

Review Article

Bi-layer tablets for various drugs: A review

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Abstract: Bi-layer tablet is a new era for successful development of controlled release formulation along with various features to provide successful drug delivery. Bilayer layer tablets have been consist of two layers which is slow release and immediate release layer. As well as improved beneficial technology to overcome the shortcoming of the single layer tablets. The preparations of bilayer tablet were needs due to separate incompatible active pharmaceutical ingredient (APIs) for each other. Bilayer tablets material involves both the compressibility and consolidation. The bilayer tablets preparing by using different techniques such as OROS® push pulls Technology, L-OROSTM Technology, EN SO TROL Technology, DUREDAS™ Technology and DUROS Technology. Various types of bilayer tablet press currently available in the market, various approaches used in bilayer tablet system, characterization as well as evaluation of the bilayer tablet system. Now a day's bilayer tablets are prepared such as "Atorvastatin, Atenolol", Nifedipine, "Aspirin, Isosorbide 5-mono-nitrate", "Pioglitazone HCl, Gliclazide", Losartan potassium, and "Trimetazidine hydrochloride, clopidogrel bisulphate".

Keywords: Bilayer tablets, Nifedipine, Sustained release, OROS® push pulls 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 an 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]. Multi-layer tablet dosage forms were designed for variety of reasons; to control the delivery rate of either single or two different active pharmaceutical ingredients (API), to separate incompatible APIs from each other, to control the release of API from one layer by utilizing the functional property of the other layer (such as, osmotic property), to modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release, to administer fixed dose combinations of different APIs, prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device, buccal/mucoadhesive delivery systems, and floating tablets for gastro-retentive drug delivery[2]. Bilayer tablets have some key advantages compared to

conventional monolayer tablets. For instance, such tablets are commonly used to avoid chemical incompatibilities of formulation components by physical separation. In addition, bilayer tablets have enabled the development of controlled delivery of active pharmaceutical ingredients with predetermined release profiles by combining layers with various release patterns, or by combining slow-release with immediate-release layers [3]. 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. Therefore, the major problem, that has to be overcome, is to understand in detail the sources of these problems in micro- and macroscales and to develop remedies to solve them during solid dosage delivery design [4, 5].

Applications [6]

- Bi-layer tablet is suitable for sequential release of two drugs in combination.
- Separate Two Incompatible Substances.

- Sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose.
- Promoting Patient Convenience and Compliance.
- Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet
- Bilayer tablets are used to deliver the loading dose and sustained dose of the same or different drugs.
- Bilayer tablets are used for bilayer floating tablets in which one layer is floating layer another one is immediate release layer of the drug.
- Bilayer tablets are used to deliver the two different drugs having different release profiles.

Advantages [7, 8]

- They are used as an extension of a conventional technology.
- Potential use of single entity feed granules.
- Separation of incompatible components.
- Patient compliance is enhanced leading to improved drug regimen efficacy.
- Patient convenience is improved because fewer daily doses are required compared to traditional delivery system.
- Maintain physical and chemical stability.
- Retain potency and ensure dose accuracy

Disadvantages [9]

- Adds complexity and bilayer rotary presses are expensive.
- Insufficient hardness, layer separation, reduced yield.
- Inaccurate individual layer weight control.
- Cross contamination between the layers.

NEED OF BILAYER TABLETS [10-12]

- 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.
- Controlling the delivery rate of either single or two different active pharmaceutical ingredients
- 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.
- 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).

CHALLENGES IN BILAYER MANUFACTURING [13]

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

Delamination

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

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.

Production yields

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

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 [14-15]

- Single sided tablet press.
- Double sided tablet press.
- Bilayer tablet press with displacement monitoring.

Single sides 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 powers, thus producing the two individual layers of the tablets. When the die passes under the feeder, it is at first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps.



Fig. 1: Single Sided Tablet Press

Limitations of single sided press

- No weight monitoring / control of the individual layers.
- No distinct visual separation between the two layers.
- Very short first layer dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping, and hardness problems.

Dwell time

Dwell time is defined as the time during which compression force is above 90% of its peak value. Longer dwell times are a major factor in producing a quality tablet, especially when compressing a difficult formulation.

Compression force

Many bilayer formulations requires a first layer compression force of less than 100 daN in order to retain the ability to bond with the second layer. Above 100daN, this ability may be lost and bonding between both layers may not be sufficient, resulting in low hardness of the bilayer tablet and separation of the two layers.

Double sided tablet press

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



Fig. 2: Double sided tablet press

Bilayer tablet press with displacement

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 pre-compression force.



Fig. 3: Bilayer tablet press with displacement

PREPARATION OF BILAYER TABLETS [16-19]

Bilayer tablets are prepared with one layer of drug for immediate release with the second layer designed to release drug later, either as a second dose or in an extended release form. The bilayer tablets with two incompatible drugs can also be prepared by compressing separate layers of each drug so as to minimize area of contact between two layers. An additional intermediate layer of inert material may also be included. 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. The compaction of a material involves both the compressibility and consolidation.

Compression

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

Consolidation

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

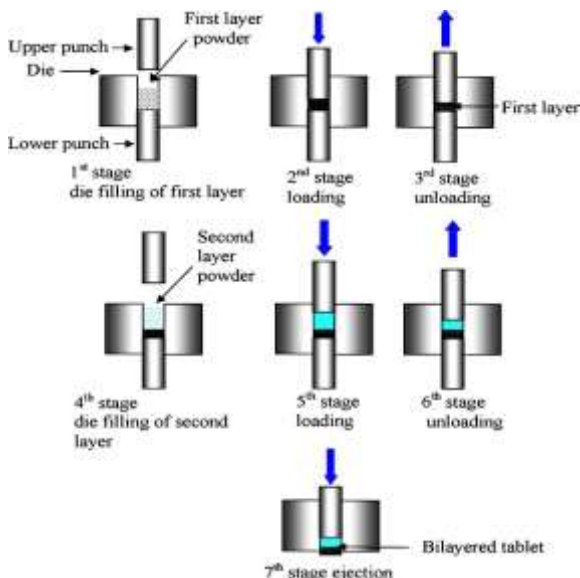


Fig. 4: Preparation of bilayer tablet Compaction

General properties of Bi-Layer Tablet Dosage Forms [20]

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

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.

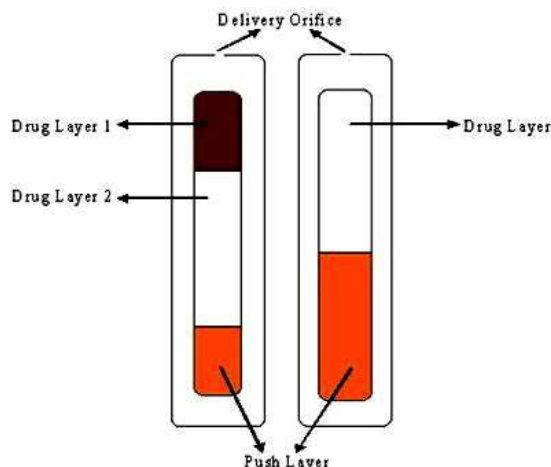


Fig. 5: Bilayer and trilayer OROS push pull technology

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.

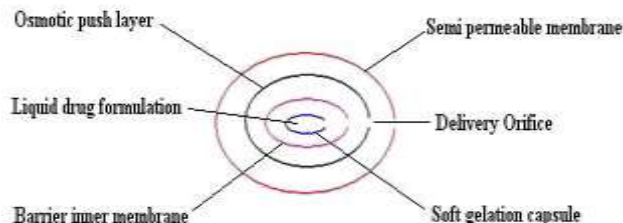


Fig.6: L-OROSTM Technology

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.

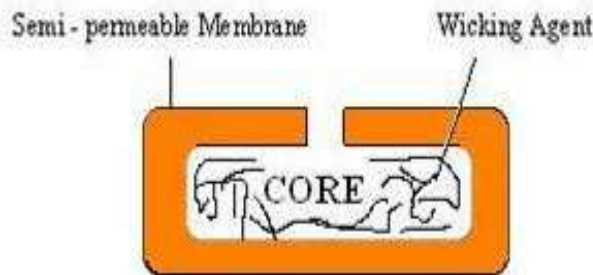


Fig. 7: EN SO TROL Technology

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.

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.

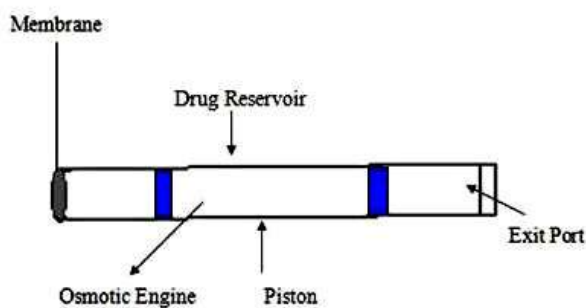


Fig. 8: DUROS Technology

Characterization of bilayer tablet [23-24]

- **Particle size distribution:** The particle size distribution was measured using sieving method
- **Photo-microscope study:** Photo-microscope image of TGG and GG was taken (X450 magnifications) by Photomicroscope.

- **Angle of repose:** The diameter of the powder cone was measured and the angle of repose was calculated using the following equation.

$$\tan \phi = h/r$$

Where, h = Height, r = Radius of the powder cone.

- **Moisture sorption capacity:** All disintegrates have capacity to absorb moisture from atmosphere which affects moisture Sensitive drugs. Moisture sorption capacity was performed by taking 1 g of disintegrate Uniformly distributed in petri-dish and kept in stability chamber at $37 \pm 1^\circ\text{C}$ and 100% relative Humidity for 2 days and investigated for the amount of moisture uptake by difference Between weights.
- **Density:** The loose bulk density (lbd) and tapped bulk density (tbd) were determined and Calculated using the following formulas.

$$\text{LBD } \frac{1}{4} \text{ weight of the powder} = \text{volume of the packing } \delta 2\text{p}$$

$$\text{TBD } \frac{1}{4} \text{ weight of the powder} = \text{tapped volume of the packing } \delta 3\text{p}$$

- **Compressibility:** The compressibility index of the disintegrate was determined by Carr's compressibility index.

$$C = 100 \times (1 - \text{pb}/\text{pt})$$

RECENT DEVELOPMENTS IN THE FIELD OF BILAYER TABLETS

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 Gastroretentive Matrix Tablet	Treatment of hypertension and hypercholesterolemia	[25]
Nifedipine	Gastro-Retentive Floating Bilayer Tablets	Treatment of hypertension and angina pectoris	[26]
Aspirin, Isosorbide 5-mono-nitrate	Sustained Bilayer tablets	Treatment of pain, fever and other inflammatory conditions	[27]
Pioglitazone HCl, Gliclazide	Bilayer Tablets	Treatment of Type II Diabetes	[28]
Losartan potassium	Bilayer tablet	Treatment of hypertension	[29]
Trimetazidine HCl, clopidogrel bisulphate	Bilayer tablets	Cytoprotective anti-ischemic, platelet inhibitor in acute coronary syndromes,	[30]
Diclofenac, Cyclobenza-prine	Bilayer tablets	Synergistic effect in pain	[31]
Granisetron HCl	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects	[32]
Metformin HCl,	Bilayer tablets	Synergistic effect in diabetes	[33]

Glimipiride			
Indomethacin	Bilayer floating tablets	Biphasic drug release	[34]
Metformin HCl, Atorvastatin Calcium	Bilayer tablets	To develop polytherapy for the treatment of NIDDS & hyperlipidemia	[35]
Cefixime Trihydrate, Dicloxacilline Sodium	Bilayer tablets	Synergistic effect in bacterial infections	[36]
Piracetam, Vinpocetin	Bilayer tablets	Synergistic effect in Alzheimer disease	[37]
Metformin HCl, Pioglitazone	Bilayer tablets	Synergistic effect in diabetes mellitus	[38]
Atenolol	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects and frequency of administration	[39]
Cefuroxime Axetil Potassium Clavulanate	Bilayer tablets	Synergistic effect against microbial infections and to minimize dose dependent side effects	[40]
Amlodipine Besilate Metoprolol Succinate	Bilayer tablets	Synergistic effect in hypertension	[41, 42]
Diclofenac Sodium, Paracetamol	Bilayer tablets	Synergistic effect in pain	[43]
Ibuprofen, Methocarpa-mol	Bilayer tablets	Synergistic effect of drugs in back pain	[44]
Atorvastatin Calcium	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects and frequency of administration	[45]
Paracetamol Diclofenac	Bilayer tablets	Synergistic effect of drugs in pain	[46]
Losartan	Bilayer tablets	Biphasic release profile	[47]
Metformin HCl, Pioglitazone	Bilayer tablets	Synergistic effect in diabetes mellitus	[48]
Guaifenesin	Bilayer tablets	Biphasic release profile	[49]
Tramadol, Acetaminophen	Bilayer tablets	Synergistic effect of drugs in pain	[50]
Atenolol, Lovastatin	Bilayer floating tablets	Synergistic effect in hypertension and biphasic release profile	[51]
Montelukast, Levocetizine	Bilayer tablets	To improve the stability of drugs in combination	[52]
Salbutamol, Theophylline	Bilayer tablets	Synergistic effect of drugs in asthma	[53]
Glipizide, Metformin HCl	Bilayer tablets	To avoid interaction b/w incompatible drugs	[54]
Telmisartan Hydrochlor- thiazide	Bilayer tablets	To minimize contact b/w hydrochlorothiazide & basic component of telmisartan	[55]
Amlodipine, Atenolol	Bilayer tablets	To improve the stability of drugs in combination	[56]
Misorostol, Diclofenac	Bilayer tablets	To minimize contact b/w drugs	[57]

CONCLUSION

Bi-layer tablets offer an excellent opportunity for manufacturers to separate themselves from their competitors, improve their products efficacy and protect against impersonator products. Bilayer layer tablets have been consist of two layers which is slow release and immediate release layer proposed a bilayer tablet, in which the one layer is formulating 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 controlling release hydrophilic matrix, which is designing to maintain an effective plasma level for a prolonged period of time. Now a day's bilayer tablets are prepared such as "Atorvastatin, Atenolol", Nifedipine, "Aspirin, Isosorbide 5-mono-nitrate", "Pioglitazone HCl, Gliclazide", Losartan potassium, and "Trimetazidine hydrochloride, clopidogrel bisulphate".

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