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Review Article

A RECENT REVIEW ON DUAL RELEASE BILAYERED TABLETS

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ABSTRACT

According to the literature review of the past decade, the design of bilayer tablets are suitable for sequential release of two drugs in which one layer is immediate release layer and the second layer as sustained release layer[1]. Bilayer tablets have been developed to achieve immediate and sustained delivery of different drugs with pre-defined release profiles. In the last decade, interested in developing a combination of two or more active pharmaceutical ingredients (API) in a single fixed dosage form has increased in the pharmaceutical industry, promoting patient convenience and compliance[2]. Bilayer tablet is suitable for sequential release of two drugs in combination or to incorporate two incompatible substances in same tablet3. This article explains about different techniques of bilayer tablet and why the development and production of quality bilayer tablets needs to be carried out and to reduce the common bilayer problems, such as layer-separation, insufficient hardness, Inaccurate individual layer weight control, cross-contamination between the layers, reduced yield etc[3].

Keywords: Bilayer tablets, common therapy, fixed dose combinations, sustained release, immediate release layer.

INTRODUCTION:

Now-a-days various developed and developing countries move towards a combination therapy for the treatment of various diseases and disorders requiring long term therapy such as hypertension, diabetes and cardiovascular diseases. Over 90% of the formulations manufactured today are ingested orally. It shows that this class of the formulation is the most popular worldwide and the major attention of the researcher is towards this direction. The major aim of controlled drug delivery is to reduce the frequency of dosing[4]. The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance.

Bilayer tablet is a fixed dose combination (FDC) intended for oral application. It contains of two layers in which one layer having conventional or immediate release part of single or multiple actives; another layer is sustained or controlled release part of single or multiple actives. They are called as "Bilayer tablets". For the identification of two drugs different colors were used[2].

Bilayer tablet is a very improved technique to overcome the single layered tablet. Bilayer tablets contain immediate, sustained release layers, and the immediate release layer delivers the initial dose, it contains super disintegrates, which promotes the drug release rate and attains the onset of action quickly (loading dose) [4]. Whereas sustained release (maintenance dose) layer releases the drug in a sustained manner for a prolonged period of time by using various polymers as release

retardants. Diabetis, antihypertensive, antihistamines, analgesics, antipyretics and antiallergenic agents are mainly suitable for this type of drug delivery[4].

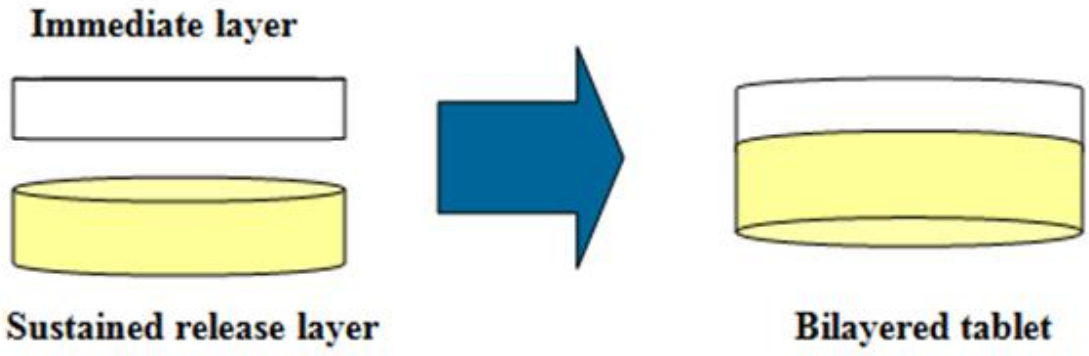

Fig. No. 1: Bilayer tablets (Same drug with different release pattern[5])

Fig. No. 2: Bilayer tablets (Different drug with different release pattern)

Multi-layer tablet dosage forms are designed for variety of reasons [6, 7]:

1. To control the drug delivery rate of either single or two different active pharmaceutical ingredients.
2. To administer fixed dose combinations of different APIs, prolong the drug product life cycle.
3. To separate incompatible APIs from each other.

General properties of bilayer tablet dosage forms [1, 5 and 6]:

1. A bilayer 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. Must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

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Bilayer tablets: quality and GMP-requirements [1, 5]:

To produce a quality bilayer 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 sufficient tablet hardness.
3. Preventing cross-contamination between the two layers.
4. Producing a clear visual separation between the two layers.
5. High yield.
6. Accurate and individual weight control of the two layers. These requirements seem obvious but are not as easily accomplished as this article aims to demonstrate.

Methods used for the preparation of bilayered tablets:

Example: combination of Antihypertension and diabetic drugs was taken as a example.

Bilayer tablets are prepared by direct compression and wet granulation technique for both immediate release VAL (Valsartan) layer and sustained release MHCl (Metformin HCl) layer. For formation of immediate release layer accurately weighed quantity of VAL, cross carmellose sodium, sodium starch glycolate, microcrystalline cellulose (Avicel PH101), were screened using screen #25. The screened powders were then transferred into the mixer and mixed for 10 mins. Magnesium stearate was sifted through screen #40 and added to the above powder mix and mixed for 3 mins at 20 rpm.

For formation of sustained release layer of MHCl was formed by wet granulation method. In this method involves sifting of drug along with the polymers and diluents like Sodium CMC, hydroxyl propyl methyl cellulose, xanthum gum, povidone K30, were passed through sieve # 80 and uniform mixing was carried out for 5 mins. Granulation was performed by using PVP K30 as a binder and Isopropyl alcohol as a solvent to form dough mass. The mass was passed through sieve #18 and the granules so prepared were dried at 25-27 °C for 2 hrs. Afterwards granules were sized through sieve #18. Finally magnesium stearate and Talc were added separately and mixed for further 2-3 mins.

Advantages [2-6]:

1. Flexible concept.
2. The cost is lower compared to all other oral dosage forms.
3. It can be designed in such a manner as to modified release of the layers can be kept as extended and the other as immediate release.
4. They are unit dosage form and offer the greatest capabilities of all dosage form for the greatest dose precision and the least content variability.
5. Elegance to the product.
6. Suitable for large scale production.
7. Greatest chemical and microbial stability over all oral dosage form.
8. Objectionable odor and bitter taste can be masked by coating technique.
9. Separation of incompatible component thus minimizes physical and chemical.
10. Incompatibilities.

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Table No. 1: Various advancements in the field of bilayer tablets[7]

Drug(s)	Dosage Form	Rationale
Atorvastatin, Atenolol	Bilayer gastroretentive matrix Table	Treatment of hypertension and hypercholesterolemia
Nifedipine	Gastroretentive floating bilayer tablets	Treatment of hypertension and angina pectoris
Aspirin, Isosorbide 5-mono-nitrate	Sustained bilayer tablets	Treatment of pain, fever and other inflammatory conditions
Pioglitazone HCl, Gliclazide	Bilayer Tablets	Treatment of Type II Diabetes
Losartan potassium	Bilayer tablet	Treatment of hypertension
Trimetazidine HCl, Clopidogrel bisulphate	Bilayer tablets	Cytoprotective anti-ischemic, platelet inhibitor in acute coronary syndromes,
Diclofenac, Cyclobenza-prine	Bilayer tablets	Synergistic effect in pain
Granisetron HC1	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects
Metformin HC1,Glimipiride	Bilayer tablets	Synergistic effect in diabetes
Indomethacin	Bilayer floating tablets	Biphasic drug release
Metformin HC1, Atorvastatin Calcium	Bilayer tablets	To develop polytherapy for the treatment of NIDDS & hyperlipidemia
Cefixime Trihydrate, Dicloxacilline Sodium	Bilayer tablets	Synergistic effect in bacterial infections
Piracetam, Vinpocetin	Bilayer tablets	Synergistic effect in Alzheimer disease
Metformin HCl, Pioglitazone	Bilayer tablets	Synergistic effect in diabetes mellitus
Atenolol	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects and frequency of administration
Cefuroxime Axetil Potassium Clavulanate	Bilayer tablets	Synergistic effect against microbial infections and to minimize dose dependent side effects
Amlodipine Besilate Metoprolol Succinate	Bilayer tablets	Synergistic effect in hypertension
Diclofenac Sodium, Paracetamol	Bilayer tablets	Synergistic effect in pain
Ibuprofen, Methocarba-mol	Bilayer tablets	Synergistic effect of drugs in back pain
Atorvastatin Calcium	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects and frequency of administration

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Disadvantages [2-7]:

1) Difficult to swallow for children and unconscious patients.
2) Capping.
3) Hardness may occur.
4) Layer separation may occur.
5) Drugs owing amorphous, low density character are easiest compression.
6) Bitter testing drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation.
7) There should be compatibility between the two active ingredients.

Applications [7, 8]:

1) Bilayer technology is suitable for sequential release of two drugs in combination.
2) Separate Two Incompatible drug Substances.
3) Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet.
4) Bilayer tablets are used to deliver the loading dose and sustained dose of the same or different drugs.
5) Sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose.

Various steps involved in bilayer tablet formulation are as follows [2, 6]:

(1) Filling of first layer
(2) Compression of first layer
(3) Ejection of upper punch
(4) Filling of second layer
(5) Compression of second layer
(6) Ejected fully bilayer tablet

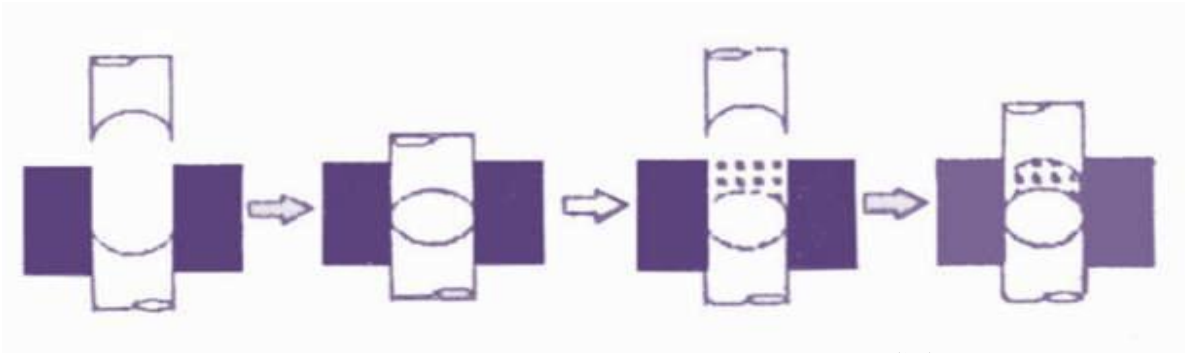

Fig. No. 3: Steps in bilayer tablet formulation [2-4]

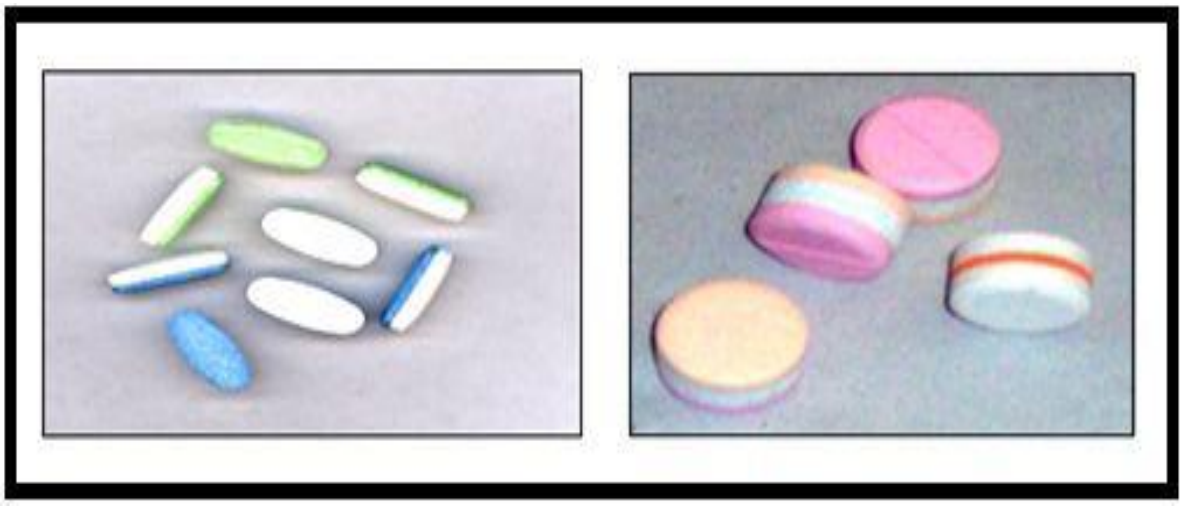

Fig. No. 4: Bilayer and trilayer tablets [5, 8]

Problems occur in developing bilayer tablets [2]:

(1) Layer separation
(2) Order of layer sequence
(3) Layer weight ratio
(4) Elastic mismatch of the adjacent layers

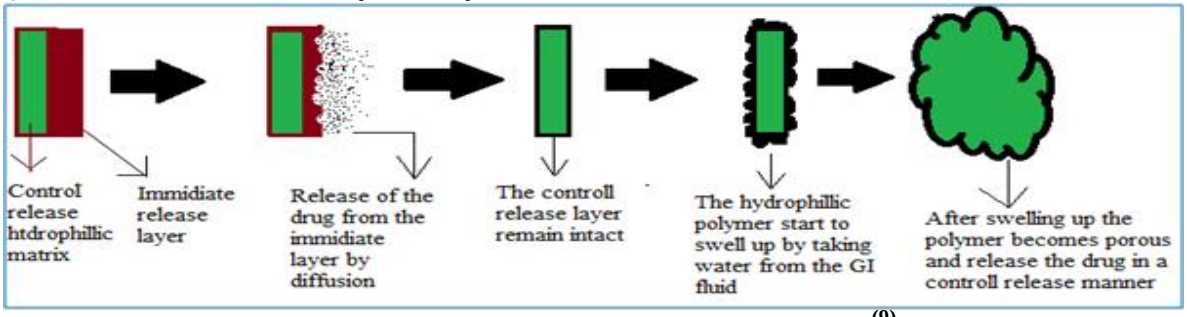

Fig. No. 5: Drug release from bilayer tablet [9]

Challenges in bilayer manufacturing [6, 7]:

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.

Evaluation of bilayer tablets:

General appearance **(21-24)**

The general appearance of tablets is visual identity and overall elegance is essential for consumer acceptance for the production process.

Size and Shape **(28-30)**

The shape and diamensions of compressed tablets are determined by the type of tooling during the compression process.

Thickness and diameter **(7, 8)**

The diameter of the tablets is determined with a Verneir Caliper (or) Screw Gauage.

Weight variation test **(31-35)**

For weight variation test, twenty tablets are selected randomly and the average weight is calculated thereafter the weight variation is calculated and weight variation is compared with IP standard.

Friability **(7, 8)**

Friability will be measured by taking randomly 10 tablets which is weighed and placed in a Friabulator (Roche Friabilator) and rotated at 25rpm for a period of 4 mins. After resolution, the tablets can be dusted and wieghed.

Friability is calculated by the following formula.

$$\%Friability = \left[\frac{Initial\ weight of\ tablet - Final\ weight\ of\ tablet}{Initial\ weight\ of\ the\ tablets}\right] X100$$

Hardness **(7, 8)**

The hardness of the tablet will be carved out using Monsanto type hardness tester. The hardness of the tablet is measured in Kg/Cm^2. The hardness is considered as an important parameter to overcome resist the tablets to shipping or breakage under conditions of storage.

In-vitro Dissolution Studies

The bilayer formulations are subjected to *in-vitro* durg release studies in simulated gastric and intestinal fluids to assess their ability in providing the desired controlled drug delivery. The *in-vitro* drug release studies are carried out using USP dissolution apparatus type-II at specified rpm (or) the procedure mentioned in official monograph.

Stability Studies

Stability study of the bilayer tablet can be evaluated as per ICH guidelines Q1C.

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Table 2: Recommended Long Term and Accelerated Storage Condition

Study	Storage Condition	Minimum Time Period
Long term	25°C±2°C / 60% RH ± 5% RH 30°C±2°C / 65% RH ± 5% RH	12 months
Intermediate	30°C±2°C / 65% RH ± 5% RH	6 months
Accelerated	40°C±2°C / 75% RH ± 5% RH	6 months

Dissolution studies **(42-47)**

Bilayer tablets were subjected to in vitro drug release studies in simulated gastric and intestinal fluids to assess their ability in providing the desired controlled drug delivery. Drug release studies were carried out using USP dissolution apparatus at 100 rpm, 37± 0.5°C and pH1.2 buffer (900mL) for 2 hrs, since the average gastric emptying time is about 2 hrs. The dissolution medium was replaced with pH6.8 buffer (900mL) and experiment continued for another 10 hrs. at different time intervals 5 mL of the samples were withdrawn and replaced with 5 mL of drug free dissolution medium. The samples withdrawn were analyzed by UV spectrophotometer using multi component mode of analysis.

Conclusion:

Bilayer tablet is improved beneficial technology to overcome the short coming 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. Now a day's bilayer tablets are prepared such as "atorvastatin-atenolol", nifedipine "aspirin-isosorbide 5-mononitrate", "pioglitazone HCl-gliclazide", losartan potassium and "trimetazidine hydrochloride-clopidogrel bisulphate". It concludes that, the FDC therapy is important in the modern era for various disease and disorders such as hypertension, diabetes, inflammatory and asthmatics. Bilayer tablet has been done with different or various combination, which is useful for different ailments. Thus bilayer formulation is safe, convenience dosage form and greater advantages to both patient and clinician that it may be administered as a single tablet in once a day. Bilayer tablet is quality and GMP requirements can vary widely. Now a days bilayer tablets are mostly prepared in pharmaceutical industry.

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