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AN OVERVIEW OF BILAYER TABLET TECHNOLOGY

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ABSTRACT

Bilayer tablet is a novel approach to achieve controlled release of a drug with predefined release pattern from the last few years, interest in designing and formulating of two or more Active Pharmaceutical Ingredients (API) in single dosage form (bilayer tablet) for treatment of a disease. bilayer tablet dosage form also promotes customer compliance and convenience. The scientists work on to developed and formulating bilayer tablets to increase the therapeutic activity of a drug .e.g diabetes, and hypertension are two chronic diseases that may coexist, the major cause of death in the diabetes mellitus patient is heart disease. So to achieve the required therapeutic effect combine nebivolol and nateglinide for better patient treatment. Bilayer tablet technique is a modified beneficial method to get a better effect as compared to single-layer tablets. This technology provides an important approach for developing and designing not only incompatible drugs but also drugs with different release patterns. sustained-release tablets are formulated by this method in which the first layer is immediately released as loading dose and the second layer is maintenance dose, the release of a drug carried out without interfering pharmacokinetic and pharmacodynamic parameters with their dose of a drug. This review focuses on various application of bilayer tablet such as synergic property, antagonistic property; certain challenges in the formulation of bilayer tablet and also explain the need to develop and design quality bilayer Tablets with tablet press using a modified tablet press to produce a high-quality bilayer tablet with GMP parameter, mainly when high production yield require.

KEYWORD: bilayer tablet, GMP preparation require, tablet press, evaluation parameter for bilayer tablet.

INTRODUCTION

The oral route is the most convenient route of drug administration due to patient acceptance. However, it is known that modified release dosage form may be one or more advantages as compared to immediate release dosage form[1,2] The formulation and development of a controlled or sustained drug delivery system have emerging trade to trade over the last decade due to focus on the preparation of new drug Moiety as the mixture of this new drug has effectively been used to treat multiple diseases that require different dosage form.[3] Mostly controlled delivery drug system has the matrix type like as granule and tablet in that drug is uniformly distributed from the polymers due to less expensive, easy to formulation and prolonged drug released time.[4,5] The basic principle of a controlled drug delivery system is to reduce the dose frequency .morever numerous technology for manufacturing different Bilayer tablets utilized for various diseases is also analyzed by this article.

Bilayer tablet:- Now a day several developing and developed countries have worked on developing a dosage form that is used to treat different diseases and drugs that needed long-term treatment such as Diabetes mellitus, cardiovascular disease, and HIV.[6,7] This treatment is achieved by Novel bilayer tablet technology bilayer tablets possess certain merits as compared to traditional monolayer tablets. such as Bilayer tablets are utilized to prevent the chemical instability of formulation ingredients with the help of physical layer separation. However, the basic main purpose of bilayer tablets is to minimize dosage frequency, additionally, bilayer tablets possess to develop controlled drug delivery of active pharmaceutical ingredients with pre-established release pattern or through a combination of slow-release with the immediate-release drug.[8]

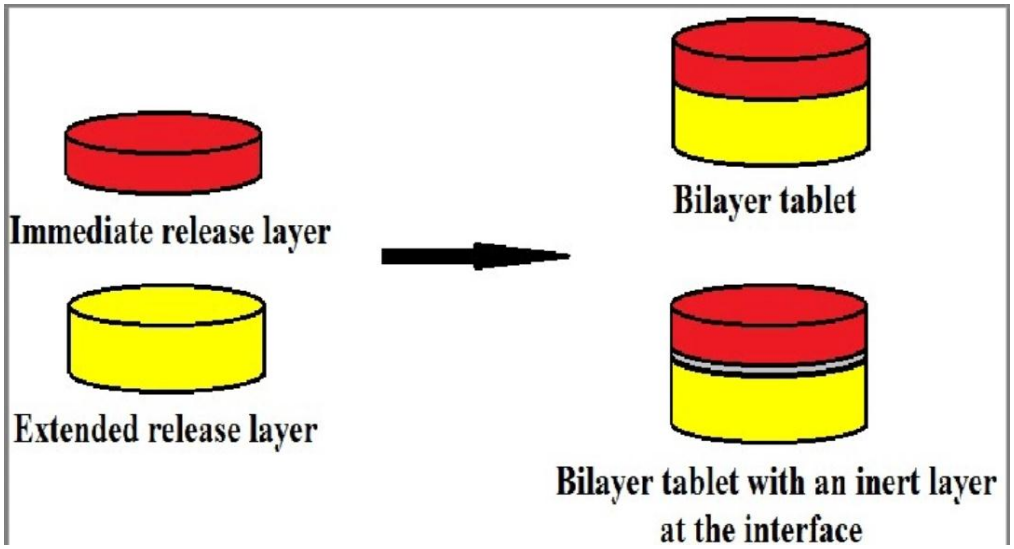

Fig 1: Releasing layers of Bilayer tablet.

Nevertheless, bilayer tablet made up of two-layer one of its layers makes sure that release of the drug immediately to attain high serum /blood concentration in the short time the second layer is controlled release which consists of the hydrophilic matrix that basic aim to maintain plasma drug concentration for the long period. The pharmacological effect of a drug depends on the release of a drug from the primary layer .which leads to increased blood concentration and suddenly the plasma drug concentration is maintained by the second layer.[9]

One of the important challenges while developing bilayer tablets is insufficient bonding and less adhesion between the primary and secondary layer, which leads to interfacial breaking which causes tablet lamination, capping, or layer separation. sometimes this defect does not occur immediately after formulation.[10]

If the compressed tablet is too hard or too soft they will not adhere to each other, which often leads to reduced mechanical strength. other problem during formulation includes maintaining the order of layer segment, layer weight ratio, elastic disparity of adjacent layers, cross-contamination between two-layer and insufficient hardness. If this parameter is not well optimized, will impact the bilayer tablet compression pressure which ultimately results in quality attribution of bilayer tablet so that's why it is important to detail understanding the main route of causes in both small and large scales formulation and find out an effective solution during the bilayer tablet formulation.[11,12]

Reason for designing bi-layer tablet

. To determine the release rate of either a single or two different APIs from the dosage form.

.To deliver a fixed-dose combination of a different drug. Extend the drug release product, various bilayer drug Delivery Systems such as a chewing tablet, buccal delivery system, gastroretentive drug delivery System floating drug delivery system.[13]

Advantage of bilayer tablet

1) Reducing the individual dose of two drugs to their additive effect.

example :- Theophylline + Salbutamol

2)chemical and physical instability can be prevented by the physical Separation of two drugs.

3)bilayer tablet are you and dosage form, it provides considerable potential by substantial dose accuracy and the minimal contain variability.

4) This dosage form is cost-effective as compared to all of the oral dosage forms and also suitable for small as well as large scale formulation.

The disadvantage of bilayer tablet

1) It is difficult to consume in children and unconscious patients.

2) Drugs with hygroscopic properties, slow dissolution, poor wetting property, less bioavailability may be difficult to manufacture into bilayer tablets.

3) Drugs with better taste, the drug that is sensitive to oxygen or humidity can be required encapsulation.

4) Drugs having slow dissolution, poor wetting property, and optimum absorption in GIT may be difficult to formulate as bilayer tablets because they provide inadequate bioavailability.

Good manufacturing practice (GMP) in bilayer tablet manufacturing.

In GMP, the press is used to prepare bilayer layer tablet should be.

1) Avoiding the capping and separation of two layers that made up the bilayer tablet.

2) Providing adequate bilayer tablet hardness.

3) Inhibiting cross-contamination between two layers.

4) Providing a completely visual separation in between two-layer and high yield.

5) Accurately control the weight of two individual layers.[14]

Type of bilayer tablets

On the base of mechanism for production, bilayer tablet have 3type.

The first type is a single side press, which is developed with the help of gravity force. The second type is a double-sided press produced by compression force, to control the weight of the tablet. However, the last type is double-sided press, which is generated by the displacement process.[15]

All the bilayer tablet detail explained below.

1. **Single sides press:-** The single-sided press is consist of a double feeder having two separated chamber. Each of these two chambers is fed by gravity or by various forces, resulting in to produce of the individual layer(two separated layers) after that filling of the first layer is done, generally, the first layer becomes granulation then feed carefully into a die with help of feeder and called as the bottom layer. After that second layer is prepared by placing the tablet granule having appropriate design size and weight than with help of compression force two-layer joined together to achieve adequate hardness to the completed bilayer tablet.

Limitation of the single side press

1 absence of distinct visual partition between individual layer.

2 absence of weight monitoring of bilayer tablet.

3 because due to small compression force very brief dwell time for the first layer lead to altering hardness.[16,17]

2. Double-sided tablet press

This type of tablet press works on automated production control and with the help of compression force to control tablet weight before ejection from the press the bilayer tablet transfer through four different stages.

E. g courtoy R292F bilayer press.

Different bilayer tablet press used in market

Table. No 1: types of tablet press.

bilayer tablet press	Feature of turret
Kambert's expert	3 piece turret with SS 316 die table
Modul^{1M} pwith bilayer ECM	Mixed turret [10B &10D stations]
XM12 tablet	Exchangeable turret design for production of any tablet size.
Xpress tablet press	Fast and tool free turret exchange system.
ADEPT double preess	Turret ring is detachable from the turret so reduce replacement cost.

E. g ADEPT double-sided tablet press

The systemic compression force exerted on each tablet is determined at the leading layer compression by the monitoring system. The compression force is utilized for the signal that controls the system to reject tablets that are out of tolerance and have a definite filling of the depth of a die based on requirement .double layer tablet contains better weight monitoring as compared to a single-layer tablet. Also, defect like capping, lamination, low compression is prevented by applying lower compression to the first layer.[18,19]

Limitation

1) generally layer separation occurs due to low compression force to the 1st layer.

3.Bilayer tablet press with displacement

The tablet monitoring principle is based on compression force the weight control using this press is based on the thickness of the layer under constant compression force .during the measurement of displacement the sensitivity control system depends mainly on precompression force instead of tablet weight. In bilayer tablet press their has two compressors that are upper pre-compression roller and the lower pre-compression roller. Generally former is connected to an air piston and the lower pre-compression roller is responsible for compression height.[20]

Advantage

1) Accurately weight controlling of the individual layer is measured by this tablet press.

2) Optimum hardness of tablet achieved at maximum turret speed.

Evaluation of bilayer tablet[20,21,22]

general properties:- The general property of a tablet include visual identity and overall appearance is important for customer acceptance it includes tablet size, shape, color, order, taste, surface, texture, flow properties, and consistency.

Size and shape:- The size and shape of the bilayer tablet can be measured, controlled, and monitored.

Tablet thickness:- Tablet thickness is an important aspect of a tablet and is determined by filling equipment and some of this equipment utilized the systemic thickness of a tablet as a counting mechanism. This thickness of a tablet should be measured by utilizing Digital Vernier caliper for that the thickness of a 10 tablet is measured and this thickness is expressed in micrometer.

Weight variation:- for determining weight variation 20 tablets are randomly selected from each batch and individually weighted then calculate average weight and compare the average weight of individual tablet weight as per USP test NOT more than 2 tablets are deviated the percentage limit and if no tablet deviated by more than 2

times the percentage limit the average weight variation determine as per U. S. pharmacopeia.[22]

The limit for weight variation given below.

Table No.2: limit of weight variation.

Average weight of Tablet	% deviation
130Mg Or less	+- 10
More than 130Mg & less than 324Mg	+- 7.5
324mg Or more	+-5

Friability Test:- friability test is a method used to the measured physical strength of a tablet upon exposure to attrition and mechanical shock. In another world, friability is related to how much mechanical stress on which tablets can withstand during the process of manufacturing, packaging, handling, and shipping. however in the pharmaceutical industry the instrument used to determine the friability of tablets is called friability tester.

There are two types of friability apparatus
1) single drum friability apparatus
2) Double drum friability apparatus.

For measurement of friability number of the tablet are weighed and kept in the friability apparatus where they are rolled repeatedly then provided the shocks and tablet fall 6 inches in each rotation taken by the Apparatus. After 100 rotations the tablets are weighed and this weight compared against initial weight loss is measured in percentage the tablet weighted and this weight compared against initial weight. This loss is measured in percentage. The tablet weight loss Not more than 1% during friability test is usually acceptable, while damaged tablets are not picked up. Whenever the capping of a tablet occurs friability values are not determined. Generally, the thick tablet may have a minimum tendency to Cap but the thin tablet has a large diameter usually maximum capping occurs. This suggests that if tablets have high thickness then they have less internal stress.

Friability (%loss) = [(Initial wt. of tablets– Final wt. of tablets)/Initial wt. of tablets]×100

Hardness

the tablet must have certain strength or hardness and its resistance to capping, abrasion, breakage, and withstand from handling, manufacturing, packaging, and transporting. The hardness of the tablet is also known as crushing strength. The crushing strength of a tablet determines by the following method.

1)Generally tablet hole between the 2nd and 3rd finger with the thumb act as a fulcrum. If the tablet is a sharp snap, the tablet is an optimum strength.

2) Tablet strength is defined as the force is required to break a tablet in a diametric compression. For that test tablet positioned in between two anvils and force is applied to this anvils due to crushing strength the tablet is break and this break recorded by using different hardness test such as.

1) Monsanto hardness tester
2) strong cobb hardness tester
3) Pfizer hardness tester
4) schleuniger hardness tester

The hardness of the tablet is a function of the applied pressure and the factor that is responsible for force also affecting it. however, the additional pressure is put into the prepared tablet .this leads to an increase in the hardness of the tablet, and ultimately capping and lamination of the tablet occur. if the tablet is extremely hard it may not be able to withstand the further manufacturing procedure such as coating, handling, packing, and shipping. in certain cases, if the tablet is extremely hard at that condition disintegration test to perform before rejection the batch, supposed Tablet disintegrated within time limit batch are acceptable. The force required to tablet broke is expressed in kilogram. 4-10 kg is the optimum range of oral tablet hardness.

Stability study:- stability study of bilayer tablet perform as per ICH guideline for this tablet is packed in acceptable packing material and stored as per the following condition.

Table no.3: stability studies.

Study	Storage condition	Minimum time period.
Long term	25°C +-2°C/60% RH or 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

In-vitro dissolution study:- in vitro dissolution study is carried out in gastric or intestinal fluid to determine or measure the percentage release of a drug from the dosage form. This dissolution study was performed by using USP dissolution test Apparatus at 37 °C ± 0.2°C temperature at specific RPM all these conditions maintain as per monograph.[23]

List of official dissolution apparatus as per IP/USP

Table No.4: list of dissolution apparatus according to USP & IP.

Apparatus	According to USP	According to IP
apparatus 1	Rotating basket type apparatus	Paddle
Apparatus 2	Paddle type apparatus	Basket
Apparatus 3	Reciprocating cylinder	
Apparatus 4	Flow through cell	
Apparatus 5	Paddle over disk	
Apparatus 6	Cylinder type	
Apparatus 7	Reciprocating disk	

Example of drug designed by bilayer tablet

Table 5: Example of bilayer tablet formulation.

First layer	Second layer	Remedies
Atrovastatin	Atenolol	Hypercholesterolemia &hypertension
Aspirin	Isosorbide 5-mononitrate	For fever, pain and inflammatory condition
Diclofenac	Cyclobenzaprine	Synergistic effect in pain
Metformine HCl	Glimipiride	Synergistic effect in diabetes mellitus
Piracetam	Vinpocetin	Synergistic effect in alzheimer disease
Metformine HCl	Pioglitazone	Synergistic effect in diabetes
Ibuprofen	Methocarbamol	Synergistic effect in back pain
Salbutamol	Theophylline	Synergistic effect in asthma
Ascorbic acid	Cyanocobalamine	For preventing interaction between mismatched vitamine.

CONCLUSION

To sum up all the data, the bilayer tablet is one of the modern tablet dosage forms. where a combination of incompatible drugs has different indications and also the same drug which have a different rate that is immediate and sustained release drug incorporated in a single unit. The basic purpose of that dosage form is to produce effective drugs having fewer adverse effects and also prevent the frequency of drug administration because of its multiple or synergistic effects. To achieve this property different principal are various presses such as single press, double-sided tablet press, and bilayer tablet press with displacement are used to increase tablet properties and minimize adverse effects. The primary objective of this dosage form is not only to provide safe and effective drugs but also to maintain quality target products. This article mainly focused on the GMP parameter to meet all quality attribution to the final product. The formulated tablet are evaluated by physical as well as chemical processes to ensure stability throughout the shelf life of the tablet. Currently, different Bilayer tablets are developed with different APIs for combined diseases like diabetes, hypertension. But in some cases, the same API is given as the initial dose and then maintenance dose to maintain plasma drug concentration for a long time period.

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