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Bilayer Tablet: Novel Technology Use in Extended Release Drug Delivery System

Shreya Saha*, Mithun Bhowmick, Rimpa Goswami

Bengal College of Pharmaceutical Sciences and Research, Durgapur, West Bengal, India

ABSTRACT

Bilayer tablet is a successful technology of controlled release formulation or extended release formulation to provide successful drug delivery. The name of this development is clear that the tablets have been consisting of two layers, these are immediate release layer (IR) and another is extended release layer (ER). In this era it is very useful in many developing countries as a combination therapy for various disease treatment purposes. Bilayer tablet are needs to separate incompatible active pharmaceutical ingredients (API) by physical separation. In this formulation IR and ER both layers are present and it form extended release layer (ER). This types of formulations helps to maintain plasma level concentration in the body. So, it is a very useful and successful technology in novel drug delivery system.

Keywords: Bilayer tablet, extended drug release, Tablet press,

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***Address for Correspondence:**

Shreya Saha, Bengal College of Pharmaceutical Sciences and Research, Durgapur, West Bengal, India

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 [1].

Advantages

- This technology helps to avoid chemical incompatibility between different API's by physical separation.
- It helps to avoid the repetitive dosage form.
- Suitable for sequential release of two drugs [1].
- Treat the co-morbidity at the same time with one pill.
- In this technology drugs are choose on their synergistic effect.
- It maintains the plasma concentration because IR and ER both layers are present.
- Easy to swallow [2].
- It helps to provide physical, chemical, microbial stability than other type formulation.
- It is an extension of conventional technology.

Disadvantages [4]

- The size of this type of tablets is bigger than another formulation. So, it is difficult to swallow for children and sometimes for unconscious people.
- Low yield, insufficient hardness &the layers gets separated.
- There is a chance of cross contamination between two layer.

Need of bilayer tablets [5]

- It maintain 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 layer in order to achieve swellable or erodible barriers for modified release.

Tablet press: A tablet press is a mechanical devices that compress powder into tablet of uniform size and weight. A tablet press can be used to manufacture tablets of wide variety of materials, including pharmaceuticals, neutraceuticals, clinic product and cosmetics. To form a tablets the granulated materials must be metered into a cavity formed by two punches and die, then the punches must be pressed together with great force to fused and the material together [11].

Types of bilayer tablet press [4]

I. Single sided tablet press

II. Double sided tablet press

III. Bilayer tablet press with displacement monitoring

Single sides press

This is the simplest design which is a single sided press with both chambers and double feeder separated from each other. Each chamber is forced fed with different powers, thus producing the two individual layers of the tablets. When the die passes under the feeder, it is at first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps.

No weight control of different layer.

It is very difficult first layer for tablet sampling to a test unit in quality control.

It is difficult for separation of two individual layer by visual observation if there is no colour in between two layer.

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 2 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.

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 provide 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.

Bilayer tablets: Quality and GMP requirements:

To procedure a quality bilayer, in a validated and GMP-way it is important that the selected press is capable of preventing capping and separation of the two individual layers that constitute the bilayer tablet. Providing sufficient tablet hardness. Preventing cross contamination between two layers. High yield. Accurate and individual weight controls the two layers [12].

Dose calculation of bilayer tablet

For immediate release layer the equation is

$D_{IR} = C_p * V_d/F$ (Where C_p is target serum level, V_d is volume of distribution, F is bioavailability factor)

For extended release layer the equation is

$D_{SR} = D_{IR} (1+ 0.693* t/t_{1/2})$ (where t is the time in hour for which the ER of the drug is desire, $t_{1/2}$ is half-life of drug)

Extended Release Drug Delivery System[9]

The extended release drug delivery system is a novel approach of modified release of drug delivery. Extended release means a dosage form which allows to reduction in dose frequency of two fold as compare to immediate release. The extended release dosage form is included controlled release, sustained release, prolong release form etc.

Advantages:

1. It helps to reduce the dosing frequency of drug.
2. This conventional dosage form helps to less fluctuation of drug in blood vessels.
3. This helps to maintain the plasma therapeutic index means maintain the minimum effective concentration.
4. It helps to improve the poor patient compliance.
5. Helps to improve the treatment efficacy.
6. In this formulation drugs are absorbed and released slowly. So, it shows less toxicity.
7. Helps to improve the bioavailability of some drugs.

Disadvantages:

1. There is a chance of dose dumping.
2. The larger size of extended release formulation may cause difficulties to swallow or transit through GI tract.
3. It may increase potential for fast pass metabolism.
4. It can decrease the systemic bioavailability than immediate release dosage form.
5. The production cost is high of this formulation.

Methods:

Various techniques are used to formulate the extend release formulation. ER formulations are divided into different categories based on their mechanism of drug release.

I. Diffusion system

II. Dissolution system

III. Osmotic system

IV. Ion-exchange resin system

Diffusion system:

Diffusion means the molecules goes to high density to low density area or media. This system depends on the rate where drug dissolves through a barrier (polymer). Diffusion controlled system is mainly two types:

a. **Matrix system:** The matrix devices form a matrix which consists of active and inactive ingredients and where drug is dissolved or dispersed. The rate of dissolution of the drug within matrix need to be higher than the rate when it is release. It cannot follow the zero order release but govern by Fick's 1st law of diffusion.

b. **Reservoir system:** This system consists of core or reservoir and coating membrane or diffusion barrier. In this system the drug is surrounded by polymeric membrane. The polymer must not dissolve and the drug release through diffusion system.

Dissolution system: It is a system where dosage forms are dissolved slowly in order for drug to have sustained release property. It is mainly used for those types of drug which are highly soluble in water. The rate of dissolution and amount of per unit time is calculated by Noyes- Whitney equation. The equation is as follow –

$dW/dtL = DA (C_s – C)$

where, dW/dt = rate of dissolution;

A = surface area of the solidification;

C = concentration of the solid in the bulk dissolution medium;

Cs = concentration of solid in the diffusion layer surrounding the solid;

D = diffusion coefficient and

L = diffusion layer thickness.

Osmotic system: These types of delivery system there form of rigid tablet with a semipermeable outer membrane. When tablet passes through the body the water is absorbed through the membrane by osmosis process. The membrane consists of one or more small drilled whole. When water is absorbed in the tablet then osmotic pressure is formed to push the active ingredients comes out from the tablet. This system less affected by pH, food habit, GI motility etc.

Ion-Exchange resin system: Ion exchange resins are cross-linked water insoluble polymers that contain insoluble functional group. In tablet formulation ion-exchange resins are mostly used as disintegrant because of their swelling ability. The drug is attached to the resin. It is released after interaction of ions and ion exchange groups occur.

Bilayer tablet: Use as a Extended release formulation

Modified release dosage is a mechanism that (in contrast to immediate release dosage) deliver a drug with a delay after its administration (delayed release dosage) or for a prolong period of time (extended release [ER] dosage) or to specific target in the body (target release dosage).

Extended release dosage consists of either sustained release (SR) or controlled release (CR) dosage. SR maintains drug release over a sustained period of time but rate is not constant. But for CR the rate nearly constant.

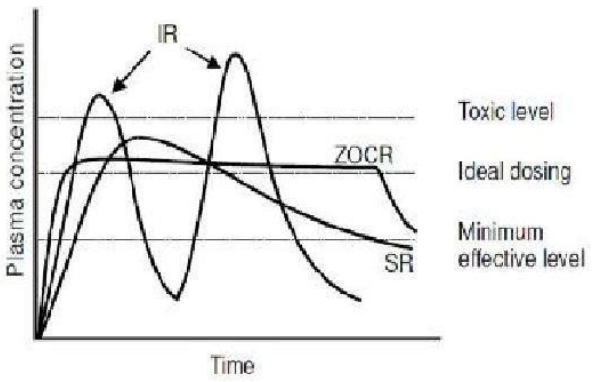

Figure 1: Plasma Concentrations

The immediate release layer reach the therapeutic level in plasma within shortest period. After this when extended release layer release the drug then it will maintain the plasma straight line in plasma concentration in body. The graphical representation will be cleared the plasma concentration of drug in body.

Evaluation of Bilayer tablet

Particle size distribution: Sieving is used to determine particle size distribution. From

Angle of repose: Angle of repose was calculated by measuring the diameter and height of the powder cone.

$$\text{Tan } \theta = h/r$$

Where "r" is the radius and "h" is height of the powder cone.

Bulk Density [7]: The powder is weighed accurately and poured into the graduated cylinder without any disturbance. Then the volume is marked.

Bulk Density = Weight of Powder / Bulk volume

Tapped density: After measuring the bulk density the cylinder is kept in tap density apparatus for checking the tapped density. The tapped density apparatus is operated for 500 taps. After this we should check the volume. If it is greater than 2ml then again it is kept for 750 tapping and after this check the weight.

Tapped density = Weight of powder / Tapped volume

Carr's Index: Compressibility index = $D_t – D_b / D_t *100$

Where Dt is tapped density and Db is bulk density.

Hausner's Ratio: Low Hausner's ratio means that the drug has high Flowability. It was calculated using equation given below.

Hausner's ratio = Tapped density/ Bulk density

Table 2: Compressibility Index limit

Carr's Index	Flow Character	Hausner's Ratio
1 – 10	Excellent	1.00-1.11
11 – 15	Good	1.12 – 1.18
16 – 20	Fair	1.19 – 1.25
21 – 25	Passable	1.26 – 1.34
26 – 31	Poor	1.35 – 1.45
32 – 37	Very poor	1.46 – 1.59
> 38	Very very poor	> 1.60

Thickness and Hardness: These are important parameters for tablet evaluation. The thickness and size is measured by vernire calipers. The hardness is measured by Monsanto hardness tester or Pfizer hardness tester.

Friability: It is used to measure the mechanical strength of the tablet or granules. The equipment used for determining friability is friabilator. 10-20 tablets are accurately weighed or tablet weight having 650mg and placed in the Rochy friabilator which revolves at 25rpm by dropping the tablets from a height of 6 inch in each revolution. Tablets are then weighed after 4mins or 100 times rotation. If it is necessary then sometimes process is continued for 300 times rotation.

% Friability = (loss of weight / initial weight) *100

Acceptance Criteria of % Friability:

For uncoated tablet it is not more than 1%.

For conventional compressed tablets it should be within 0.5% - 1%.

Weight variation: 20 tablets (not less than 10) are collected randomly and checked individual weight by electronic balance. The average weight and standard deviation of 20 tablets are calculated. After this we can decide it is passed or not compare with standard value which is shown in the table.

Avg. weight of tablets as per IP/BP	Limit	Avg. weight of tablets as per USP
80mg or less	±10%	130mg or less
More than 80mg or less than 250mg	±7.5%	130mg to 324mg
250mg or more	±5%	More than 325mg

In-vitro dissolution study : Tablets are subjected to in vitro drug dissolution studies in simulated gastric & intestinal fluid to evaluate the controlled drug delivery potential. This is done by mostly USP II paddle type apparatus. There maintain the rpm 75-100 and temperature 37°C±2°C. Dissolution study is carried by pH 1.2 buffer for 1-2 hours and pH 6.8 buffer for minimum 10 hours because there present both immediate and extended release layer. Then samples are analysed by UV spectrophotometer.

Conclusion

Bilayer tablet is a technology which is beneficial for patient and excellent opportunity for manufacturer which make separate then others or competitors. Bilayer tablet consists of two layer where one is immediate release and another is extended release layer. So, the IR drug reach high serum concentration in a short period of time and ER layer maintain the an effective plasma level for prolong period of time. So, it maintain the straight line in zero order kinetics in plasma and maintain therapeutic concentration. So, now a days bilayer tablets are prepared such as "Sitagliptin, Metformin HCl", "Atorvastatin, Atenolol" etc. in market.

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