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Review article

Bilayer tablets

Navidita Sharma*, Sonia Pahuja, Nancy Sharma, Naveen Sharma

Swami Vivekanand College of Pharmacy, Banur, Punjab, India

Corresponding author: Navidita Sharma, ✉ nitunavi@gmail.com

Swami Vivekanand College of Pharmacy, Banur, Punjab, India

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ABSTRACT

Among various dosage forms used for oral drug delivery, bilayer tablet technology is one of the most successful and popular technology as it provides several advantages over conventional dosage forms. It is suitable for release of two drugs which may be incompatible with each other as this technology allows us to separate such drugs. One of the two layers may be immediate release as initial dose and second layer as sustained release is maintenance dose. In this way, gradual drug level is achieved in blood. It also overcomes the shortcomings of single layered tablets. In this article, various techniques and approaches for bilayer tablets have also been discussed such as floating bilayer tablets, geomatrix tablets, swelling bilayer tablets and polymeric bio adhesive bilayer tablets.

Keywords: Bilayer tablets, Controlled release, Immediate release, Floating polymeric.

INTRODUCTION

Bilayer tablets are a form of drug delivery system intended to deliver two or more drugs in a single tablet unit. It is a novel approach whose use has been increasing at a substantial pace due to its patient convenience and compliance. Bilayer tablets physically separate the active pharmaceutical ingredients which overcomes chemical incompatibilities. Apart from incorporating two incompatible drugs in a single drug delivery system, bilayer tablets also control the drug release rates. Two different release rates can be achieved in a single dose of administration such as immediate release or sustained release or combination of both. Such release system can also overcome the problem of wide ranging fluctuation in drug concentration in body as seen in conventional dosage forms. Thus, ultimately overcomes poor efficacy and undesirable toxicity due to dose administration. Approximately 90% of the formulations manufactured today are taken by oral route. Bilayer tablets have become popular and a source of attention not only because they can be taken orally but also due to their capability to overcome problems related to conventional single layered tablets. Several pharmaceutical companies are presently developing bi-layer tablets for a number of reasons such as to decrease capital investment and cost of production, for patent extension and marketing. Various developed and developing countries are also moving towards combination therapy as it plays a major role in clinical treatment because of its better and wider curative synergism and lesser side effects.

Tablets

A tablet is a solid unit dosage form containing drugs in granular, powder or crystalline form compressed into a disk or molded. The medicaments or APIs can be present with or without excipients. Tablets are most popular dosage forms due to their simplicity, ease of administration, relative stability, accurate dosing as well as provide convenience in manufacturing, shipping and storage. Most of the drug molecules can be formulated into tablets. They can be classified into various types based on their release profile, type of coating or route of administration which are shown in figure 1 [1, 2].

Layered tablets or multiple compressed tablets

Layered tablets can be classified into:

Compression coated tablets

Inlay tablets

Multilayered tablets

The classification of layered tablets has been shown in Figure 2.

Figure 1: Classification of tablets

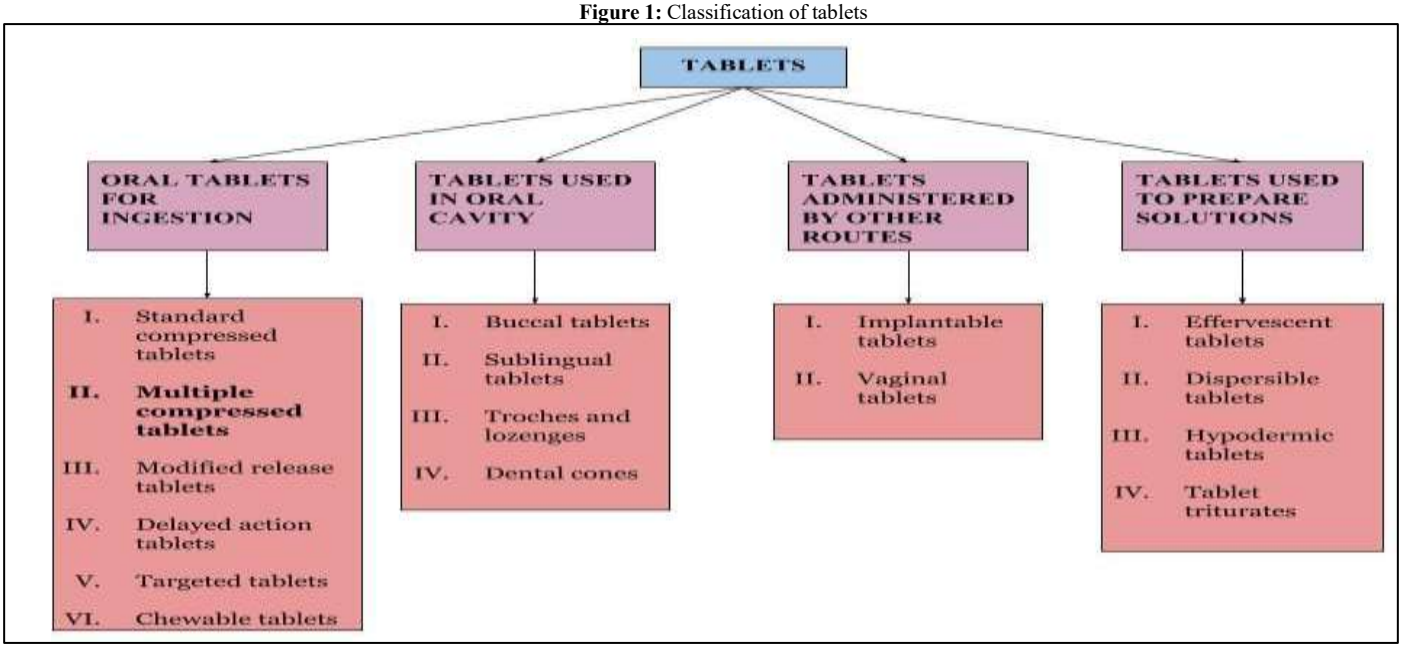
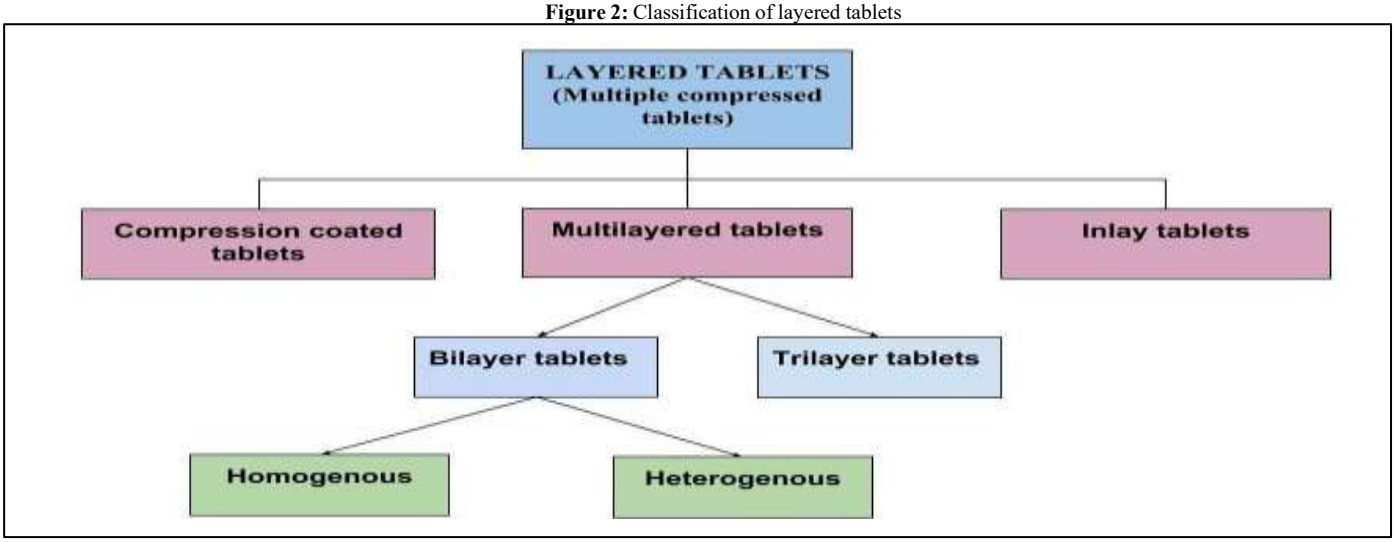


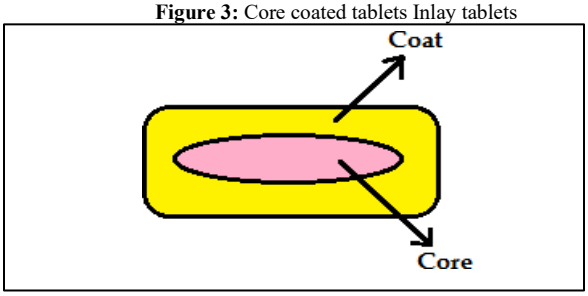
Figure 2: Classification of layered tablets



Compression coated tablet

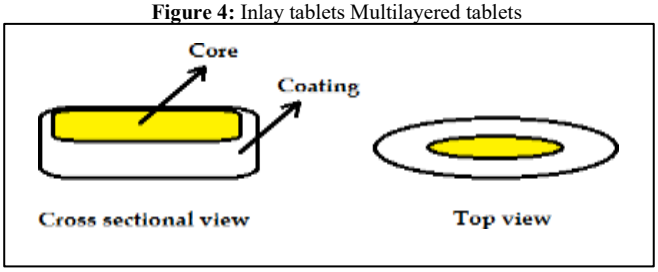
Compression coated tablets are also known as tablet within a tablet or core coated tablets. This tablet-in-tablet technology involves the compaction of granules around a preformed tablet core with the help of specially designed tableting equipment. Thus, these tablets have two parts: the internal coat and the surrounding coat. The outer layer provides the initial dose while the inner core release the drug later on which also makes such tablets having dual release technology in which drug release profiles can be manipulated. Figure 3 shows the compression coated tablets.

Figure 3: Core coated tablets Inlay tablets



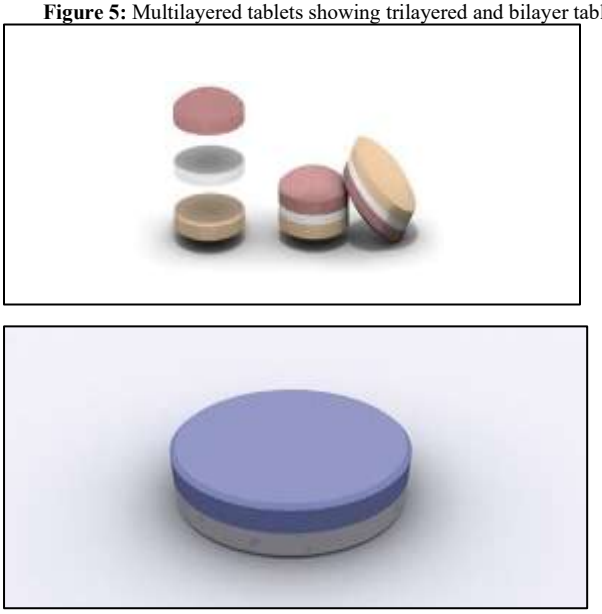
Inlay tablets are a type of layered tablet in which the top surface of core tablet is exposed instead of being completely surrounded by coating. When these tablets are manufactured, only the bottom of the die cavity is filled with coating material and core is placed upon it. Then compression force is applied to compress the whole tablet. The coating thus takes the shape of a cup in which core in placed. It is a novel platform technology for decreasing the mechanical shear on double compressed products which can lead to decrease in unknown process related impurities. By using this novel technology incompatible drugs can also be designed. Figure 4 shows inlay tablets.

Figure 4: Inlay tablets Multilayered tablets



Multilayered tablets can be bilayered or trilayered. These tablets are novel drug delivery systems which consist of several different granulations that are compressed to form a single unit composed of two or more layers. Usually different colors are given to each layer to produce a distinctive looking tablet.

Figure 5: Multilayered tablets showing trilayered and bilayer tablets

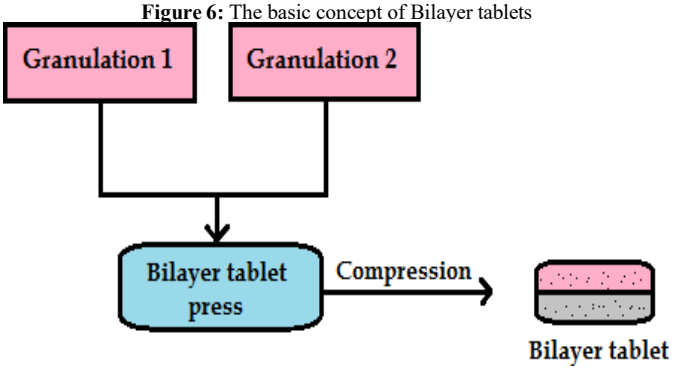


Multilayered tablets possess various benefits over conventional dosage form of tablets; the most important is to prevent incompatibility between drugs and excipients. As these are combination of two or more drugs in a single unit different release profiles can be achieved which improves patient compliance and also prolongs the drug(s) action. Figure 5 shows multilayered tablets.

Bilayer tablets

Bilayer tablets are composed of two layers of granulation compressed together to form a single unit. These tablets can be prepared with one layer of drug for immediate release and second layer for sustained release or both for sustained release or for immediate release. Bilayer tablets possess several advantages over conventional single layer tablets. These tablets have enabled the development of dosage forms with predetermined release profiles. The general concept of bilayer tablets is shown in figure 6.

Figure 6: The basic concept of Bilayer tablets



Bilayer tablets can be classified as:

Homogeneous type

Heterogeneous type

The concept of bilayer in flexible in which drug release rates can be altered.

Objectionable odor and bitter taste can be masked by coating technique.

It is cost effective and suitable for large scale production.

When the subunits have the same active pharmaceutical ingredients, such bilayer tablets are called homogeneous type. On the other hand, if the layers contain different active pharmaceutical ingredients they are termed as heterogeneous type bilayer tablets.

Advantages

The most important advantage is the separation of incompatible APIs or components.

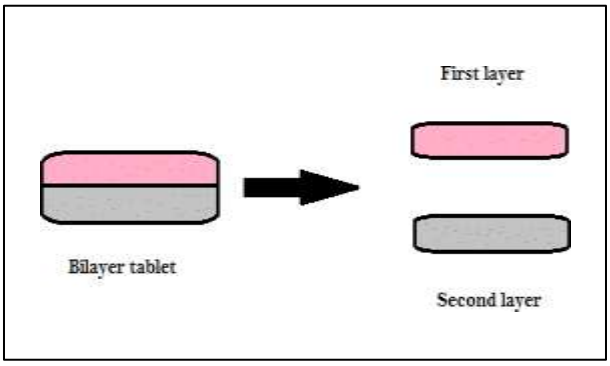
They maintain physical and chemical stability.

Patient compliance is enhanced leading to improved drug regimen efficacy.

They are economical as compared to other dosage forms.

They provide great dose precision and least content variability.

Figure 7: Bilayer tablets comprising same APIs having different release pattern from each layer (Homogeneous)



Disadvantages

Bilayer tablets may lack sufficient bonding between the interfaces of two layers which leads to separation.

During compression some drugs may resist compression into dense compacts, owing to amorphous nature, low density character.

Insufficient hardness, layer separation and reduced yield remain a major problem.

Cross contamination between the layers may take place while manufacturing.

They add complexity and bilayer rotary presses are expensive.

Ideal drug candidates for bilayer tablets

The drug candidates should possess the following characters:

The drug candidates should produce synergistic or additive effect.

They should be incompatible so that incompatible drugs can be formulated into single unit which by other means could not be possible.

High first pass metabolism with low biological half-life (ideal for baculo adhesive bilayer tablets).

Low biological half-lives. Such types of drug candidates are suitable for modified release bilayer tablets.

Unstable at intestinal pH. Such drugs are ideal for formulating floating bilayer tablets.

Figure 8: Bilayer tablets comprising different APIs (Heterogeneous)

Approaches to design bilayer drug delivery systems

Various approaches to design bilayer drug delivery systems are given below:

Floating drug delivery systems

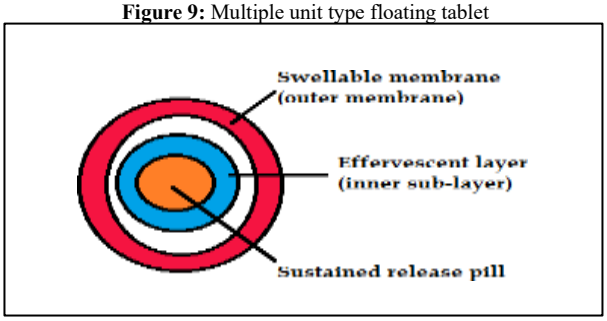
Floating drug delivery system is a class of gastro retentive drug delivery system. These systems remain in the gastric region for several hours, thus significantly prolonging the gastric residence time of drugs. This system improves bioavailability. The solubility of drugs which are less soluble in high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

Intragastric bilayer floating tablet

Multiple unit type floating tablet

Intragastric 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 9: Multiple unit type floating 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 buccoadhesive. 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.

Buccoadhesive bilayer tablets release the drug in the buccal cavity and avert the first pass metabolism which leads to high bioavailability. Buccoadhesive 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 bypasses 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).

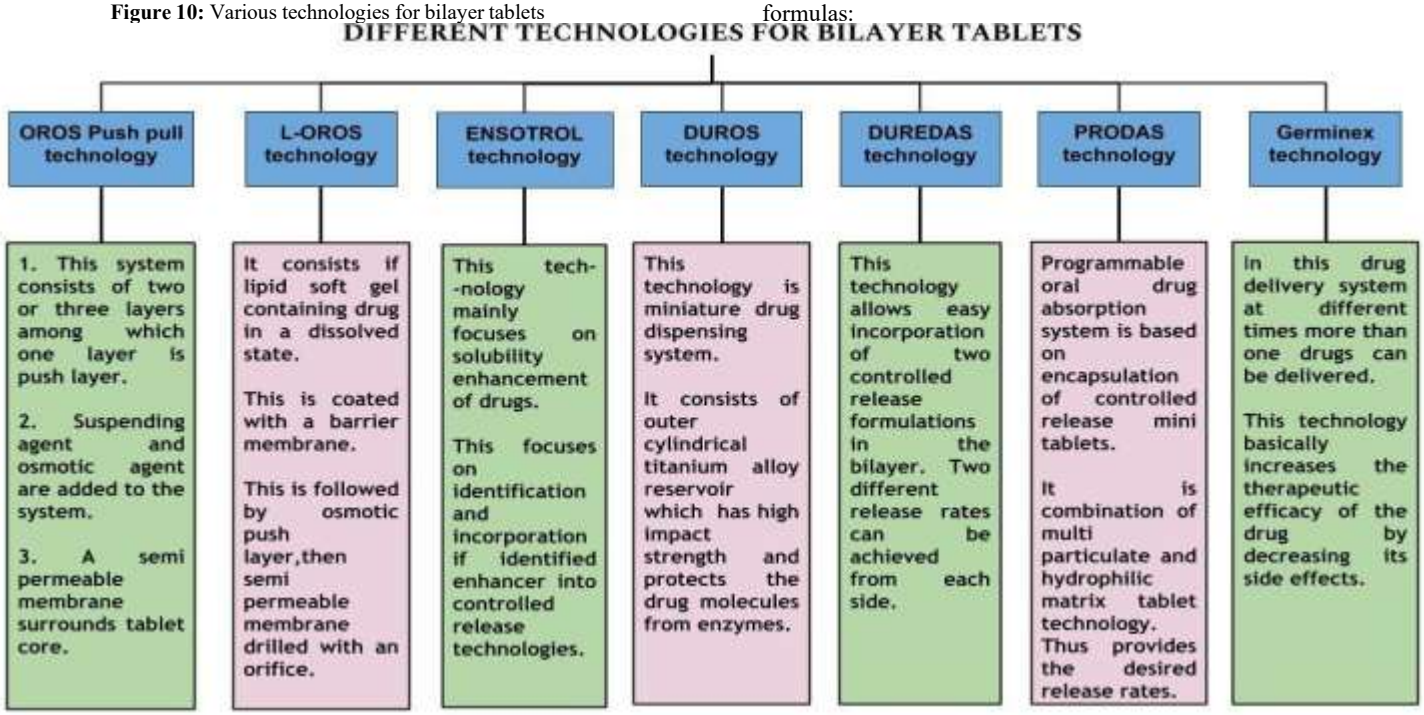
Biphasic release (combination of slow and fast release for a same drug).

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.

Technologies for bilayer tablets

Various bilayer tablet technologies have been summarized in figure 10.

Figure 10: Various technologies for bilayer tablets



formulas:

Characterization and evaluation of bilayer tablets

Pre-compression evaluation

Particle size distribution

The particle size distribution can be measured using sieving method using particle size analyser.

Angle of repose

The flow property of powders can be measured by determining angle of repose. It is the maximum angle that can be obtained between the free standing surface of the powder heap and the horizontal plane. It can be calculated using the following formula –

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

Where,

h = Height of the pile r = Radius of the pile

Photo-microscope study

Photo-microscope image of TGG and GG can be taken at 450x magnification by Photomicroscope.

Moisture sorption capacity

Disintegrant present as excipients in the tablets have the tendency to absorb moisture from the atmosphere which may affect moisture sensitive drugs if the moisture content is not controlled. Moisture sorption capacity is the tendency of the powder to absorb moisture. Thus it can be determined by taking 1 g of disintegrate and uniformly distributing in petri-dish. Keep the petri-dish in stability chamber at 37±1°C and 100% relative humidity for 2 days. The amount of moisture uptake can be determined by calculating difference between weights.

Determination of bulk density and tapped density

The bulk density and tapped density are calculated using the following

Where, ρT = Bulk density of the powder

ρB = Tapped bulk density of the powder

Post compression evaluation

General appearance

Tablet's visual identity, appearance and

Bulk density =

Tapped density =

Initial volume

Weight of the powder Final volume overall elegance are very important for consumer acceptance. This includes in are tablet's size, color, shape, presence or

absence of an odor, taste, surface texture,

Compressibility index (Carr's index)

Carr's index can be obtained from the bulk and tapped densities. It tells about the flow ability of the material. The less compressible a material the more flowable it is. A material having values of less than 20-30% is defined as a free-flowing material. physical flaws and consistency and legibility of any identifying marking.

Thickness and size

Thickness and diameter of tablets are important for uniformity of tablet size.

Thickness and diameter can be measured using vernier caliper.

Hardness (crushing strength).

The resistance of tablet from breakage during shipping, under conditions of storage, transportation and handling before usage depends on its hardness. Thus hardness test is important to measure tablet strength. The Monsanto tablet hardness tester is most commonly employed to determine the hardness of the tablets.

Friability

Friability of tablets can be determined using various friabilators the most common are Roche friabilators and Electrolab friabilator (USP). It is calculated using the following formula:

Friability (%) =

Initial weight of tablets − Final weight of tablets × 100

Initial weight of tablets

Weight variation or uniformity of weight Weight variation can be calculated by weighing twenty tablets selected at random and calculating their average weight. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

According to U.S Pharmacopeia a little variation is allowed in the weight of a tablet. Table 1 shows the per cent deviation which is allowed in weight variation.

Table 1: Weight variation parameters

Average weight of tablets	Percentage deviation
130 mg or less	±10
>130 mg and <324 mg	±7.5
324 mg or more	±5

Swelling property

Swelling property can be determined using dissolution test apparatus. Swelling characteristics are expressed in terms of percentage water uptake (WU %). WU% =

Wt. of swollen tablet – Initial wt. of tablet × 100

wt.of tablet

In-vitro dissolution studies

USP dissolution test apparatus I is usually employed for drug release studies according to pharmacopoeia standards. The samples withdrawn during dissolution test are then analyzed by UV spectrophotometer or High-Performance Liquid Chromatography.

Disintegration test

Disintegration test apparatus is generally employed to measure disintegration time of tablet. For Disintegration time, one tablet is placed in each tube and the basket arch is positioned in specified solvent at 37°C ± 2°C. A standard motor driven device is used to move the basket assembly up and down. To comply with USP standard, all tablets must disintegrate at specified time.

Stability studies

Stability studies are performed to check or determine the time period during which drug substance (API) or drug product retains the same properties and characteristics that it possessed at the time of manufacture. To perform stability studies the bilayer tablets are packed in suitable packaging and then stored under the following conditions for a specified period according to ICH guidelines. The tablets should be withdrawn after specified period and analyzed for physical characterization such as visual appearance, hardness, friability, drug content etc. The data obtained is then fitted into first order equations to determine the kinetics of degradation. Type and gender wise distribution of adverse drug reactions.

Table 2: ICH guidelines for stability studies of tablets

Study	Storage Condition	Time period
Long term	30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

CONCLUSION

Bilayer tablet technology has offered various advantages over single layer or conventional dosage forms. It has proved to be a beneficial technology to overcome shortcomings related to single layered tablets. It is most suitable means to deliver sequential release of drugs from its layers. One layer may serve as initial dose, thereby second layer as maintenance dose. Apart from the approaches to design bilayer tablets mentioned in the article, there exists more development in this field which may lead to development of new approaches to design such tablets. It is a growth area which may play an important role in the development of new pharmaceuticals.

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