMENTS (Darekar, Jadhav, and Saudager, n.d.)

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

1. Preventing capping and separation of the two individual layers that constitute the bilayer tablet.
2. Providing adequate hardness.
3. Avoid cross-contamination in between the layers.
4. Making the two levels' visual differences from one another obvious.
5. High yield Accurate and individual weight control of the two layers.

VARIOUS STEPS INVOLVED IN BILAYER TABLET FORMULATION (P. Reddy, Rao, and Kumar, n.d.)

- (A) Filling of first layer into die
- (B) First compression for first layer
- (C) Filling of second layer
- (D) Second compression for second layer
- (E) Ejection of bilayer tablet

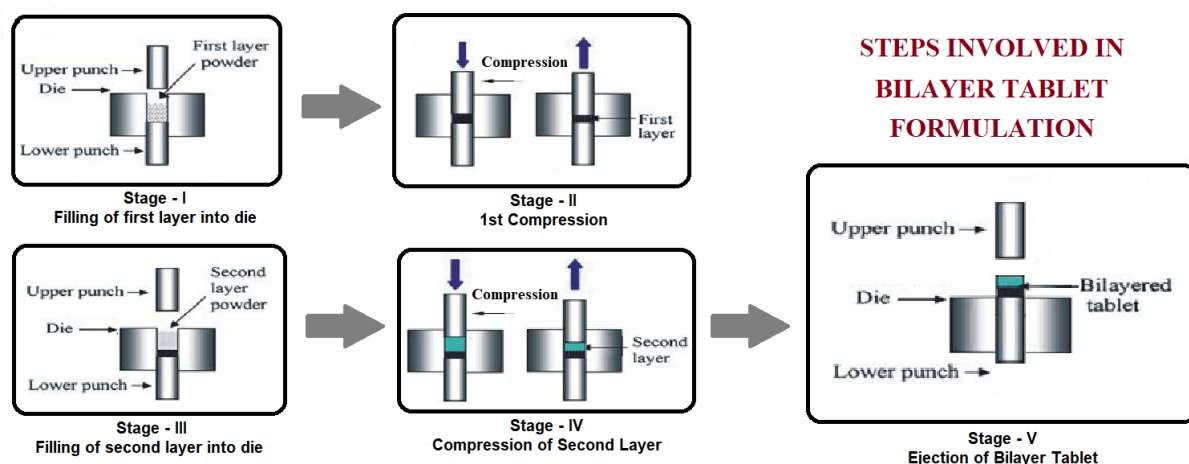


Figure 5. Various steps involved in bilayer tablet formulation

NEED FOR BILAYER TABLET (Mondal, Bhowmick, and Datta 2019)

1. For the administration of fixed-dose combinations of various APIs, to extend the shelf life of pharmaceutical products, buccal/mucoadhesive delivery systems, and creation of innovative drug delivery systems such as chewing devices and floating tablets for gastro-retentive drug delivery.
2. Controlling the delivery rate of either single or two different active pharmaceutical ingredients.
3. To swellable/erodible barriers for modified release by either sandwiching one or two inactive layers between the total surface area available for the API layer or both.
4. To isolate Active Pharmaceutical Ingredients (APIs) that are incompatible from one another and to control API release from one layer by employing a functional attribute of the other layer (such as osmotic property).

RECENT DEVELOPMENTS IN BILAYER TABLET

Bi-layer tablets have made it possible to create active ingredient release profiles that are predetermined and to incorporate incompatible active ingredients into a single unit dosage form. There has been a significant amount of research in this area. The table below provides explanations for a few of the most recent findings.

S.NO.	Drug	Dosages	Techniques	Type of Release	Treatment	Reference
1.	ATORVASTATIN AND CAPTOPRIL	10 mg and 25 mg	Melt granulation	Sustained Release	hyperlipidaemia and hypertension	(Hari et al. 2020)
2.	Diclofenac Sodium with Ranitidine HCL	1500 mg and 1000 mg	Dry granulation	Sustained Release	reduces the symptoms of Ulcer	(Shirse 2012)
3.	BACLOFEN	5mg and 21mg	Dry granulation	Sustained Release	spasticity	(Makwana et al. 2015)
4.	Nebivolol Hydrochloride and Nateglinide	10 mg and 60 mg	Wet granulation	Sustained Release	Diabetes and Hypertension	(Ryakala et al. 2015)
5.	ATENOLOL	10mg and 25 mg	Dry granulation	Sustained Release	antihypertensive drug to diagnose and cure hypertension and angina pectoris for chronic patients	(Parashar and Singh 2018)
6.	ATORVASTATIN AND ATENOLOL	40mg and 50 mg	Kneading\ wet granulation	Sustained release	hypertension and hypercholesterolemia	(Dey, Chattopadhyay, and Mazumder 2014)
7.	Metoclopramide HCl and Aceclofenac	15mg and 60mg	Wet granulation	Fixed release	Metoclopramide HCl effective in the treatment of nausea and pain associated with migraine Aceclofenac useful in the treatment of migraine	(Jethara and Patel 2015)
8.	PROPRANOLOL HYDROCHLORIDE	25mg and 55mg	Wet granulation	Sustained release	IR layer reduces Blood pressure within a short period of time while a maintenance dose of Propranolol HCl will maintain plasma concentration within the therapeutic range for 12hrs having a short half-life (3-5 hr)	(Momin Shahanoor, Khan Shadab, and Ghadage D.M. 2017)
9.	Ramipril and Propranolol Hydrochloride	2.5mg and 80mg	Dry granulation	Sustained release	Ramipril is an ACE inhibitor and propranolol hydrochloride is a beta-blocker they are used to the treatment of hypertension	(M. S. Reddy and Kumari, n.d.)

10.	Paracetamol and Tizanidine	600mg and 2.29mg	Wet granulation	Sustained release	treating Rheumatoid arthritis, Osteoarthritis & other severe pain syndromes	(Kumar Sarangi et al. 2014)
11.	Lornoxicam	4mg and 12mg	Dry granulation	Sustained release	It is widely used for the symptomatic treatment of pain and inflammation in patients with rheumatoid arthritis and osteoarthritis	(Vishal et al., n.d.)
12.	Bimodal release of venlafaxine hydrochloride	37.5mg and	Wet granulation	Sustained release	antidepressant	(Momin, Kane, and Abhang 2015)
13.	Losartan Potassium	5mg and 45mg	Dry granulation	Sustained release	hypertension and congestive heart failure	(Chinchulkar et al. 2021)
14.	ATENOLOL AND LOVASTATIN	50mg and 50mg	Wet granulation	Sustained release	hypertension	(Saikrishna et al., n.d.)
15.	Metoclopramide Hydrochloride and Diclofenac Sodium	10mg and 50mg	Dry granulation	Sustained release	treatment of migraine headaches	(Gattani et al. 2012)
16.	Esomeprazole and Clarithromycin	20mg and 250mg	Direct compression	Controlled release	treatment of Helicobacter pylori infection	(Israr et al. 2022)
17.	Lornoxicam	4mg and 12mg	roll-compaction (IR) and wet granulation method (SR)	Sustained release	for anti-inflammatory effect	(Vishal et al., n.d.)
18.	Metformin and Glipizide	500mg and 5mg	two controlled release system	Extended-release	type II noninsulin-dependent diabetes mellitus	(Defang et al. 2005)

CONCLUSION

The bilayer tablet is an improved advanced technology to overwhelm the inadequacy of the single-layered tablet. It offers an excellent opportunity for manufacturers to separate themselves from their competitors, improve the efficacy of their products, and protect against impersonator products. There are numerous applications of the bilayer tablet it consists of massive partially coated or multi-layered matrices.

Bilayer tablets contain two distinct layers, immediate release layer and sustained release layers. The initial dose is present in the immediate release layer, which contains super disintegrants to promote drug release rate and attains the onset of action (quick release) as loading dose. Whereas the sustained release (maintenance bioavailability of drug) layer releases the drug in a sustained manner for a prolonged time period. It is basically popular for successfully obtaining the sequential release of such different drugs that are incompatible and use to incorporate in one dose to formulate combination dosage forms while separating two incompatible substances. Bi-layer tablet quality and GMP requirements can vary widely. This explains why a wide variety of presses, from simple single-sided presses to highly complex equipment, are utilized to create bi-layer tablets. Compression force-controlled press has its limits when a high-quality bi-layer tablet is to be made together with precise weight control of each layer due to their inadequate sensitivity and, consequently, lack of accuracy at low compression pressures essential to secure bound between the interlayer. When punching press speed is high, these issues are significantly more obvious. With the shift weight control system-based presses, precise layer weight monitoring for individual layers and control can be accomplished at high speeds while also lowering the risk of layer separation.

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