International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 1 Jan-Feb 2024, pp: 1798-1803www.ijprajournal.com ISSN: 2249-7781

A Review on Bilayer Tablets: Dual- Release Systems for Controlled Drug Administration

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Submitted: 18-02-2024 Accepted: 26-02-2024

ABSTRACT
The creation of the bi-layer tablets, which combines several qualities with a controlled release formulation, is a new chapter in the successful delivery of medication. Two layers make up bilayer layer tablets: an immediate release layer and sustained release layer. Additionally, more advantageous technology was developed to address the drawbacks of the single-layer tablets. Due to different active pharmaceutical ingredients (APIs) that were incompatible with one another, bilayer tablet formulations were necessary. There are numerous varieties of bilayer tablet presses on the market today, and different methods are employed in bilayer tablet systems. Weight variation, thickness, hardness, friability, and in vitro research are used to evaluate bilayer tablets.

KEY WORDS: Bilayer tablet, IR, SR, Incompatible, Active pharmaceutical ingredient (API).

I. INTRODUCTION:

Bilayer tablets is the new era for the successful development of controlled release formulation. Another name for it is a dual or multi-component tablet. The bilayer tablets is preferable to the dosage form that is currently in use. It works well for the combined sequential release of two medications. Additionally, it can separate two different kinds of incompatible substances and work with sustain release tablets, which have two layers: an immediate release layer for the initial dose and a maintenance layer for the ongoing dose. Immediate and sustained release layers are present in bilayer tablets. whereby the first dose, which comprises superdisintegrants to accelerate drug release and achieve an early start of action, is administered via an immediate release layer. Another name for it is a loading dose. Sustained release (maintenance dose) is the second layer, which releases the medication for prolong period of time.[1]

Certain antidiabetic medicines, for instance, have both layers of a bilayer tablets acting as the sustain release layers. For anti-hypertensive, anti-diabetic, anti-inflammatory, and analgesic medications drugs where combination therapy is frequently used-the usage of bi-layer tablets is a quite different matter. Compressing multiple distinct granulations put into a die successively, one on top of the other, creates bi-layer tablets. Every layer has its own weight control and is derived from a different feed frame. Two or three layers can be configured for rotary tablet presses. Additional options exist, but the design becomes really unique. Ideally, weight checking for control reasons is made possible by a small compression of each layer and individual layer ejection.[1]

ADVANTAGES:

1.They function as an addition to traditional technologies.
2.Single entity feed granules may be used.
3.Dividing components that are incompatible.
4.Improved patient compliance results in a more effective medication regimen.
5.Compared to a typical delivery system. Fewer daily dosages are needed improving patient convenience.
6.Preserve the chemical and physical stability.
7.Preserve potency and guarantee dosage precision.

DISADVANTAGES:

1. The cost of Bilayer rotary presses is high.
2. Contamination that crosses over between layers.
3. Inadequate hardness and layer separation lower yield.
4. In precise personal weight management.
5. It can be challenging to synthesize and manufacture drugs with poor wetting, slowdissolution properties or optimal absorption high in the gastrointestinal tract as tablets that will nonetheless give sufficient or complete drug bioavailability.
6. Tough to swallow when a patient is unconscious or a youngster.[3]

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IDEAL CHARACTERISTICS:

- When it comes to production, shipping, dispensing and packaging a bi-layer tablet should be strong enough to withstand mechanical shock while maintaining an exquisite appearance and being devoid of flaws like chips, cracks, discoloration, and contamination.
- It must be able to release the therapeutic substances in a consistent and repeatable manner.
- The bi-layer tablet must be able to release the therapeutic agents in a consistent and repeatable manner.
- It must possess the chemical and physical stability to retain its physical attributes throughout time.
- When a bi-layer tablet is being manufactured, packaged, shipped, or dispensed, it needs to be robust enough to endure mechanical shock.[3]

APPLICATIONS:

- Bilayer tablets are used to create bilayer floating tablets, which have two layers: one for the drug's quick release and the other for floating
- A bilayer tablet is appropriate for the simultaneous sequential delivery of two medications keep two incompatible substances apart.
- Bilayer tablets can be utilized to administer a distinct or same medication at both the loading and sustained doses.
- Bilayer tablets are used to administer two distinct medications with various release patterns.

DIFFERENT TYPES OF BILAYER TABLET

1.Bilayer modified release tablet
2.Bilayer floating tablet
3.Bilayer Bucco adhesive tablet

1.Bilayer modified release tablet: This kind of bilayer tablet has two distinct release profile layers. Within thirty minutes, the drug in the immediate release layer will release ninety percent of its concentration. Sustained release is the other layer, when the medication releases gradually over a period of 12 to 24 hours.[4]

e.g. Metoclopramide HCl+ Ibuprofen

2.Bilayer floating tablet: This type of bilayer tablet consists of Such a pharmacological combination that is sensitive to the pH of the gastrointestinal tract makes up this kind of bilayer tablet. The stomach metabolizes one layer of the medication, while the colon breaks down the other layer.[4]

e.g. Rosiglitazone Maleate

3.Bilayer Bucco adhesive tablet: Drugs with mucoadhesion—the ability to adhere to the mucous membrane of the buccal area and maintain drug release—are the ingredients in this kind of bilayer tablet.[4]

e.g. Propanolol HCl

THE PHARMACEUTICAL INDUSTRY CHOOSE BILAYER TABLETS FOR THE FOLLOWING REASONS.

1. To achieve synergistic effects.
2. To prevent drug incompatibility, drug interaction, and patent extension. Theoretical rationale.
3. To lower capital expenditures
4. To prepare a combination of sustained release tablets, with an immediate release layer and maybe a prolonged release layer.

CHALLENGES IN BILAYER MANUFACTURING

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

Delamination: When the tablet's two halves don't fully bind together, the tablet breaks apart. When crushed, the two granulations should be stick together. [3]

Cross-contamination: This happens when the granulation from the first layer mixes with the granulation from the second layer, or the other way around. It might even defeat the dual-layer tablet's original intent one major factor in reducing cross contamination is effective dust collection.

Production yields: Dust collection is necessary to avoid cross-contamination, which results in losses. Bilayer tablets yield less than single-layer tablets as a result. [3]

Cost: For a number of reasons, bilayer tableting is more expensive than single-layer tableting. The tablet press costs extra, to start. Second, the press generally runs more slowly in bilayer mode. Third, it is necessary to establish two compatible granulations, which requires extra time to develop,analyse, and validate the formulation. These parameters will affect the bilayer compression and the quality attributes of the bilayer tablets (enough mechanical strength to maintain integrity and individual layer weight management) if they are not sufficiently regulated or adjusted.

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Thus, in order to enable the creation of a resilient product and process, it is imperative to get insight into the underlying causes[3]

TYPES OF BILAYER TABLET PRESSES:

1. Single sided tablet press.
2. Double sided tablet press
3.Bilayer tablet press with displacement monitoring.
4. Multilayer compression basics.

1.Single sided tablet press

Over time, many varieties of bilayer presses have been developed. The most basic version consists of a single-sided press with the double feeder's two chambers kept apart. Each chamber is either force-fed or gravity-fed with a distinct powder, resulting in the two distinct tablet layers. The first layer of powder is initially put into the feeder when the dye passes beneath it, and then the second layer of powder is added, and finally the entire tablet is squeezed in one or two steps. This is the simplest method of creating a bilayer: the two layers in the dye mix slightly at their interface and, in most circumstances, connect sufficiently to prevent layer separation when the tablet is made[6].

Limitations: No weight monitoring or control of the individual layers, No distinct visual separation between the 2 layers, Dwell time due to the small compression roller possible resulting in poor de aeration capping and hardness problems.[6]

2.Double sided tablet press

The compression force is used by the majority of double-sided tablet presses, which automate production management, to track and regulate the weight of the tablet weights. The effective compression force that the compression mechanism at the primary compression point applies to each individual tablet of the stratum. When necessary, this method assists in correcting the dies fill depth and rejecting out the tolerance tablets.[6]

Advantages : Low compression force exerted on the first layer to avoid chapping and separation of the individual layer, Increased dwell time at pre-compression of both first and second layer to provide sufficient hardness at maximum turret speed, Maximum prevention of cross contamination between two layers, A clear visual separation between the two layers, Displacement weight monitoring for accurate and independent weight control of the individual layer, Maximized yield, Separation of the two individual layers is due to insufficient bonding between the two layers during final compression of bi-layer tablet.

Limitations: Correct 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 a final compression, Bonding is too restricted if the first layer is compressed at a high compression force, The low compression force required when compressing the first layer, unfortunately reduces the accuracy of the weight monitoring/control of the first layer in the case of tablet presses with compression force measurement.[6]

3.Bi Layer Tablet Presses with Displacement

The principles of a bilayer tablet press and compression force are essentially distinct from one another. In this instance, less compression force results in increased precision. The risk of capping and separation rises with increasing production speeds, but it can be decreased with enough dwell time at each of the four compression stages. [6]

Advantages: Displacement weight monitoring /control for accurate independent weight control of the individual layers, Low compression force exerted on the first layer to avoid chapping and separation of the 2 individual layers, Increased dwell time at pre-compression of both first and second layer to provide sufficient hardness at maximum turret speed, Maximum prevention of cross contamination between the layers, A clear visual separation of the layers, Maximized yield.

4.Multilayer compression basics

Standard double presses can be modified for multipliers, or presses can be built expressly for multilayer compression. The idea of the multilayer tablet has long been used to create formulations with prolonged release. These tablets may have three or more layers in order to maintain the drug release from the tablet, as well as a fast-releasing layer. The pharmacokinetics advantage is based on the fact that drug release from sustained granules causes a rapid rise in blood concentration, but drug release from fast-releasing granules keeps blood levels stable [6].

FORMULATION OF BILAYER TABLETS BY TWO METHODS: -

Wet granulation method

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Direct compression technique Wet granulation technique Weigh all medications and excipients precisely, then strain through sieve number 100. Get the binder solution ready. Using a pestle and mortar, the combination is wet massed with the binder solution. Using sieve #10, filter the moist substance. Make sure the granules are dry. Running powder is created by blending after drying with the use of lubricants and disintegrants. Using a flat punch, flatten the mixture into tablet form.[7]

Direct compression method

Weigh every ingredient and medication precisely, then strain through sieve #100. Combine all the ingredients in a pestle and mortar and directly compress them into a tablet shape.[7]

STEPS FOR COMPRESSION CYCLE OF BILAYER TABLETS

- Filling of first layer.
- Compression of first layer.
- Ejection of upper punch.
- Filling of second layer.
- Compression of both the layers together.
- Ejection of bilayer tablet.[4]

EVALUATION OF BILAYER TABLETS

General Appearance A tablet's overall elegance, visual identity, and general appearance are crucial factors in determining consumer adoption. Included are the tablet's dimensions, form, color, taste, consistency, surface roughness, physical defects, odor, and legibility of any identifying markings.[8]

Tablet Size and Thickness: Tablet size homogeneity depended on tablet thickness and diameter. A vernier calliper was used to measure the thickness and diameter.[8]

Tablet Hardness: A tablet's ability to withstand breakage or shipping during handling, storage, and transit prior to use is determined by its hardness. The Monsanto hardness tester was used to determine the tablet's hardness for each formulation. kg/cm2 was used to measure the hardness.

Friability: The strength of a tablet is measured by its friability. The following method was used to assess the friability using the Electro lab EF-2 friabilator(USP). After precisely weighing twenty tablets, they were put in the tumbling device, which rotates at a speed of 25 rpm and drops the tablets six inches at a time. The tablets were weighed after four minutes to calculate the percentage of weight loss.[8]

(% loss = (Initial wt. of tablets – Final wt. of tablets)×100
Initial wt. of tablets]

Weight uniformity:After choosing twenty tablets at random, the average weight was determined. We computed the weight variation and compared it to I.P standards.

Dissolution tests: To assess the potential for controlled medication delivery, tablets are put through in vitro drug dissolution tests in simulated gastric and intestinal fluid. Using a 900 ml 0.1N HCL buffer and a USP I dissolution apparatus, dissolution investigations are conducted for two hours at 100 rpm and 37±0.5°C. Later on, 900 millilitres of pH 6.8 phosphate buffer are added to the dissolution medium. For an additional four hours, this is done. Remove five millilitres of the drug sample and replace with the drug-free dissolving media. The samples are examined with the aid of four UV spectrophotometers.[8]

MARKETED PRODUCTS OF BILAYER TABLETS

Drug(s)	Dosage Form	Rationale
Atorvastatin, Atenolol	Bilayer Gastro-retentive Matrix Tablet	Treatment of hypertension and hypercholesterolemia
Nifedipine	Gastro Retentive 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 HC l, Gliclazide	Bilayer Tablets	Treatment of Type II Diabetes
Losartan potassium	Bilayer tablet	Treatment of hypertension
Trimetazidine HCl ,	Bilayer tablets	Cyto protective anti-ischemic,

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clopidogrel bisulphate		platelet inhibitor in acute coronary syndromes,
Diclofenac ,Cyclobenza-prine	Bilayer tablets	Synergistic effect in pain

II. CONCLUSION:

A bilayer tablet is a technologically advanced solution that addresses the shortcomings of a single layered tablet. The bilayer tablet, which is made up of multiple matrices, has many uses. A bilayer tablet can be used for the sequential release of two medications in combination, to separate two substances that are incompatible, or it can be used for sustained release, where the first layer serves as an initial dose and the second layer as a maintenance dose. Tablets prepared in the multilayer form are utilized to give incompatible drug delivery methods and to provide control release tablet preparations through the employment of surrounding or multiple swelling layers. This explains why bilayer tablets are made using a wide variety of presses, from straightforward single-sided presses to highly sophisticated machines.

Compliance with ethical standards

Acknowledgments

Would like to thank Dr. M. Sunitha Reddy and K. Anie. Vijetha for proper Guidance and support and the Department of Pharmaceutics, Centre for Pharmaceutical Sciences, JNTUH UCESTH, and JNTUH. For providing lab facilities for this research work.

Disclosure of conflict of interest

All the authors declare no conflict of interest.

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