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Bilayer Tablet Technology: A Review

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ABSTRACT

Bilayer tablet is the novel technology for the development of controlled release formulation. Developing a combination of two or more active pharmaceutical ingredients in a single dosage form is known as a bilayer tablet. Bilayer tablet is more suitable for gradual release of two active ingredients in combination. The preparations of bilayer tablet were needed due to separate incompatible active pharmaceutical ingredient (APIs) for each other. Bilayer tablets material involves both the compressibility and consolidation. The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance. 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. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. In the case of bi-layered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper non-adhesive layer its delivery occurs into the whole oral cavity.

Keywords: Active Pharmaceutical Ingredient, Bi-layer tablet

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INTRODUCTION

Bilayer tablet is the technology used for extended or sustained release formulation. It is developed by combination of two or more active pharmaceutical ingredients in a single dosage form which makes compatible dosage form. In bilayer tablet there one layer is immediate release, and another is extended release layer. This technology also helps to avoid chemical incompatibilities between different APIs by physical separation. This technology is developed in order to achieve modified release of a drug. In case of conventional dosage forms, there will be a wide range of fluctuations in the drug concentration, which shows unwanted toxicity & low efficiency. Usually conventional dosage form produces wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency^[1-3]. This factor such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance. Bi-layer tablets can be a primary option to avoid chemical incompatibilities between APIs by physical separation, and to enable the development of different drug release profiles (immediate release with extended release). Bi-layer tablet is suitable for sequential release of two drugs in combination it is also capable of separating 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. Bilayer tablets contain immediate and sustained release layers. The immediate release layer delivers the initial dose, it contains super disintegrates which promotes drug release rate and attains the onset of action quickly (loading dose) whereas sustained release (maintenance dose) layer releases drug in sustained manner for prolonged time period. Significance in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bi-layer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance. Bi-layer tablets can be a primary option to avoid chemical incompatibilities between APIs by physical separation, and to facilitate the development of different drug release profiles (immediate release with extended release).

Need of Bilayer Tablet^[4-6]

- It maintains the prolong drug product life cycle because of administration of fixed dose combination of API.

- 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 inactive layers in order to achieve swellable or 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).
- For the purpose of developing novel drug delivery system. Such as buccal/mucoadhesive delivery system and floating tablets for gastro protective drug delivery system.

Advantages of The Bilayer Tablet ^[7-9]

- They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and least content variability.
- Patient compliance is improved due reduced frequency and lesser number of dosage unit to be taken.
- Economical, versatile and flexible.
- Bilayer tablets can be designed in various modified / novel drug delivery systems like mucoadhesive, floating, chronotherapeutic and combined dosage form for extended and immediate release.
- Suitable for large scale production.
- Chemical and microbial stability of overall oral dosage form with greatest precision and least variation in content uniformity.
- Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.

Disadvantages of Bilayer Tablet ^[5, 8-9]

- ❖ Adds complexity and bi-layer rotary presses are expensive.
- ❖ Insufficient hardness, layer separation, reduced yield.
- ❖ Imprecise individual layer weight control.
- ❖ Cross contamination between the layers.
- ❖ Difficult to swallow in case of children and unconscious patients.
- ❖ Some drugs resist compression into dense compacts, due to amorphous nature, low density nature.

- ❖ Drugs with poor wetting, slow dissolution properties, optimal absorption high in GIT may difficult to manufacture as a tablet that will still provide ample drug bio availability.

Ideal Characteristics of Bilayer Tablet [2]

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

Applications [10]

- ❖ Bi-layer tablets are used to deliver the two different drugs having different release profile.
- ❖ Bi-layer tablets are used to deliver the loading dose and maintenance dose of the same or different drug.
- ❖ Bi-layer tablets are mainly used in combination for modified release.

INNOVATIVE APPROACHES TO DESIGN BILAYER DRUG DELIVERY SYSTEMS [11-15]

FLOATING DRUG DELIVERY SYSTEMS

Floating drug delivery system is a class of gastro retentive drug delivery system. These systems remain in the gastric region for several hours, thus significantly prolonging the gastric residence time of drugs. This system improves bioavailability. The solubility of drugs which are less soluble in high pH can be improved by such systems. Floating drug delivery systems for bilayer tablets can be of two types:

- ✓ Intra-gastric bilayer floating tablet
- ✓ Multiple unit type floating tablet

Intra-gastric bilayer floating tablets are compressed bilayer tablets intended to remain in the stomach or gastric region and produce suitable therapeutic effects. On the other hand, Multiple unit type floating tablets are systems which consist of sustained release pills as 'seeds' surrounded by double layers. The outer layer is a swellable membrane while the inner layers have effervescent

agents. In the body, they form swollen pills like balloons and float due to low density. It is also known as multi particulate floating reservoir type of delivery system.

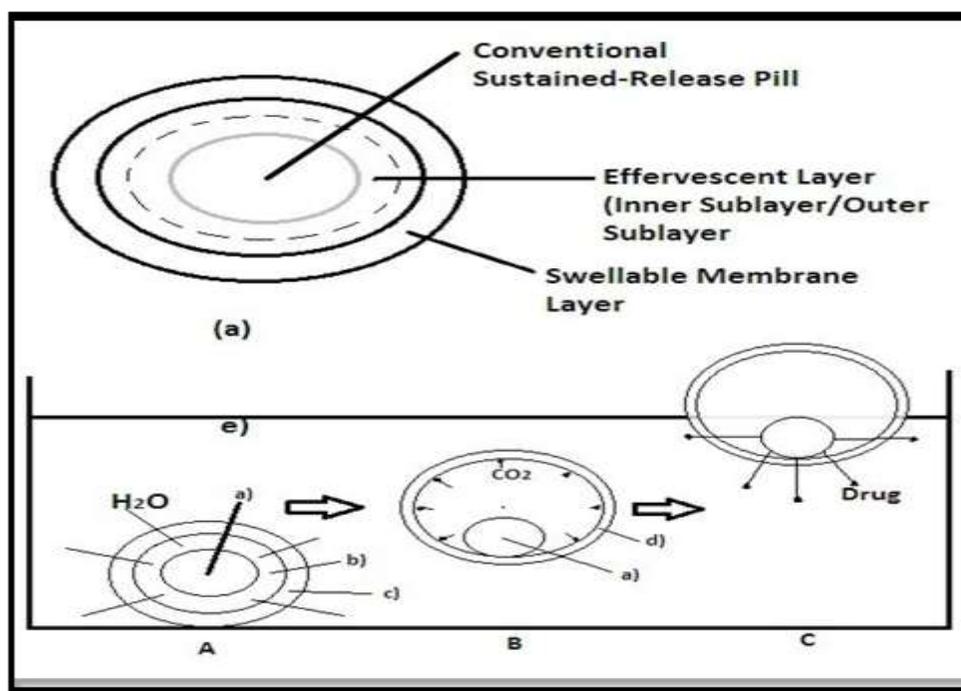


Figure 1: Intra gastric-floating Bi-Layer Tablet.

POLYMERIC BIO-ADHESIVE SYSTEM

Bio-adhesion may be defined as the state in which two materials are held together for extended periods of time by interfacial forces. Polymeric bio-adhesive bilayer tablets can be mucoadhesive or bio-adhesive. Mucoadhesive bilayer tablets adhere to the stomach mucosa and release active pharmaceutical ingredients gradually or in sustained manner. These tablets can persist in the stomach for several hours and thus extend the gastric residence time of therapeutics. These enhance bioavailability due to extended gastric retention the potential use for mucoadhesive systems as drug carriers lies in its prolongation of the residence time at the absorption site, allowing intensified contact with the epithelial barrier.

However, a disadvantage of such systems is the removal of preparation by mucociliary clearance system which is a natural defense mechanism of the body but by coupling mucoadhesive properties to bilayer tablets has additional advantages such as high bioavailability, efficient absorption and intimate contact with the mucous layer.

Bucco adhesive bilayer tablets release the drug in the buccal cavity and avert the first pass metabolism which leads to high bioavailability. Bucco adhesive system is the interaction between a drug carrier polymer along with other excipients and the mucin in the buccal mucosa surface. This

system offers various advantages such as by passes first pass metabolism, allows optimum absorption of APIs as well as self-placement and removal. However, a suitable buccal drug delivery system should have good bio-adhesive properties, so that it can be retained in the oral cavity for desired duration of time.

Swelling System

Swelling systems are designed in a way that upon ingestion they swell or rapidly unfold to release drug to a required degree. They are sufficiently small on administration as they swell inside the body. They may contain immediate release layer with the other layer as extended release or immediate release. The system gradually breaks down into smaller particles to leave the stomach.

Geomatrix System

Geomatrix bilayer tablet system is composed of different layers which allow incorporation of more than one drug into single dosage form. It is a biphasic system in which drugs from different layers may release at different rates e.g. drug may be released with a bolus and then at an extended or controlled rate or by targeted drug delivery in the GI tract using pH dependent polymers system. This technology can control release of one or more drugs from a tablet containing different drugs in different layers. Different layers in the tablet with different swelling, gelling, and erosion behaviors can provide separate drug release modes. Various release mechanisms can be achieved using the Geomatrix technique. These include:

- ❖ Zero order (constant rate over time).
- ❖ Binary (release of two drugs at different rates and times).
- ❖ Biphasic release (combination of slow and fast release for a same drug).

Biphasic delivery can be further sub grouped as "quick-slow" release and "slow-quick release". Matching of drug(s) and polymer is very important for desired flux of APIs from the matrix

TYPES OF BILAYER TABLET [23, 24]

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.

Heterogeneous Type

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

TYPES OF BILAYER TABLET PRESS [25-29]

1. Single sided tablet press.
2. Double sided tablet press.
3. Bilayer tablet press with displacement monitoring.

1. Single sided 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.

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. Very short first layer dwell time due to the small compression roller, possibly resulting in poor Deaeration, capping and hardness problems.
4. This may be corrected by reducing the turret rotation speed (to extend the dwell time) but with The consequence of lower tablet output.

2. Double sided tablet press

Most double-sided tablet presses with automated production control use compression force to control tablet weight. The effective peak (Dwell time) compression force exerted on each individual tablet or layer is measured by the control system at the main compression of the layer. The limitations of single sided press are overcome in double sided tablet press. The two individual layers are separated because of insufficient bonding between them during final stage of compression. Because of low compression force the first layer is interact with second layer.

Limitations of the double-sided press:

1. Separation of the two individual layers is due to insufficient bonding between the two layers during final compression of bi-layer tablet.
2. 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”.

3. Bilayer tablet displacement with monitoring

Displacement tablet weight control is based upon the tablet compression force. We can alternate the compression force measurement by displacement measurement. If we measure the displacement the control system not depends on the tablet weight but depends on the pre-

compression force of tablet. It provides the high accuracy by reducing the compression force. Because of the low compression for we can avoid capping problem and get sufficient hardness with maximum turret speed.

Advantages

- ❖ Displacement“ weight monitoring/control for accurate and independent weight control of the individual layers.
- ❖ Low compression force exerted on the first layer to avoid capping and separation of the two 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 two layers. A clear visual separation between the two layers - maximized yield.

EVALUATION OF BILAYER TABLETS ^[19, 31-36]

Pre-compression evaluation:

- ❖ Particle size distribution
 - The particle size distribution is 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. $\Theta = \tan^{-1} (h/r)$ Where ‘h’ and ‘r’ are the height and 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 bulk density (BD) and tapped density (TD) were determined and calculated using the following formulas.

Bulk density = Weight of powder/Bulk volume

Tapped Density = Weight of powder/Tapped volume

- Compressibility

The compressibility index of disintegrate was determined by Carr's compressibility index. Carr's

$$\text{Index \%} = \frac{(\text{TD}-\text{BD})}{\text{TD}} \times 100$$

- Hausner's ratio

It is calculated by the formula, Hausner's Ratio = $\frac{\text{TD}}{\text{BD}}$

POST-COMPRESSION PARAMETER:

General Appearance:

The general appearance of a tablet, its visual identity and overall "elegance" is essential for consumer acceptance. Includes in are tablet's size, shape, color, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

Size and Shape:

The size and shape of the tablet can be dimensionally described, monitored and controlled.

Tablet thickness:

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken, and their thickness was recorded using micrometer. Generally, thickness should be within 30% to 50% of tablet dimension.

Weight variation: -

Standard procedures are followed as described in the official books.

Friability:

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked up. Normally, when capping occurs, friability values are not calculated. A thick tablet may have less tendency to cap whereas thin tablets of large diameter often show extensive capping, thus indicating that tablets with greater thickness have reduced internal stress.

Hardness (Crushing strength):

The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The small and portable hardness tester was manufactured and introduced by Monsanto in the Mid 1930s. The Strong-Cobb Pfizer

and Schleuniger apparatus which were later introduced measures the diametrically applied force required to break the tablet. If the tablet is too hard, it may not disintegrate in the required period to meet the dissolution specifications; if it is too soft, it may not be able to withstand the handling during subsequent processing such as coating or packaging and shipping operations. The force required to break the tablet is measured in kilograms and crushing strength of 4 Kg is usually considered to be the minimum for satisfactory tablets.

CONCLUSION

Over the years, advancements in technology and innovation have brought about increasing interest within the pharmaceutical industry in developing tablets containing two or more Active Pharmaceutical Ingredients (API) in a single dosage form, promoting customer convenience, compliance, and marketing. Bilayer tablets offer several advantages over conventional single layer tablets in that respect and also offer an excellent opportunity for manufactures to separate themselves from their competitors, improve their product efficacy, and protect against impersonator products. To overcome this hurdle a complete mechanistic understanding must be developed through the application of scientific and quality risk management tools: Pharmaceutical development and quality risk management.

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