A Review on Bilayered Tablets
Anusha JSK¹* and Karthik M²
¹Department of Pharmaceutics, Annamacharya college of Pharmacy, Rajampet, Andhra Pradesh, India
²Bharat Institute of Technology, Ibrahimpatnam, Hyderabad, India

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*Corresponding author: Anusha JSK, Annamacharya college of pharmacy, Rajampet, Andhra Pradesh, India; Tel: 9666522108;
E-mail: anujuluru@gmail.com

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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. Nowadays the use of bilayered tablets has been increased. Bilayer tablet is more suitable for gradual release of two active ingredients in combination. Bilayered tablet technology helps in separating the two incompatible substances in which one layer is immediate release as loading dose and second layer is controlled/sustained release as maintenance dose. Two incompatible drugs can also be formulated into a bilayer tablet by adding an inert intermediate layer.

INTRODUCTION
These are 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 therefore results in unwanted toxicity & low efficiency [1,2].

Advantages
- It helps in avoiding chemical incompatibilities between API’s by physical separation.
- Suitable for sequential release of two drugs [3,4].
- Repetitive dosing is required in conventional dosage forms which can be avoided by bilayer tablet.
- Lower dose of drug is required compared to conventional dosage forms.
- It is the most preferred & convenient route of administration.
- Chemical & microbial stability is more compared to other oral dosage forms.
- Taste & odor can be masked by coating technique.
- They show highest dose precision & low content variability.
- Easy to swallow [5,6].
Disadvantages

• Drugs with objectionable odour & with bitter taste cannot be formulated.
• Swallowing is difficult for children & for unconscious people [7,8].
• Formulation is difficult for drugs with poor wettability, slow dissolution rate & high absorption in the GIT.
• Cross contamination may occur between the 2 layers.
• Individual layer weight is inaccurate.
• Low yield, insufficient hardness & the layers gets separated [9,10].

IDEAL CHARACTERISTICS

• It should be elegant & free from chipping, cracking, discoloration and contamination [11].
• It ought to have adequate quality to withstand mechanical shock during its tablet formulation process [12].

CHALLENGES

Tablet breaks in to pieces when the two parts of the tablet don't bond totally. The two granulations should adhere properly when compressed into a bilayer tablet [13].

• At the point when the granulation of the main layer blends with the granulation of the second layer or vice versa, cross-contamination happens.
• Much expensive compared to conventional dosage forms or single layer dosage forms.
• The equipment used for formulation of bilayer tablet i.e., tablet press costs high [14-16].
• Development of two compatible granulations is must, which implies additional time spent on formulation, analysis & validation [17].

TECHNIQUES

Several techniques are used for bilayer tablets. They are as follows [18]
En So Trol Technology
Oros® Push Pull Technology
L-Oros Tm Technology
Duros Technology

TYPES OF BILAYER TABLET PRESSES

Various types of tablet presses are given below:

Single Sided Tablet Press

This is the simplest design containing two chambers which are separated from each other. Both the chambers are fed with different type of powders hence producing the two individual layers of a tablet [19-21]. Whenever the die goes under the feeder, the die is first filled with the first layer powder and then with the second layer powder [22,23].

Limitations

Exact weight of the individual medicament cannot be obtained. Discrimination of the two layers is difficult by visual observation [24]. As the compression roller is small, the dwell time of the first layer is very low which results in capping and variation the hardness. To extend the dwell time the torrent rotation speed is reduced which results in low tablet output [25,26].

Double Sided Tablet Press (Or) “Compression Force” Controlled Tablet Presses

Double sided tablet press contains an individual fill station. For each layer it offers pre-compression and main compression. Therefore each bilayer tablet undergoes four compression stages before ejecting from the tablet press [27,28]. In double sided tablet press with automated production control, compression force is used to check and control the weight of the tablet. Control system measures the peak compression force exerted on every individual layer or tablet. Out of tolerance tablets are rejected by the control system. The control system utilizes
the peak compression force as the sign to reject out of tolerance tablet and corrects the die fill depth when necessary [29-32].

**Limitations**

The 2 individual layers are separated because of insufficient bonding between them during final stage of compression [33]. For correct bonding the first layer should be compressed at a low compression force, hence therefore during final compression the first layer continues its interaction with the second layer. Accordingly the lower compression force diminishes the accuracy of the weight [34-37].

**Bilayer Tablet Press With Displacement Monitoring**

The principle of displacement tablet weight control varies from the compression force. While measuring displacement, control system sensitivity depends on the pre compression force but not on the operation point. For good inter layer bonding of bilayer tablet the lower the pre-compression force the more is the monitoring control system [38-40].

**Advantages**

As the compression force is low on the first layer capping can be avoided. Sufficient hardness can be obtained with maximum turret speed. Cross contamination is prevented between the two layers. Maximum yield can be obtained. Visual separation of the layers is very clear [41-45].

**CHARACTERIZATION OF BILAYER TABLET**

**Particle Size Distribution**

Sieving is used to determine particle size distribution [46].

**Angle of Repose**

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

\[
\tan \theta = \frac{h}{r}
\]

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

**Moisture Sorption Capacity**

Disintegrates are capable of absorbing moisture from the atmosphere and thus affects the hygroscopic drugs. Moisture sorption capacity is carried out by taking 1g of disintegrate in a petridish by distributing evenly over it and is placed in stability chamber at 37±1°C with 100% relative humidity for about 2 days. Moisture uptake is measured by calculating the difference in weights [48,49].

**Density**

Ratio of mass to volume for an untapped powder is known as the bulk density. A graduated cylinder containing sample is tapped mechanically until volume changes and thus tapped density is obtained [50].

**Compressibility**

It is the indirect measure of bulk density. To determine compressibility of the disintegrate carrs compressibility index [51].

\[
\text{Carr’s Index} = \left( \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \right) \times 100 / \text{tapped density}
\]

**Hausner’s ratio**

It is used to determine powder flow.

Hausner’s ratio = tapped density / pour density [53]
EVALUATION TESTS

Tablet Thickness and Size

Diameter & thickness are important for tablet uniformity. Vernier calipers are used for the determination of tablet thickness & diameter [54].

Tablet Hardness

Tablet hardness is measured by using Monsanto hardness tester. It is performed to find out the tablet breaking point and to test the structural integrity during handling, storage & transportation [55].

Friability

It is used to measure the mechanical strength of the tablet or granules. The equipment used for determining friability is friabilator [56]. 20 tablets are accurately weighed and placed in the friabilator which revolves at 25rpm by dropping the tablets from a height of 6" in each revolution. Tablets are then weighed after 4min to determine the percentage loss [57,58].

Uniformity of weight

Randomly 20 tablets are collected and the average weight is calculated. Weight variation is calculated and compared with the I.P. standards [59].

Dissolution Studies

Tablets are subjected to in vitro drug dissolution studies in simulated gastric & intestinal fluid to evaluate the controlled drug delivery potential [60]. Dissolution studies are carried out using USP I dissolution apparatus at 100 rpm at 37±0.5 °C with 900ml pH 1.2 buffer for 2 hours. Later on the dissolution medium is replaced with 900ml of pH 6.8 phosphate buffer. This is continued for other 10 hour. Drug samples of about 5ml are withdrawn and replaced with the drug free dissolution medium. The samples are analysed using UV spectrophotometer [61-65].

Advancement in the Field of Bilayer Tablets

Development of predetermined release profiles of active ingredients. Incorporation of incompatible active ingredients into single dosage form. Following are the few recent findings [66-69].

Tramadol and Acetaminophen - synergistic effect in pain

Cefixime trihydrate and Dicloxacilline sodium – synergistic effect in bacterial infections.

CONCLUSION

Bilayer tablet is the beneficial technology when compared to single layered tablet. By this technique even the incompatible drugs can be compressed into a single tablet. Bilayer tablet helps in sequential release of two drugs in which one as the immediate release and the other as the controlled release. The quality & GMP requirements of bilayer tablet vary widely. This explains why different kinds of tablet presses are used to produce bilayer tablets starting from single sided press to highly sophisticated machines.

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