**Journal of Biomedical and Pharmaceutical Research**
**Available Online at www.jbpr.in**
**CODEN: - JBPRAU (Source: - American Chemical Society)**
**NLM (National Library of Medicine): ID: (101671502)**
**Index Copernicus Value 2021: 83.38**
**Volume 11, Issue 6, November-December: 2022, 33-41**

**ISSN (Online): 2279-0594**
**ISSN (Print): 2589-8752**

**Review Article**

# A Review on Bilayer Tablet Technology for Multi Modal Drug Delivery

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**Article Info:** Received 14 October 2022; Accepted 27 November 2022
DOI: https://doi.org/10.32553/jbpr.v11i6.947
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**Conflict of interest statement:** No conflict of interest

**Abstract:**
Bilayer tablets are cutting-edge drug delivery technologies that enable the delivery of two medicines with various release patterns combined in a single unit. Bilayer tablets can deliver two incompatible medications in a single formulation, prolong the effect of the drug(s), and increase patient compliance. Bilayer tablets feature an active substance in one layer that is released immediately and another layer that is released later, either as a second dosage or in a prolonged release manner. The drawbacks of single-layered tablets are being overcome by the advancement of useful technology in bilayer tablets. Bilayer tablet technology requires a lot of resources, though. For each technical stage, a careful selection of excipients and manufacturing conditions is also necessary. High blood pressure patients frequently struggle or fail to control their BP with a single medication. To achieve treatment objectives, the majority of hypertension patients will require the use of two or more antihypertensive medications. When treating hypertension in patients whose blood pressure cannot be well controlled with monotherapy, combinations of antihypertensive medications from different categories have been demonstrated to be more successful than either medication alone. Combining two antihypertensive drugs with complementary modes of action may decrease blood pressure more effectively than using any one of these drugs by alone.
**Keywords:** Bi-layer tablet, Tablet manufacturing, Bi-layer tableting techniques.

## Introduction

In the recent years, pharmaceutical drug product manufacturers have oriented their product development activities to fixed dose combinations (FDCs) for treatments like type 2 diabetes, hypertension, pain and HIV/AIDS to advert a few. Several different approaches are been employed to deliver the FDC products to the patients such as multilayer tablets (Benkerrour et al., 2004), bilayer floating tablet (Ranade et al., 2012; Lalita et al., 2013), compression coating, active coating (Desai et al., 2013; Charlton and Nicholson, 2010) and buccal/mucoadhesive delivery systems (Park and Munday, 2002; Yedurkar et al., 2012).

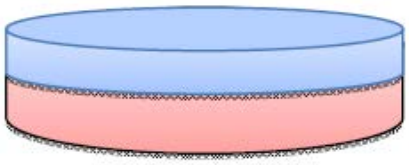

**Figure 1.1: Bilayer Tablet**

Among these approaches, the multilayer tablets drug delivery is gaining popularity and particularly the bilayer technology has attracted formulator's attention for the development of products for life cycle management (LCM). The residual stress distribution in the tablet is suspected to be a major cause of the resultant tablet in homogeneity causing the tablet to fracture and split apart (Inman et al., 2007). The fracture of multilayered tablets is often the result of an interfacial crack driven by residual stresses in the tablet and propagating a finite distance within the tablet. This leads to capping and lamination, which may not always be immediately apparent after compaction (Hiestand et al., 1977; Abdul and Poddar, 2004; Inman et al., 2007).

**1.1 Objectives for designing bilayered tablets:**

1. To control the delivery rate of either single (Bogan et al., 2008) or two different active pharmaceutical ingredients(s) (Kulkarni et al., 2009; Nirmal et al., 2008).
2. To separate incompatible APIs from each other, to control the release of one API from one layer by utilizing the functional property of other layers (such as osmotic properties).
3. To modify the total surface area available for API layer by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release (Efentakis et al., 2008; Phaechmud et al., 2008).

**1.2 Key advantages of bilayer tablets**

Multi-layer tablet dosage forms are designed for variety of reasons:

1. 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).
2. To modify 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 modified release (Efentakis and Peponaki et al., 2008; Phaechamud et al., 2008).

**1.3 Quality and GMP requirements for bilayer matrix technology:**

To produce a quality bilayer tablet, in accordance with GMP, it is important that the selected press should be capable of:

1. Preventing capping and separation of the two individual layers that constitute the bilayer tablets.
2. Providing sufficient tablet hardness.
3. Preventing cross-contamination between the two layers.

**1.4 Challenges related to bilayer technology:**

The formulators and process scientists need to overcome the challenges to deliver a robust bilayer tablet and manufacturing process. Some of the key challenges are:

1. Inaccurate individual layer weight control (Charman et al., 2002)
2. Cross contamination between the layers (Hiestand et al., 1977; Karehill et al., 1990; Poon and Bhushan, 1995; Inman et al., 2007; Akseli et al., 2013)
3. Elastic modulus mismatch between the adjacent layers. High elastic modulus ratio between adjacent layers could cause insufficient layer bonding and relatively low interfacial strength (Akseli et al., 2010)

**1.2 Factors affecting the oral sustain release dosage form design**

**(A). Pharmacokinetics factor:**

**1. Biological half-life** Drug with biological half-life of 2-8 hours are considered suitable candidate for sustain release dosage form, since this can reduce dosing frequency. However this is limited in that drugs with very short biological half-lives may require excessive large amounts of drug in each dosage unit to maintain sustained effects, forcing the dosage form itself to become limiting large.

**2. Absorption** Rate of absorption of a sustained formulating depends upon release rate constant of the drug from the dosage form, and for the drugs that are absorbed by active transport the absorption is limited to intestine.

**3. Distribution** The distribution of drugs into tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending on the time course of drug disposition. Thus for design of sustain release products, one must have information of disposition of drug.

**4. Metabolism** The metabolic conversion to a drug is to be considered before converting into another form. Since as long as the location, rate, and extent of metabolism are known a successful sustain release product can be developed (Kumar et al., 2012).

**(B). Drug properties relevant to sustain release formulation:**

**1. Dose size** A dose size of 500-1000mg is considered maximal for a conventional dosage form. This also holds true for sustain release dosage forms. Since dose size consideration serves to be a parameter for the safety involved in administration of large amounts with narrow therapeutic range.

**2. Ionization, pka and aqueous solubility** Most drugs are weak acids or bases and in order for a drug to get absorbed, it must dissolve in the aqueous phase surrounding the site of administration and then partition into the absorbing membrane.

**3. Partition coefficient** Bioavailability of a drug is largely influenced by the partition coefficient, as the biological membrane is lipophilic in nature transport of drug across the membrane largely depends upon the partition coefficient of the drug. Drugs having low partition coefficient are considered as poor candidate for the sustain release formulation as it will be localized in the aqueous phase.

**4. Drug stability** When drugs are orally administered, they come across acid-base hydrolysis and enzymatic degradation. In this case, if the drug is unstable in stomach, drug release system which provides medication over extended period of time is preferred, whereas in contrast the drug unstable in intestine will face problem of less bioavailability (Kumar et al 2012, Islam et al., 2011).

**1.2.1 Design of oral sustained release drug delivery system**

The oral route administration is mostly adopted route because of its comfortable dosage form, design and patient care. Several parameters should be kept in mind before formulating sustain release dosage form which includes various pH in GIT, the gastrointestinal motility, the enzyme system and its effect on the dosage form and the drug. Most of sustained release dosage form follows the mechanism of diffusion, dissolution or combination of both, to produce slow release of drug at predetermined rate. Plasma drug concentration-profiles for conventional tablet or capsule formulation, a sustained release formulation, and a zero order sustained release formulation are as follow (Lachman et al., 2009).

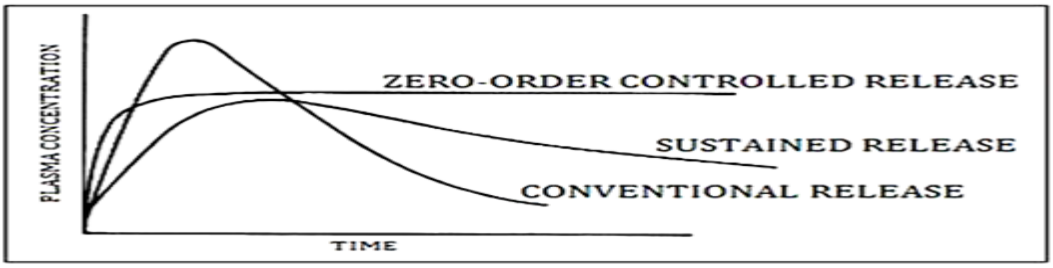


**Figure 1.2: Plasma drug concentration profile for conventional release, sustained release and zero order controlled release formulation**

**Merits**

a) Control of drug therapy is achieved.
b) Rate and extent of drug absorption can be is modified
c) Frequency of drug administration is reduced.
d) Patient compliance can be improved.
e) Drug administration can be made convenient
f) Maximizing the availability of drug with minimum dose.
g) The safety margin of high potency drug can be increased.

**Demerits**

a) It not permits prompt termination of therapy.
b) Less flexibility in dose adjustment.
c) These dosage forms are designed on the basis of average biological half life.
d) They are costly (Lachman et al., 2009).

**1.2.2 Immediate Release** (Bhavesh et al., 2008)

An immediate release dosage form allows a manufacturer to extend market exclusivity, while offering patients a convenient dosage form or dosage regimen. Immediate Release Tablets are those tablets which are designed to disintegrate and release their medication with no special rate controlling features, such as special coatings and other techniques. Recently immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer, has quick onset of action is economical and lead to better patient compliance. Three major factors that govern the rate and extent of drug absorption of immediate release (IR) solid oral dosage forms:

1. Dissolution rate.
2. Solubility.
3. Intestinal permeability.

For IR dosage forms containing active pharmaceutical ingredients (APIs) showing high solubility, high intestinal permeability and rapid dissolution, a waiver from performing bioequivalence studies (biowaiver) can be scientifically justified.

**1.3 Bilayer tablet compression machines:**

Several bilayer tabletting presses such as Kilian, Oystar Manesty, Hata, Korsch, Courtoy, Fette, Kilian and Piccola are commercially available for formulators and process development scientists. Most instrumented bilayer presses are equipped with control systems to automatically evaluate compression forces and punch displacements on the presses. Recent advances in the compression machine design and its accessories have provided opportunities to choose the features (first layer sampling, sealed feeders, precompression rolls, sensitivity of layers strain gauge, maximum upper punch penetration) as per the requirements of the product under study.

new model presses are equipped with software packages for data acquisition, calculate results compare parameters within and among the batches, correlate material properties to product quality, and to monitor and control the critical bilayer compression parameters. The precision needed for controlling the individual layer weight demands consistent behavior of the final blend such as flow property and particle size distribution (Akhtar et al., 2020).

**1.3.1 Bi-Layer Tablet Press (Present Technology):**

The XM 12 Bi-Layer Tablet Press features a retractable second layer feeder that permits automated first layer sampling at production speeds. The first layer sampling capability also offers a hardening feature, which the main compression station will automatically compress, the first layer tablet for in-process measurement. The two feeders are zero clearance and are configured with an integrated dust extraction manifold which cleans the die table and completely eliminates any potential for cross contamination. WipCon® solution available for potent for layer Tablet Press is a small-scale press which is ideal for product development scale-up, clinical trials and midrange production. Bi-layer execution, single-layer conversion kit and exchangeable turret offer unprecedented flexibility. The XM 12 Bi-Layer Tablet Press offers a new standard in GMP with extreme accessibility to the compression zone and a combination of quick disconnects and smooths surfaces which permit fast cleaning.

**1.3.2 Advantages:**

- Flexible Concept
- Fast and Easy Changeover
- Design Advantages
- Full instrumentation
- Containment Solution

**1.3.3 For Small-Scale Bi-layer Applications:**

The KORSCH XM 12 Bi-Layer Tablet Press is a small scale press which is ideal for product development, scale-up, Clinical trials, and midrange production. The bi-layer execution, single-layer conversion kit, and exchangeable turret Offer unprecedented flexibility. The XM 12 Bilayer tablet Press offers a new standard in GMP with extreme accessibility to the compression zone and combinations of quick disconnects and smooth surfaces that permit fast cleaning and changeover. The machine features a 5 kN tamping station, 40 kN precompression station, 80 kN main compression station, and a unique structural design that eliminates vibration to the head piece and base frame. The result is an extreme reduction in the operating noise level. The XM 12 Bilayer tablet Press features a retractable second speeds. The first layer sampling capability also offers a hardening feature, in which the main compression station will automatically compress the first layer tablet for in-process measurement. The two feeders are zero clearance and are configured with an integrated dust extraction manifold, which cleans the die table and completely eliminates any potential for cross-contamination.

**1.3.4 Properties**

- Free format graphic and statistical analysis to allow the export of many data formats.
- Reports can be automatically generated in a variety of data formats with and without an electronic signature.
- Charts can be dimensioned, comments added, formatted and exported before being processed in the MS Office world.
- Finger print recording during production. Overlay Technology allows safe and quick recognition of subsequent waveforms.
- Correlation Analysis to establish a "Knowledge Database" that serves to easily compare the properties of known and unknown ingredients. The database enables the user to correlate measuring values from the tabletting process and derived and externally recorded quantities (e.g. tablet hardness, density, etc.).

**1.3.5 XM 12 WipCon® Development & Analysis:**

- Minimum space requirements, portable design
- Best cleaning / decontamination results for product specific demands
- Optimized glove port configuration
- All types of make/break connections possible
- High containment range for lab scale and medium size batches OEB 5 (1 μg/m³ > OEL >0.1 μg/m³) with RTP transfer system

Negative pressure control and safe-change filter box attached or separate, depending on space availability.

**1.3.6 Technologies Presently Available: (Satpute and Rache, 2020)**

**1. OROS® Push Pull Technology:** This system 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 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 semi permeable membrane surrounds the tablet core. (Mishra et.al., 2013)

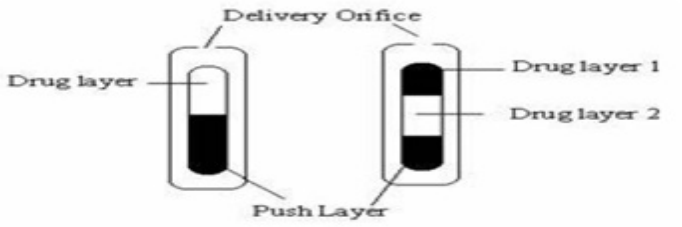


**Figure 1.3: OROS® Push Pull Technology**

**2. L-OROS$^{TM}$ 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, than osmotic push layer and than a semi permeable membrane, drilled with an exit orifice.

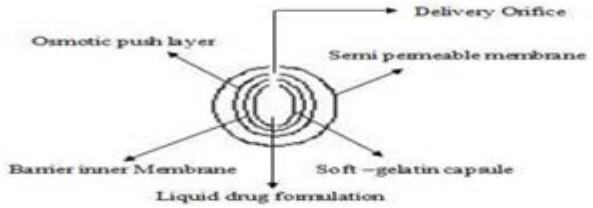


**Figure 1.4: L-OROS$^{TM}$ Technology**

**3. EN SO TROL Technology:** Solubility enhancement of an order of magnitude or to create optimized dosage form Shire laboratory use an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies (Kale et al.,2011).


**Figure 1.5: EN SO TROL technology**

**4. 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 opposes like a miniature syringe and reglious minute quantity of concentrated form in continues and consistent from over months or Year.

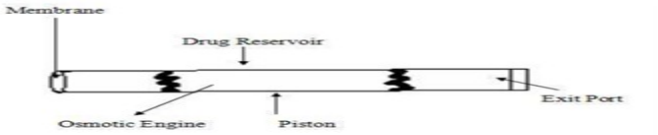


**Figure 1.6: DUROS Technology**

**5. Elan drug technologies' Dual release drug delivery system: (DUREDAS™ Technology):** It is a bilayer tablet which can provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form. The tabletting process can provide an immediate release granulate and a 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. (mishra et al.,2013)

**1.3.7 Benefits offered by the DUREDAS™ technology include:**

a. Bilayer tabletting technology.
b. Tailored release rate of two drug components.
c. Capability of two different CR formulations combined.
d. Capability for immediate release and modified release components in one tablet.
e. Unit dose, tablet presentation.

The DUREDAS™ system can easily be manipulated to allow incorporation of two controlled release formulations in the bi-layer. Two different release rates can be achieved from each side. In this way greater prolongation of sustained release can be achieved.

**Conclusion**

Bi-layer pills can help producers differentiate themselves from rivals, increase the potency of their goods, and protect themselves from counterfeiters. The GMP standards and the quality of bi-layer tablets can vary greatly. This explains why a variety of presses, from straightforward single-sided presses to highly complex equipment, are used to produce bilayer tablets. Compression forcecontrolled presses are undoubtedly limited in producing a high-quality bi-layer tablet with precise weight control of both layers because of their inadequate sensitivity and, consequently, lack of precision at the modest compression pressures required for interlayer bonding. Such issues are exacerbated by high or increased tableting rates. Punches based on displacement weight control systems can monitor and manage individual layer weights accurately at high speeds while also lowering the possibility of layer separation.

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