INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

**Review Article**

# Novel Approach And Current Applications Of Bilayer Tablet

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ARTICLE INFO

Received: 27 June 2024
Accepted: 01 July 2024
Published: 20 July 2024

Keywords:
Bi-layer tablet, Sustained release, Tablet presses, OROS® push pulls Technology, Modified release dosage form

DOI:
10.5281/zenodo.12740601

## ABSTRACT

The bi-layer tablet represents a new era in the successful creation of controlled release formulations with numerous characteristics to ensure successful drug delivery. Bi-layer tablets may be the best solution for avoiding chemical incompatibilities across APIs by physical separation and for developing distinct medication release patterns. A bi-layer tablet is appropriate for the sequential release of two medications in combination, as well as for the sustained release of a tablet, with one layer for rapid release as a loading dosage and the second layer for maintenance dose. As a result, the usage of bi-layer tablets is considerably different for anti-hypertensive, diabetic, anti-inflammatory, and analgesic medications, where combination therapy is frequently utilized. Several pharmaceutical firms are now developing bi-layer tablets for a number of reasons, including patent extension, therapeutic, and marketing. Although general tablet production principles remain the same, there is considerably more to consider since producing multi-layer tablets requires several, frequently incompatible components, extra equipment, and other formulation and operational issues. The current article introduces bi-layer tablet technology, challenges in bi-layer tablet manufacturing, various tablet presses used, various bi-layer Tabletting techniques, and current application in the field of bi-layer technology.

## INTRODUCTION

On the basis of these considerations, we have proposed a bilayer tablet, in which the one layer is formulated to obtain immediate release of the drug, with the aim of reaching a high serum concentration in a short period of time. The second layer is a controlled release hydrophilic matrix, which is designed to maintain an effective plasma level for a prolonged period of time. The pharmacokinetic advantage relies on the fact that drug release from fast releasing layer leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining layer [1]. The design of multi-layer tablet dosage forms was motivated by several factors: regulating the rate of

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**Relevant conflicts of interest/financial disclosures**: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

delivery of one or two distinct active pharmaceutical ingredients (API); separating incompatible APIs from one another; regulating the release of API from one layer by leveraging the functional property of the other layer (e.g., osmotic property); altering the total surface area available for API layer by sandwiching with one or two inactive layers to achieve erodible/swellable barriers for modified release; administering fixed dose combinations of various APIs; extending the life cycle of drug products; and creating innovative drug delivery systems like chewing devices, buccal/mucoadhesive delivery systems, and floating tablets for gastro-retentive drug delivery[2]. Comparing bilayer tablets with conventional monolayer tablets, there are a few significant benefits. For example, these tablets are frequently used to physically separate formulation components in order to avoid chemical incompatibilities. Additionally, by combining layers with different release patterns or slow-release with immediate-release layers, bilayer tablets have made it possible to develop controlled delivery of active pharmaceutical ingredients with predefined release profiles [3]. However, due to 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, these drug delivery devices are mechanically complicated to design and manufacture, and it is harder to predict their long-term mechanical properties. As a result, the main challenge that needs to be addressed is to fully comprehend the causes of these issues at both the micro- and macroscales and to create solutions for them during the solid dosage delivery development [4, 5].

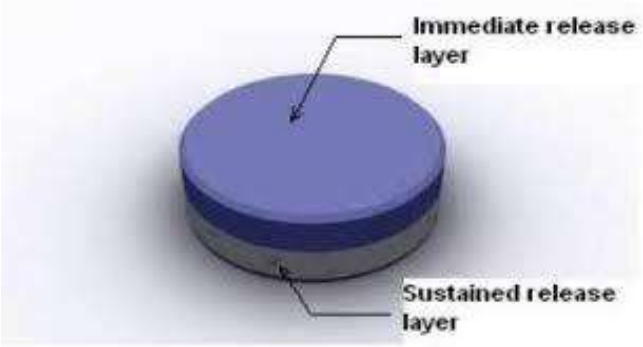


**Figure 1: Image of bilayer tablet**

## NEED OF BILAYER TABLETS [6,7,8]

1. For the administration of fixed dose combinations of different APIs, prolong the drug product life cycle, buccal/mucoadhesive delivery systems; fabricate novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery.
2. Controlling the delivery rate of either single or two different active pharmaceutical ingredient(s)
3. To modify the total surface area available for API layer either by sandwiching with one or two in active layers in order to achieve swellable/erodible barriers for modified release.
4. To separate incompatible Active pharmaceutical ingredient (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)

## ADVANTAGES OF BILAYER TABLET DOSAGE FORM

1. Bi-layer execution with optional single-layer conversion kit.
2. Cost is lower compared to all other oral dosage form.

3. Greatest chemical and microbial stability over all oral dosage form.
4. Objectionable odour and bitter taste can be masked by coating technique.
5. Flexible Concept.
6. They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
7. Easy to swallowing with least tendency for hangup.
8. Suitable for large scale production.

**DISADVANTAGES OF BILAYER TABLET DOSAGE FORM**

1. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
2. Bitter tasting drugs, drugs with an objectionable Odour or drugs that are sensitive to oxygen may require encapsulation or coating.
3. Difficult to swallow in case of children and unconscious patients.
4. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.

**IDEAL CHARACTERSTICS OF BILAYER TABLETS**

1. A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration and contamination.
2. It should have sufficient strength to with stand mechanical shock during its production packaging, shipping and dispensing.
3. 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 man.
4. It must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

**TYPES OF BILAYER TABLETS**

**a. 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.[9]

**b. Heterogenous Type**

Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances.[9]

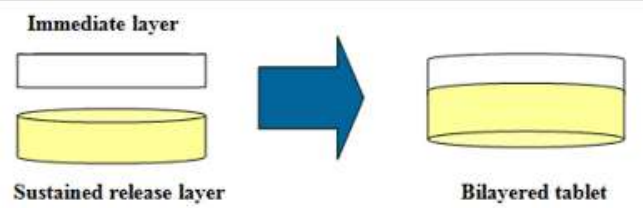


**Figure No. 2: Bilayer Tablets (the same drug with different release pattern) homogeneous)**

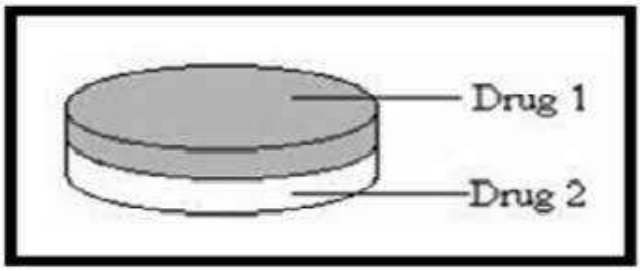


**Figure No. 3: Bilayer Tablets (with two drugs heterogenous)**

## MECHANISM OF DRUG RELEASE [10]

Bilayer tablet has a matrix core containing active drug and modulating layers or barriers in it having the ability to erode. These layers act by limiting the surface available for drug release. Thus, the interaction between active solute and dissolution medium is delayed, along with this solvent penetration rate is controlled and core is preserved for some duration. Hence, the Burst effect can be achieved in the desired range and constant drug release can be maintained. After this phase due to barrier erosion surface available for drug release increases and there is a decrease in delivery rate due to the saturation effect. Various dissolution patterns can be achieved such as pulsatile, extended-release for different drugs by varying the formulation of
layers.

## CHALLENGES IN BILAYER MANUFACTURING.[11]

Conceptually, bilayer tablets can be seen as two single-layer tablets compressed into one. In Practice, there are some manufacturing challenges.

1. **Delamination:**

Tablet falls apart when the two halves of the tablet do not bond completely. The two granulations should adhere when compressed.

2. **Cross-contamination:**

When the granulation of the first layer intermingles with the granulation of the second layer or vice versa, cross-contamination occurs. It may conquer the very purpose of the bilayer tablet. Proper dust collection goes a long way toward preventing cross contamination.

3. **Production yields:**

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

4. **Cost:**

Bilayer tableting is more expensive than single-layer tableting for several reasons. First, the tablet press costs more. Second, the press generally runs more slowly in bilayer mode. Third, development of two compatible granulations is must, which means more time spent on formulation development, analysis and validation. These factors, if not well controlled/optimized, in one way or another will impact the bilayer compression per se and the quality attributes of the bilayer tablets (sufficient mechanical strength to maintain its integrity and individual layer weight control). Therefore, it is critical to obtain an insight into the root causes to enable design of a robust product and process.

## TYPES OF BILAYER TABLET PRESS

1. **Single sided tablet press**

**Figure No.4 : Single tablet press**

The simplest design is a single sided press with both chambers of the doublet feeder separated from each other. Each chamber is gravity or forced fed with different power, producing the two individual layers of tablets. When die passes under the feeder, it is first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps [12].

**Limitations of the single sided press**

1. No weight monitoring / control of the individual layers.
2. No distinct visual separation between the two layers.
3. Capping and hardness problems

**2. Double sided tablet press**

In most double-sided tablet presses with automated production control use compression force to monitor and control tablet weight. The compression force exerted on each individual tablet or layer is measured by the control system at main compression of the layer [13]. This compression force is the signal used by the control system to reject out of tolerance and correct the die fill depth when required.

**Advantages [15,16,17]**

1. Displacement weight monitoring for accurate and independent weight control of the
2. individual layer.
3. Low compression force exerted on the first layer to avoid capping and separation of the
4. individual layer.
5. Increased dwell time at pre-compression of both primary and secondary layer to provide
6. sufficient hardness at maximum turret speed.
7. Maximum prevention of cross-contamination between two layers.


**Figure No.5: Double sided tablet press**

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

The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied precompression force [14].

**Advantages**

1. Weight monitoring / control weight of the individual layers.
2. Avoid capping and separation of the two individual layers.
3. Independence from the machine stiffness.
4. Provide sufficient hardness at maximum turret speed.
5. Maximum prevention of cross-contamination between the two layers.

**Figure No.6: Bilayer tablet press with displacement monitoring**

6. **Clear visual separation between the two layers and maximized yield.**

**Preparation of bilayer tablets**

Bilayer tablets are prepared with one layer of drug for immediate release and second layer designed to release drug either as a second dose or in an extended release form. To produce adequate tablet formulation, certain requirements such as sufficient mechanical strength and desired drug release profile must be met. At times, this may be difficult task for formulator to achieve these conditions especially in bilayer tablet formulation, where double compression technique is involved, because of poor flow and compatibility characteristic of the drug which will result in capping and/or lamination [18].

1. **Compaction:**

The process by which the porosity of a given powder is decreased as a result of its grains being squeezed together by the weight of mechanical means. The compaction of a material involves both the compressibility and consolidation.

2. **Compression:**

It is defined as reduction in bulk volume by eliminating voids and bringing particles into closer contacts.

3. **Consolidation:** It is the property of the material in which there is increased mechanical strength due to inter particulate interaction (bonding). The compression force on layer 1 was found to be major factor influencing tablet delamination.

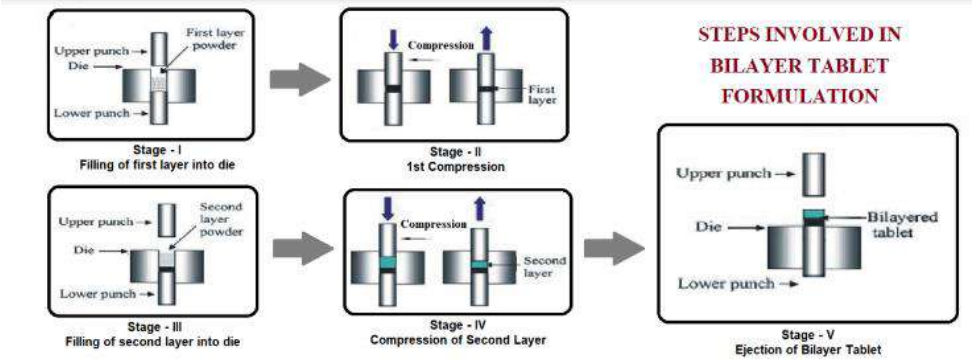


**Figure No 7 : Various steps involved in bilayer tablet formulation**

**General properties of Bi-Layer Tablet Dosage Forms [19]**

1. A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration, and contamination.
2. Should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
3. 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.
4. Must have a chemical stability shelf-life, so as not to follow alteration of the medicinal
5. agents.

GMP-requirements of quality bi-layer tablet [20]

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

**VARIOUS TECHNIQUES FOR BILAYER TABLET [21-22]**

**OROS® push pulls 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.

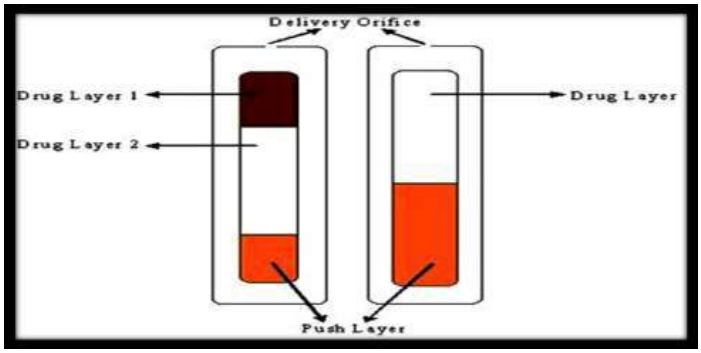


**Figure No 8: OROS® push pulls Technology**

**L-OROSTM 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 then a semi permeable membrane, drilled with an exit orifice.

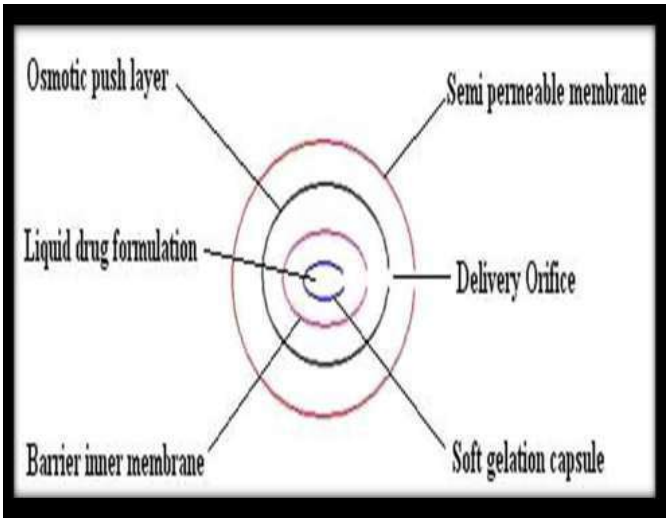


**Figure No.9: L-OROSTM Technology**

**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.

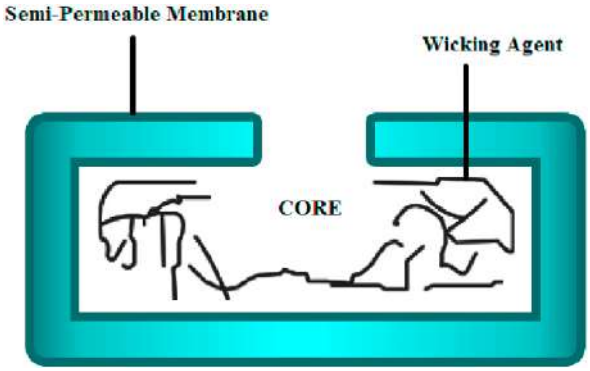


**Figure No 10: EN SO TROL Technology**

**DUREDAS™ Technology**

This system is also known as Elan drug technologies' Dual release drug delivery system. DUREDAS™ Technology 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 tableting 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.

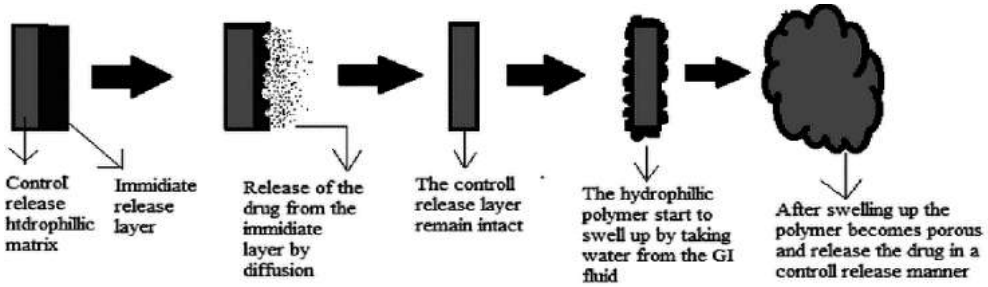


**Figure No 11: DUREDAS™ Technology**

**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 release minute quantity of concentrated form in continues and consistent from over months or year.

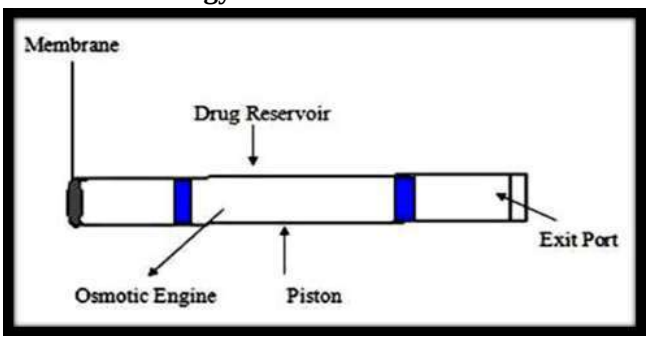


**Figure No 12: DUROS Technology**

**CURENT APPLICATION OF BILAYER TABLET**

The introduction of bilayer tablets into the pharmaceutical industry has enabled the development of pre-determined release profiles of active ingredients and incorporation of incompatible active ingredients into the single unit

dosage form. Large number of work has been done in this field. Some of the recent findings are explained in the preceding.

**Table 1 : Various advancements in the field of Bilayer Tablets**

| Drug(s) | Dosage Form | Rationale | Ref. No. |
|---|---|---|---|
| Atorvastatin, Atenolol | Bilayer Gastroprotective Matrix Tablet | Treatment of hypertension and hypercholesterolemia | [23] |
| Nifedipine | Gastro- Retentive Floating Bilayer Tablets | Treatment of hypertension and angina pectoris | [24] |
| Aspirin, Isosorbide 5- mono-nitrate | Sustained Bilayer tablets | Treatment of pain, fever and other inflammatory conditions | [25] |
| Pioglitazone HCI, Gliclazide | Bilayer Tablets | Treatment of Type II Diabetes | [26] |
| Losartan potassium | Bilayer tablet | Treatment of hypertension | [27] |
| Trimetazidine HCI, clopidogrel bisulphate | Bilayer tablets | Cytoprotective anti-ischemic, platelet inhibitor in acute coronary syndromes, | [28] |
| Diclofenac, Cyclobenza-prine | Bilayer tablets | Synergistic effect in pain | [29] |
| Granisetron HC1 | Bilayer buccal tablets | To overcome bioavailability problem, reducing side effects | [30] |
| Metformin HC1, | Bilayer tablets | Synergistic effect in diabetes | [31] |
| Indomethacin | Bilayer floating tablets | Biphasic drug release | [32] |
| Metformin HC1, Atorvastatin Calcium | Bilayer tablets | To develop polytherapy for the treatment of NIDDS & hyperlipidemia | [33] |
| Cefixime Trihydrate, Dicloxacilline Sodium | Bilayer tablets | Synergistic effect in bacterial infections | [34] |
| Piracetam, Vinpocetin | Bilayer tablets | Synergistic effect in Alzheimer disease | [35] |
| Metformin HCI, Pioglitazone | Bilayer tablets | Synergistic effect in diabetes mellitus | [36] |
| Atenolol | Bilayer buccal tablets | To overcome bioavailability problem, reducing side effects and frequency of administration | [37] |
| Cefuroxime Axetil Potassium Clavulanate | Bilayer tablets | Synergistic effect against microbial infections and to minimize dose dependent side effects | [38] |
| Amlodipine Besilate Metoprolol Succinate | Bilayer tablets | Synergistic effect in hypertension | [39, 40] |
| Diclofenac Sodium, Paracetamol | Bilayer tablets | Synergistic effect in pain | [41] |
| Ibuprofen, Methocarba-mol | Bilayer tablets | Synergistic effect of drugs in back pain | [42] |
| Atorvastatin Calcium | Bilayer buccal tablets | To overcome bioavailability problem, reducing side effects and frequency of administration | [43] |
| Paracetamol Diclofenac | Bilayer tablets | Synergistic effect of drugs in pain | [44] |
| Losartan | Bilayer tablets | Biphasic release profile | [45] |

| | | | |
|---|---|---|---|
| Metformin HCI, Pioglitazone | Bilayer tablets | Synergistic effect in diabetes mellitus | [46] |
| Guaifenesin | Bilayer tablets | Biphasic release profile | [47] |
| Tramadol, Acetaminophen | Bilayer tablets | Synergistic effect of drugs in pain | [48] |
| Atenolol, Lovastatin | Bilayer floating tablets | Synergistic effect in hypertension and biphasic release profile | [49] |
| Montelukast, Levocetrizine | Bilayer tablets | To improve the stability of drugs in combination | [50] |
| Salbutamol, Theophylline | Bilayer tablets | Synergistic effect of drugs in asthma | [51] |
| Glipizide, Metformin HCI | Bilayer tablets | To avoid interaction b/w incompatible drugs | [52] |
| Telmisartan Hydrochlor-thiazide | Bilayer tablets | To minimize contact b/w hydrochlorothiazide & basic component of telmisartan | [53] |
| Amlodipine, Atenolol | Bilayer tablets | To improve the stability of drugs in combination | [54] |
| Misorostol, Diclofenac | Bilayer tablets | To minimize contact b/w drugs | [55] |

## CONCLUTION

Bilayer tablet is new novel of tablet for the successful development of controlled release formulation along with many features to provide a way of successful drug delivery system. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. 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. So use of bi-layer tablets is a very different aspect for anti-hypertensive, diabetic, anti-inflammatory and analgesic drugs where combination therapy is often used. Bilayer tablet quality and GMP requirements can vary widely. This explains why many different types of presses are being used to produce bilayer tablets, ranging from simple single-sided presses to highly sophisticated machines. Compression force-controlled press is limited when a quality bi-layer tablet needs to be produced in conjunction with accurate weight control of both layers. Low precompression forces are necessary to secure interlayer bonding. But at low forces, the compression force control system is not sufficiently sensitive and therefore lacks accuracy. The use of higher compression force may rapidly result in separation and Hardness problems when compressing bilayer tablets. Present review mainly emphasizes, why bilayer tablet is considered as better option than conventional tablet.

## ACKNOWLEDGEMENT

All authors have taken part in the design and drafting of the article and revising it critically.

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HOW TO CITE: Akshay Y. Sonawane, Shubham S. Sonawane, Jyoti Khapre, Novel Approach And Current Applications Of Bilayer Tablet, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 7, 1491-1504. https://doi.org/10.5281/zenodo.12788774