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Novel Approach in Development of Bilayer Tablet - A Review

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ABSTRACT

In the past 30 years, as the costs and complications of marketing new drug entities have increased and the therapeutic benefits of controlled drug delivery have been recognized, more attention has been focused on developing sustained or controlled release drug delivery systems. Bilayer tablet is a new era for the successful development of controlled release formulation along with various features to provide a way of a successful drug delivery system. The primary objective of bi-layer tablets is to avoid chemical incompatibilities between Active Pharmaceutical Ingredients by physical separation and to develop different drug release profiles (immediate release and modified release). In case of bilayer tablets drug release can be rendered almost unidirectional if drug can be incorporated in the upper non adhesive layer its delivery occurs into the whole oral cavity. The immediate release layer of the bilayer tablet has worked as the loading dose and the sustained release layer has maintained therapeutic plasma drug concentration for prolonged time. Several pharmaceutical companies are currently developing bilayer tablets for a variety of reasons: patent extension, therapeutic, marketing to name a few. To reduce capital investment, quite often existing but modified tablet presses are used to develop and produce such tablets.

INTRODUCTION

In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bilayer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance.[7] Bilayer tablet is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system.[8] Bilayer tablets are a very common dosage form for drugs such as captopril, metoprolol, amoxicillin and potassium clavuanate, propranolol hydrochloride, bambuterol hydrochloride. According to Joint National Committee VI (JNC VI), combination therapy can often provide better control through the use of fewer doses of drugs with different modes of action and a reduction of potentially harmful side effects. JNC VI recommended that the combination of a low dose of two drugs in fixed dose combination is an appropriate choice for initial treatment of any chronic disease. Hence management of multiple diseases can be effectively and better done by bilayer tablet or layering in tablet.[1]

The term bilayer tablets contain subunits that may be either the same (homogeneous) or different (heterogenous). Homogenous type bilayer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug, later, either as second dose or in an extended-release manner.[2] Heterogeneous type bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances.[1]

Need of designing bi-layer tablet involves,

- Managing the rate at which a single active pharmaceutical ingredient or two active pharmacological components are administered.

- Alter the overall surface area available for API layer by sandwiching with one or two active layers to achieve swellable/erodible barriers for modified release.

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- Longer drug product life cycle, buccal/mucoadhesive delivery systems; develop new drug delivery methods for gastro-retentive drug delivery, such as chewing devices and floating tablets. [10]

Bilayer tablets have an advantage as compared to conventional monolayer tablets. The use of these tablets reduces the use of chemical incompatibilities between formulation components by separation by physical means. In addition, bilayer tablets can also be used for controlled delivery of APIs by combining slow-release and immediate-release layers. It is, however, difficult to manufacture such drug delivery devices mechanically, and they can also be difficult to evaluate their long-term performance due to their poor mechanical and compression properties of the materials in the adjacent layers that have been compacted, insufficient hardness, inaccurate individual mass control, reduced yield, cross-contamination between layers, and the ability of the layers to delaminate at the interface when compaction is in progress. The major problem that has to be overcome is to find out in detail the sources of these problems at lower scales and to find out remedies to solve them.[13]

Major disadvantages include difficulty in swallowing in case of children and unconscious patients. 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.[9]

Moreover, this review discusses various challenges associated with bilayer manufacturing, types of bilayer presses, preparation of bilayer tablets, different techniques for the development of bilayer tablets, various approaches to bilayer tablet development, evaluations for tablets as well as recent developments.

CHALLENGES IN BILAYER MANUFACTURING

Ideally, Bilayer tablets are the single-layered tablets compressed into one. In the past few years several issues related manufacturing and compression have been reported. The main challenges faces are:

• **Weight Variation**: Due to low flow trait of the fabric, also during die filling.

• **Hardness**: Factors related to machines and also the decrease in the lubricant level.

• **Effect of high temperature and humidity**: Increase in tablet size, which can affect the swallow ability of unit dose. The swallow ability of the unit dose can be impacted by the large tablet size.

• **Contamination between the layers**: It occurs when the first layer is mixed with the second layer.

• **Cost:** Bilayer tablets are more expensive than single-layered tablets due to the press runs slower in bi-layer mode.

• **Picking and Sticking**: Excessive heat generation can be caused at the time of compression.

• **Production Yields:** Bilayer tablets have lower yields than single-layer tablets because of the need for dust collection.[1,13]

TYPES OF BILAYER TABLETS PRESS

- Single sided tablet press.
- Double sided tablet press.
- Bilayer tablet press with displacement monitoring.[12]

Single Sided Press:

The most basic layout is a single-sided press where the doublet feeder of two chambers are kept apart.[6] The two distinct layers of the tablets are produced by gravity or force-feeding each chamber with a separate amount of energy. The first layer of powder and then the second layer of powder are put into the die as it moves beneath the feeder. The tablet is then crushed completely in one or two processes.[12] In most situations, the two layers in the die bind well enough to prevent layer separation when the tablet is formed. The two layers in the die mix somewhat at their interface.[9]

Figure No. 1: Single sided tablet press [12]

Limitations of tablet press with single side-

1. There is no weight monitoring or control of the individual layer.[6]

2. There is no obvious visual difference between the two Layers.[7]

3. Due to the tiny compression roller, the initial layer's dwell time was very short, which might have an impact on deaeration, capping, and hardness issues.[9]

4. In order to increase dwell duration, the turret rotation can be slowed down, but this will reduce tablet production.[9]

Double Sided Tablet Press:

In double-sided tablet presses with automated production control, weight is monitored and controlled by compression force. At the main compression of the layer, the control system measures the peak compression force exerted on each individual tablet or layer. When necessary, the control system uses this measured peak compression force to reject out-of-tolerance tablets and correct the die fill depth.[12]

Figure No. 2: Double sided tablet press [12]

Limitations of tablet press with double side-

1. Due to inadequate bonding between the two layers during final compression of the bilayer tablet, the two individual layers split from one another.

2. If the first layer is compressed with a high compression force, bonding is too restricted.

3. Only when the first layer is compressed at a low compression force, A proper bonding can occur.[1]

Bilayer Tablet Press with Displacement Monitoring:

The displacement tablet weight control principle differs greatly from the compression force-based principle. The applied pre-compression force determines the sensitivity of the control system when sensing displacement, not the weight of the tablet.[6,12]

Figure No. 3: Bilayer table press with displacement [12]

Advantages-

1. For precise and independent weight management of the different layers, weight monitoring and control are used.

2. Low compression force applied to the first layer to prevent capping and layer separation.

3. To ensure sufficient hardness at maximum turret speed, dwell times were increased when pre-compression was performed on both the first and second layers.

4. Maximum cross-contamination avoidance between the two layers.[9]

5. Maximum yield and clear visible difference between the two layers.[6]

PREPARATION OF BILAYER TABLETS

Bilayer tablets are made with a layer of medication intended for immediate release and a second layer intended for delayed release, either as a second dose or in a shape for a prolonged release. In order to reduce the area of contact between two layers, bilayer tablets with two incompatible medications can also be made by compressing distinct layers of each drug. It's possible to add another inert layer as an intermediary layer.

The necessary drug release profile and a particular level of mechanical strength must be reached in order to make an appropriate tablet formulation.[6]

Compaction: The method through which a powder's porosity is reduced as a result of the grains being compressed together by the force of mechanical methods. A substance's compressibility and consolidation are both factors in its compaction.

Compression: In order to reduce bulk volume, voids must be filled and particles must make closer contact with one another.

Consolidation: The characteristic of a material whereby there is a gain in mechanical strength as a result of interparticulate interaction (bonding). It was discovered that a significant element impacting tablet delamination was the compression stress on layer.[8]

Completing the top layer's fill

1. Compress the top layer
2. Upper punches are expelled
3. Filling of the second layer
4. Second layer compression
5. Fully ejected the bi-layer tablet [13]

VARIOUS TECHNIQUES FOR BILAYER TABLET DEVELOPMENT

A) OROS® Push Pulls Technology:

The majority of this system consists of two or three layers, of which one or more are push layers and one or more are needed for the drug. Drugs as well as two or more distinct agents, make up the majority of the drug layer. As a result, the medication in this layer is in a form that is poorly soluble. Suspending and osmotic agents have been added in greater quantities. The tablet core is enclosed by a semi-permeable membrane.[4]

B) L-OROS ™ Technology:

The solubility issue was addressed by this system. Alza created the L-OROS system, which involves manufacturing a lipid soft gel product initially coated with a barrier membrane, followed by an osmotic push layer, an intermediate semi-permeable membrane, and an exit orifice.[5]

C) EN SO TROL Technology:

Enhancing the solubility by an order of magnitude or developing an ideal dose form using an integrated strategy for drug delivery, Shire Laboratory is identifying the indicated enhancer and incorporating it into controlled release technologies.[6]

D) DUREDAS Technology:

In order to give two separate release rates or dual release of a medicine from a single dosage form, Duredas or Dual Release Drug Absorption System (Elan Corporation) uses bilayer tableting technology**.** A controlled release hydraulic matrix complex and an immediate release granulate (for a quick beginning of action) are combined into one tablet during two distinct direct compression procedures. This causes the matrix to become porous and viscous, acting as a barrier between the fluid and the drug. As the gel expands, fluid seeps deeper into the dosage form, dissolving the medication and enabling the resulting solution to be administered.[9]

The DUREDAS technology has several advantages, including:

1. Bilayer tableting technology.

2. A tailored rate of release for two medication components.

3. The option to blend two different CR formulas.

4. The possibility to combine components with modified release and quick release in a single tablet.

5. Unit dose presentation tablet.[11]

E) DUROS Technology:

The implant based DUROS (Alza Corporation) system offers a different method for the delivery of a variety of therapeutic substances, such as peptides, proteins, and other bioactive macromolecules. These implants are tiny titanium cylinders intended to give medication continuously for up to a year by osmotically driven absorption. The therapeutic chemical can be delivered continuously and precisely using DUROS implants after insertion at rates as low as 1% of a drop of water every day. Due to titanium's lengthy history of use in medical equipment like implantable defibrillators and joint replacements, which are tolerable to human tissue, the cylinder is made from this material. The cylinder shields medicinal substances from deterioration in the body and allows them to stay stable for lengthy periods of time.[9]

F) GEMINEX:

Geminex is a dual drug delivery system that allows for the simultaneous or sequential administration of two or more medications. For each drug's unique therapeutic benefit to be maximized and side effects to be reduced, the Geminex technology regulates the rate of release. Geminex's ability to deliver two active ingredients or the same ingredient at different rates in a single tablet benefits the pharmaceutical industry and, ultimately, patients. Cardiovascular illness, diabetes, cancer, and central nervous system disorders are all therapeutic areas in which Penwest is actively utilizing its Geminex technology.

VARIOUS APPROACHES FOR BILAYER TABLET

A) Floating Drug Delivery System –

These are made with a low density so that they will float on the contents of the stomach after administration. This will continue until the device either disintegrates or its density decreases to the point where it loses buoyancy and can pass more easily from the stomach with the wave of motility that causes gastric emptying. The bilayer tablet is made in such a way that one layer delivers the drug immediately, resulting in a rapid start of effect, while the other layer is made to be a floating layer that floats in the stomach (GI-fluid).

Methods for creating a floating drug delivery system:

The design of floating dosage forms for both single unit systems and multi-unit systems has been done using the following strategies.

(1) The same as compressed tablets, intra gastric bilayer floating pills have two layers- immediate and sustained release.

(2) Floating pills of the multiple unit type: These systems use sustained release pills as "seeds" that are encircled by two layers. While the outside layer is a swellable membrane layer, the interior layer is made up of effervescent chemicals. When the system is submerged in a dissolution medium at body temperature, it sinks instantly and then forms swollen pills that resemble balloons. These pills have a lower density than the system and float as a result.

B) Polymeric Bio Adhesive Systems -

These are made to absorb fluid after delivery such that the outer layer hardens into a sticky, tacky substance that sticks to the mucus layer of the stomach. Up until the adhesive forces are weakened, this ought to promote gastric retention.

These are manufactured in two layers, one of which has an instant dosage and the other of which has a bioadhesive feature.

C) Swelling System -

These systems are easy to digest because they are tiny upon administration. They quickly expand or unfold after consumption, making it impossible to pass through the pylorus until the requisite level of drug release has been reached. It is able to exit the stomach through slow erosion or breaking down into tiny pieces. A layer for immediate release may be present in the bilayer tablet, while a traditional release layer may be present in the other layer.

Evaluation for Bilayer Tablets:

General Appearance

Consumer acceptability of a tablet depends heavily on its overall look, visual identity, and overall "elegance." includes the size, shape, color, taste, texture, physical faults, consistency, and readability of any identifying marking of the tablet.[2]

Size and Shape

Dimensionally describing, tracking, and controlling the tablet's size and shape is possible.[2]

Tablet Hardness

The hardness of tablets determines how resistant they are to being shipped or breaking under various circumstances, such as storage, transportation, and handling prior to use. Monsanto's hardness tester was primarily used to measure the hardness of each formulation's tablet. In kg/cm2, the hardness was determined.[4]

Friability

The strength of a tablet is measured by its friability. The following approach was done to assess the friability using an Electrolab EF2 friabilator (USP).

Twenty tablets were precisely weighed and put in the tumbling device, which rotates at 25 revolutions per minute and drops the tablets six inches at a time.

The tablets were weighed after 4 minutes to assess the percentage of weight loss.

% loss = [(Initial weight. of tablets – Final weight. of tablets)/ Initial weight. of tablets] ×100 [5]

Uniformity of Weight

The average weight of twenty tablets was determined randomly. And weight variation was calculated.[4]

Dissolution Studies

In vitro drug release tests were performed on bilayer tablets. Tests were done to determine whether simulated stomach and intestinal fluids can give the necessary controlled medication distribution. Since the typical stomach emptying duration is around two hours, drug release tests were performed using the USP dissolution test equipment I at 100 rpm, 370.5°C, and pH 1.2 buffer (900 ml) (i.e., 0.1 N HCl) for two hours. After 10 hours, the experiment was repeated with a pH 6.8 phosphate buffer in place of the dissolving media. 5 ml of each sample was taken out and replaced with 5 ml of a drug-free dissolving media at various time intervals.

The samples were removed, and the UV spectrophotometer used a multi-component mode of analysis to evaluate them.[5]

Recent Developments in the Field of Bilayer Tablets

Drug(s)	**Dosage Form**	**Rationale**	**Methods**	**Author**	**Ref. No.**
Diclofenac, Cyclobenzaprine HCl	Bilayer tablets	Synergistic effect in pain	Wet granulation	Jamunadevi *et al*	4
Metformin HCl, Atorvastatin Calcium	Bilayer tablets	To develop polytherapy for the treatment of NIDDS & hyperlipidemia	Wet granulation	Mohindeen *et al*	3
Metformin HCl, Pioglitazone	Bilayer tablets	Synergistic effect in diabetes mellitus	Wet granulation & direct compression	Rajendran *et al*	4
Atorvastatin Calcium	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects and frequency of administration	Direct compression	John *et al*	3
Paracetamol, Diclofenac	Bilayer tablets	Synergistic effect of drugs in pain	Wet granulation	Gohel *et al*	3

Drug(s)	Dosage Form	Rationale	Methods	Author	Ref. No.
Piracetam, Vinpocetine	Bilayer tablets	Synergistic effect in Alzheimer disease	Wet granulation	Jadhav *et al*	4
Atenolol	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects and frequency of administration	Direct compression	Shirsand *et al*	4
Guaifenesin	Bilayer tablets	Biphasic release profile	Wet granulation	Kumar *et al*	3

CONCLUSION

Bilayer tablet is an improved beneficial technology to overcome the shortcoming of the single layered tablet. A bilayer tablet can be monolithic, partially coated or multilayered; it has various applications. A bilayer tablet can be used for sequential release of two drugs in combination, or for sustained release tablets in which one layer constitutes the initial dose and the other is the maintenance dose. The bilayer tablet technology allows us to administer incompatible drugs in combination, as well as the same drug at different release rates. The quality of bilayer tablets and GMP requirements can vary widely. As a result, many different types of presses are used to produce bi-layer tablets, from simple single-sided presses to highly sophisticated machines such as the Courtoy-R292F.

Therefore, bilayer tablets are used very differently for anti-hypertensive, diabetic, anti-inflammatory, and analgesic drugs, where combination therapy is often used. There are currently bilayer tablets for medicines such as Atorvastatin, Atenolol, Nifedipine, Aspirin,

Isosorbide 5-mononitrate, Pioglitazone HCl, Gliclazide, Losartan potassium, and Trimetazidine hydrochloride.

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