Review Article

Emerging Trends in Bilayer Tablet Technology: Review

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ABSTRACT

Bilayer tablet is a new concept for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. Bilayer tablets can be a primary option to avoid chemical incompatibilities between Active Pharmaceutical Ingredient (API) by physical separation and to enable the development of different drug release profiles-immediate release with extended release. Bi-layer tablets have been developed to achieve controlled delivery of different drugs with pre defined release profiles. In the last decade interest in developing a combination of two or more API's in a single dosage form has increased in the pharmaceutical industry, promoting patient convenience and compliance. Several pharmaceutical companies are presently developing bi-layer tablets, for a variety of reasons. In this review we discuss the preparation, stability, formulation and characterization of bilayer tablets.

Keywords: Bi-layer tablet, chemical incompatibilities, physical separation.

INTRODUCTION

Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor such as repetitive dosing and unpredictable absorption gave an emergence 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[1]. 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[2,3,]. There are various applications of the bi-layer tablet it consist of monolithic partially coated or multilayered matrices.

Need for Bilayer Tablet[4-7]

1. 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. 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.
3. To separate incompatible API 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).
4. To control the delivery rate of either single or two different active pharmaceutical ingredients.

Challenges to Develop Bilayer Tablets

1. To achieve immediate release of the drug.
2. To control the release of the drug.
3. To improve the stability and bioavailability of the drug.
4. To give a good package design.
5. To make Compatible with taste masking technology.
6. To see that drug properties are not affected.

Advantages of bi-layer tablets[4, 8]

1. Bi-layer execution with optional single layer conversion kit.
2. Low cost compared to other dosage forms.
3. Greatest chemical and microbial stability compared to other oral dosage forms.
4. Objectionable odor and taste can be masked by coating technologies.
5. Offer greatest precision and the least content uniformity.
6. Easy to swallow with least hang up problems.
7. Fit for large scale production.
8. Bi-layer tablet is suitable for preventing direct contact of two drugs and thus to maximize the efficacy of combination of two drugs.

9. Bi-layer tablets can be designed in such a manner as to modified release as either of the layers can be kept as extended and the other as immediate release.
10. Expansion of a conventional technology.
11. Prospective use of single entity feed granules.
12. Separation of incompatible components.
13. Patient compliance is improved leading to improve drug regimen efficiency.

Disadvantages of Bi-Layer Tablet Dosage Form are:[4, 8]

1. Difficult to swallow in case of children and unconscious patients.
2. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
3. 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.
4. Bitter testing drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.

VARIOUS TECHNIQUES FOR BILAYER TABLET:

1. OROS® push pull technology [4,9-11]

This system consist of mainly two or three layers among which the one or more layer are essential of the drug and other layer are consist of push layer (Fig.1). 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.

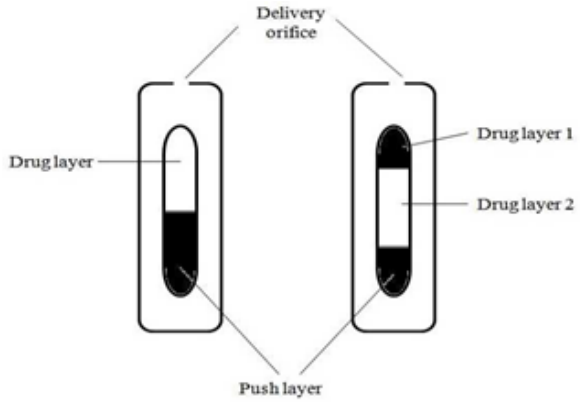

Figure 1: Bilayer and trilayer OROS Push pull technology

2. L-OROS tm technology [4,9-11]

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 than a semi permeable membrane, drilled with an exit orifice (Fig.2).

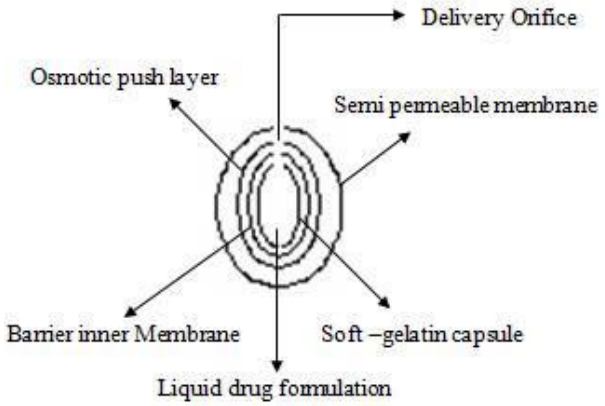

Figure 2: L-Oros tm technology

3. DUROS technology [4,9,12,13]

The system consists from an outer cylindrical titanium alloy reservoir (Fig.3). 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 reglious minute quantity of concentrated form in continues and consistent from over months or Year.

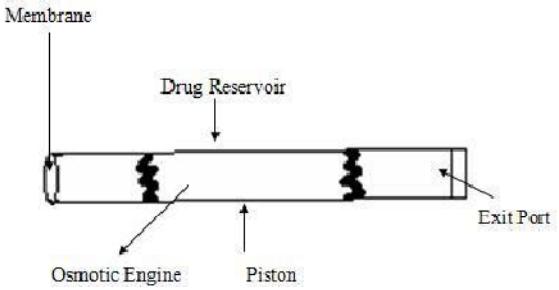

Figure 3: DUROS Technology

4. EN SO TROL technology [4,14]

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. 4).

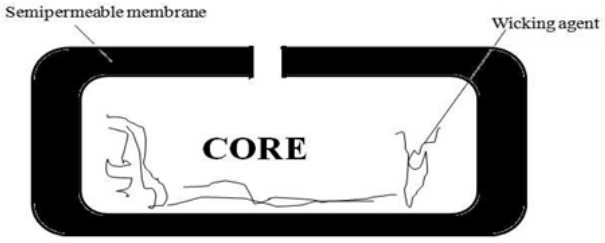

Figure 4: EN SO TROL technology

BILAYERED TABLETS: QUALITY AND GMP REQUIREMENTS[15-17]

To produce a quality bi-layered tablet, in a validated and GMP way, it is important to select a bilayered tablet press is capable of:

- Preventing capping and separation of the two individual layers that constitute the bi-layer tablet.

- Providing sufficient tablet hardness.
- Preventing cross contamination between the two layers.
- Producing a clear visual separation between the two layers.
- Precise and individual weight control of the two layers.

TYPES OF BI-LAYER TABLET PRESSES:

1. Single sided tablet press.
2. Double sided tablet press.
3. Bi-layer tablet press with displacement.

(1) Single sided tablet press [4, 10, 18]

The simplest design is the single sided press with both chambers of the double feeder separation from each other. Each chamber is gravity or forced fed with different powder, thus producing the two individual layers of the tablets. When the die passes under the feeder, it is first loaded with the first-layer powder followed by the second layer powder. Then the intact tablet is compressed in one or two steps.

Limitations of the single sided press [10,19-21]

- No weight monitoring / control of the individual layers.
- No distinct visual separation between the two layers.
- Very difficult first-layer tablet sampling and sample transport to a test unit for in-line quality control and weight recalibration.

(2) Double sided tablet press or "compression force" controlled tablet presses [4, 18]

A double sided press offers an individual fill station, pre – compression and main compression for each layer. In fact the bi-layer tablet will go through four compression stages before being ejected from the 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 main compression of the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance tablet and correct the die fill depth when mandatory.

Advantages:

- Displacement weight monitoring for accurate and independent weight control of the individual layer.
- Low compression force exerted on the first layer to avoid capping 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.

Limitations [5, 22]

Separation of the two individual layers is due to insufficient bonding between the two layers during final compression of bi-layer tablet. 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 final compression. Bonding is too restricted if 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". Most of the double sided tablet presses with automated production control use compression force to monitor and control tablet weight. Compression force control system is always based on measurement of compression force at main compression but not at pre-compression.

(3) Bilayer tablet press with displacement [23, 24]

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 operation point, but depends on the applied pre-compression force. In fact the lower the pre-compression force, the more the monitoring control system and this ideal for good interlayer bonding of the bi-layer tablet.

The upper pre-compression roller is attached to an air-piston which can move up and down in air cylinder. The air pressure in the cylinder is set as a product parameter at initial product set-up and is kept at a constant value by the machine's control system. This pressure multiplied by the piston surface is the constant force at which the piston and consequently the roller are pushed downwards against affixed stop.

The lower pre-compression roller is mounted on a yoke and its vertical position can be adjusted through the control system by means of a servomotor. The position of the lower pre-compression determines the precompression height. At every pre-compression the upper punch hits the upper roller and is initially pushed downwards into the die. As the lower punch is pushed upwards by the lower roller the power is being compressed, while the exerted compression force increases. At a certain point the reaction force exerted by the power on the

Upper punch equals the force exerted by the air pressure on the piston. The punch has to continue its way under the roller because the torrent is spinning.

Advantages:

- 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.
- Provide sufficient hardness at maximum turret speed.
- Maximum prevention of cross contamination between the two layers.
- Clear visual separation between the two layers and maximized yield.

VARIOUS ASPECTS USED IN THE BI-LAYER TABLET:[25]

Floating Drug Delivery Systems [26]

From the formulation and technological point of view, the floating drug delivery systems are significantly easy and consistent approach in the development of Gastro retentive dosage forms (GRDFs).

Approaches to design floating drug delivery system

The following approaches have been used for the design of floating dosage forms of single-and multiple unit systems.

Intra gastric bi-layered floating tablets:

These are also compressed tablet contain two layers i.e.

i) Immediate release layer ii) Sustained release layer.

Multiple unit type floating pills:

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density.

CHARACTERIZATION OF BLEND:[27]

Prior to compression, the blend was evaluated for their characteristics parameters such as Bulk Density, Tapped Density, Carr's Index and Hausner's ratio, angle of repose.

1. Bulk Density [28]

Blend was poured gently through a glass funnel into a graduated cylinder exactly to 10ml mark. The weight of the cylinder along with granules required for filling the cylinder volume is calculated. The cylinder was then tapped from a height of 2 cm until the time when there is no more decrease in the volume (Tap density tester USP, Campbell Electronics). Bulk Density (gm/ml) and Tapped Density (gm/ml) are calculated using the following equation:

Bulk Density (gm/ml) $\mathbf{Db = M / Vb}$

Where, M=Weight of Blend taken and Vb= Bulk Volume

Tapped Density (gm/ml) $\mathbf{Dt = M / Vt}$

Where, M =Weight of Blend taken and Vt=Tapped Volume

2. Angle of Repose

The angle of repose of granules is determined by the funnel method. The accurately weighed granules are taken in a funnel. The height of the funnel is adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules are allowed to flow through the funnel freely onto the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation:

Angle of Repose $\mathbf{\theta = \tan^{-1} (h/r)}$

Where, h = Height of the powder cone.

3. Compressibility Index

The compressibility index of the granules is determined by Carr's compressibility index:

Carr's index (%) $\mathbf{CI = \{(Dt - Db) X 100\}/Dt}$

4. Hausner's ratio [29]

Hausner's ratio indicates the flow property of powder Hausner's ratio is calculated by following equation

Hausner's ratio $\mathbf{HR = Dt / Db}$

Where, Dt = Tapped Density

Db = Bulk Density

5. Particle size distribution

The particle size distribution is measured using sieving method.

EVALUATION OF BILAYER TABLETS:

1. General Appearance [33]

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.

2. Thickness [33]

The thickness of the tablet is measured by vernier calipers scale. Thickness of the tablet related to the tablet hardness and can be used an initial control parameter.

3. Hardness [27-32]

The hardness test is performed to provide a measure of tablet strength. The resistance of tablet from shipping or breakage, under conditions of storage, transportation and handling before usage depends on its hardness. A Monsanto tablet hardness tester is employed to determine the hardness of the tablets. For each batch three tablets are tested and the hardness is measured in kg/cm^2.

4. Friability [31,33]

Friability is determined using a Friabilator and it is expressed in terms of weight loss and is calculated in percentage. Twenty tablets are randomly selected, dusted and weighed accurately and placed in the plastic chamber and subjected to its tumbling action at 25 rpm for 4 mins, dropping the tablets through a distance of six inches with each evaluation. After 100 revolutions the tablets are once again dusted and reweighed to determine the percentage loss of weight. The weight loss should not be more than 1%.

$$\% \text{ loss} = \frac{\text{Initial weight of tablets} - \text{Final weight of tablets} \times 100}{\text{Initial weight of tablets}}$$

5. Uniformity of Weight [33,34]

Twenty tablets are randomly selected and weighed individually. The average weight is determined then percentage deviation from the average weight is calculated.

Table 1: Average weight of tablets with % deviation

Average weight of tablets (mg)	% Deviation
80mg or less	10
More than 80mg but less than 250 mg	7.5
250 mg or more	5

6. Disintegration time [35,36]

The disintegration time is recorded using an USP disintegration test apparatus with distilled water at 37±0.5°C. The disintegration time is taken to be the time when no granules of any tablets are left on the mesh of the apparatus. The time reported to obtain complete disintegration of six tablets is recorded and mean value is reported.

7. Dissolution Studies [29]

Bilayer tablets are 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 are carried out using USP dissolution test apparatus I at 100 rpm, 37±0.5°C, and pH 1.2 buffer (900 ml) (i.e. 0.1 N HCl) for 2 hours, since the average gastric emptying time is about 2 hours. The dissolution medium is replaced with pH 6.8 phosphate buffer (900ml) and experiment continued for another 10 hours. At different time intervals, 5ml of the samples were withdrawn and replaced with 5ml of drug-free dissolution medium. The samples withdrawn are analyzed by UV spectrophotometer using multi component mode of analysis.

8. Stability studies [37,38]

In order to determine the change on storage, stability study is carried out a 25°C / 60% RH and 40°C / 75% RH in a stability chamber. Samples are withdrawn at regular intervals. Formulation is evaluated for changes in Hardness, Thickness, Disintegration time and in vitro release studies.

CONCLUSION

Bi-layer tablet is improved beneficial technology to overcome the limitation 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. The preparation of tablets in the form of multi layers is used to provide systems for the administration of drugs, which are incompatible and to provide controlled release tablet preparations by providing surrounding or multiple swelling layers.

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