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Review article

Bilayer tablet overview: A revolutionary approach in sustained drug release & combination drug therapy

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Abstract

A fresh method of administering drug, the bilayer tablet is a single dosage form containing 2 or more Active Pharmaceutical Ingredients (API). By incorporating two distinct layers, bilayer tablets provide improved drug release profiles and enhanced therapeutic efficacy. This review's objective is to pinpoint the challenges that arise when making bilayer tablets and to suggest solutions for these difficulties. To help you better grasp bilayer tablets, types like double side presses, single side presses, and bilayer tablet displacement presses are discussed along with their uses, advantages, and disadvantages. In this thorough guide, we will look into the design, manufacturing, and applications of bilayer tablets.

Introduction

Administering drugs has been significantly improved by using bilayer tablets. In comparison to single-layered tablets, bilayer tablets have so many advantages. It permits the release of two medications in turn, either separately or in combination to break up incompatible substances. These tablets increase the drug's bioavailability, decrease the frequency of drug administration, and deliver the medication consistently. The tablet is made up of two layers: one for immediate release and the other for prolonged release. Among its layers is designed to guarantee the drug's immediate extraction and to quickly attain a high serum concentration. Its second layer is a hydrophilic matrix with controlled release that seeks to sustain an effective plasma level over an extended period of time. This technology can physically separate incompatible drugs i.e. (APIs) and target a variety of diseases, including inflammation, diabetes, and hypertension. The same manufacturing principles apply to conventional and bilayer tablets; however, incompatible APIs, equipment, and other operational issues require special consideration. Bilayer tablet formulation is appealing to various pharmaceutical companies because of its potential therapeutic benefits, patent extension, and potential for marketing [1, 2].

Challenges in the formulation of bilayer tablets

Drug delivery medium production, especially the production of bilayer tablets, is a difficult process with many moving parts. These comprise mechanical challenges, long-term property prediction, layer management, individual mass control, and cross-contamination prevention. The procedure may lead to a lower yield and possible layer delamination. Layer separation or delamination can result from interfacial cracks and residual stresses brought on by inadequate adhesion and bonding. The ability of compacted layers to adhere firmly is also influenced by their hardness. To guarantee the quality of the tablets, additional variables such as the layer sequence order, layer weight ratio, first layer damping force, and cross-contamination must be managed.

A thorough comprehension of these problems and specialized techniques for failure prediction are essential for the successful development of bilayer tablets [3].

Material properties

1. Consider the fundamental characteristics of materials (API and excipients) i.e. Brittleness (e.g., lactose, di-calcium phosphate), Plasticity (e.g., microcrystalline cellulose), Visco-elasticity (e.g., pre-gelatinized starch).
2. The formulation's compaction property will be determined due to the effect of the properties of the excipients and/or API.
3. Recognise how brittle and plastically deforming materials affect the compression process. Plastic materials compress because of plastic flow, whereas brittle materials break and fill up spaces when compression force is applied.
4. Take into account the variations in the elastic Young's modulus. During decompression, materials relax at various rates. Elastic mismatch between neighbouring layers in a bilayer structure can lead to the bilayer tablets delaminate.
5. Recognize how the compression force propagates or is transmitted through the materials. The applied compression stress can be responsible for the greater particle deformation in the lower central region of the die compared to the outside radial regions.
6. Take into account the effect of wall friction, which slows the particles' vertical travel as they come into touch with the die.
7. Recognize that a tablet expands (elastic recovers) over a few days following its ejection from a die. The level of expansion varies according on the materials assessed.
8. Take into account the composition of the materials, since this influences both the mode of fracture and the strength of the bilayer compacts.
9. Recognize how the rigidity of the brittle materials affects the initial layer's particle deformability. Significant surface roughness is maintained to allow for mechanical interlocking to occur. For materials that deform plastically, the bonding strengths between adjacent layers decrease as the interfacial surface roughness decreases. The bonding strengths between layers of fragmenting materials are insensitive to roughness [2].

Compression forces

1. Careful monitoring of the compression force is necessary to prevent delamination due to mechanical stresses during compression.
2. Compression forces on both layers have a major impact on the interfacial strength and adhesion, contributing to the mechanical integrity of the tablet.
3. The strength of the tablet may be weakened if the substance in the first layer is more elastic.
4. Layer adhesion is significantly impacted by the first layer's compression.
5. Punch velocity and compaction pressure have an effect on compact densification and resistance to compressibility.
6. Because of decreased adhesive and bonding surface area, axial tensile strength decreases as first layer compression force increases.
7. Tablet delamination may result from compaction stresses and elastic material mismatches.
8. When tablets are made of plastic material, the interfacial strength depends on the forces acting on the first and second layers
9. The amount of particle assembly deformation is determined by the strength of the layer forces.
10. It is the level of compression force in the first layer that determines the surface roughness of the first layer, which in part affects the interfacial strength.
11. The interfacial zone experiences shear stress due to elastic mismatch between layers.
12. The compact will break if the energy dissipation is greater than the energy contained in the adhesive bonds.
13. As the first layer force increases, the strength of fragile bilayer tablets falls.
14. Fracture in the first layer of brittle material tablets indicates a higher interfacial strength than individual layer strength.
15. In plastic material tablets, breakage along the interface suggests that layer strength is more than interfacial strength.
16. The consolidation mechanism of brittle materials, known as volume reduction by fragmentation, effectively increases the surface areas available for particle bonding.
17. For adequate interfacial strength to endure mechanical shock during manufacture, packaging, and transportation, bristle excipients are preferred [4].

Lubricant

As the lubricant coats the particles uniformly, increased lubricity of a powder blend decreases friction between the particles during compression. Greater interfacial interaction in a bilayer structure can be achieved with lower lubricant levels for the first layer. For plastic materials, the effect of lubricant level on tablet strength is particularly noticeable. The quantity of lubricant increases tablet surface smoothness, which affects interfacial interaction between layers. It is necessary to determine the quantity of lubricant required to prevent the initial layer from picking and sticking. External lubricant can boost the crushing strength of monolayer tablets by 40%, which involves spraying lubricant onto dies and punches without extending tablet disintegration [2].

Layer ratio and layer sequence

It is discovered that, in general, there are three possible ratios between the first and second layers: 1:1,1:2, and even 1:3. However, it is challenging to get the second layer's weight to match the first layer's, which is mostly heavy, and this creates an issue when bilayer medications are being formed. When the first layer weight is high, it can be difficult to keep the second layer weight constant. Although it is ideal in these situations to press the smaller layer weight

first, this isn't always achievable because of the mechanical constraints of the bilayer presses in use today [1].

Environmental conditions

Research has been done on how moisture affects the strength of bilayer tablets. Relative humidity causes hygroscopic materials to absorb or desorb moisture, which can cause layer expansion and modifications to the Young's modulus of elasticity. This may lead to time-dependent delamination by weakening the layer-to-layer contact. Ad-hoc delamination is typically caused by a reduction in Young's modulus following an increase in moisture. It is advised that materials be preconditioned to guarantee that the moisture content of the air in the production area is balanced. Because it may affect quality qualities including tensile strength, layer adhesion, friability, and dissolution, the physical stability of bilayer tablets during storage is an important consideration. As humidity and storage duration increased, the tablet's interfacial strength declined [5, 6]

Layer weight control

Careful control over a number of variables is necessary during the manufacture of bilayer tablets. To ensure homogeneous content of the APIs, it is important to consider the particle size distribution of the materials, their flow properties, and the bilayer press's capacity to adjust layer weight. Depending on the seller's identity, every bilayer press has a distinguished weight control system. Presses used for development and commerce today are able to track both the initial layer's and the bilayer's overall weight. The procedure is made more difficult by the fact that no bilayer press that is sold commercially can sample the second layer weight independently. Since the first layer typically receives a limited precompression force, sampling can be difficult since the tablets could not be sufficiently firm for accurate weighing. Kilian, Fette, and Korsch bilayer presses, for example, include a sampling device for the first layer compact. The device itself permits an extra compression force [2].

Bilayer tablet characterization

When talking about bilayer tablets, this is one of the most fundamental topics that shouldn't be overlooked. Although it is ideal in theory to have a material that can compact and compress without deforming when compression is applied, as this will strengthen the bond between the two layers of the bilayer tablet, other factors also contribute to the formation of the desired quality of bilayer tablets. Characterization includes factors such as particle size distribution, response angle, photo-microscopic analysis, density, compressibility, and moisture sorption capacity. Characterizing bilayer tablets is essential to comprehending and creating these kinds of tablets. It calls for more methods like interface characterization tools and 3D characterization tools [1].

Advantages and disadvantages of bilayer tablet

Advantages and disadvantages of bilayer tablet is illustrated in figure 1 and 2.

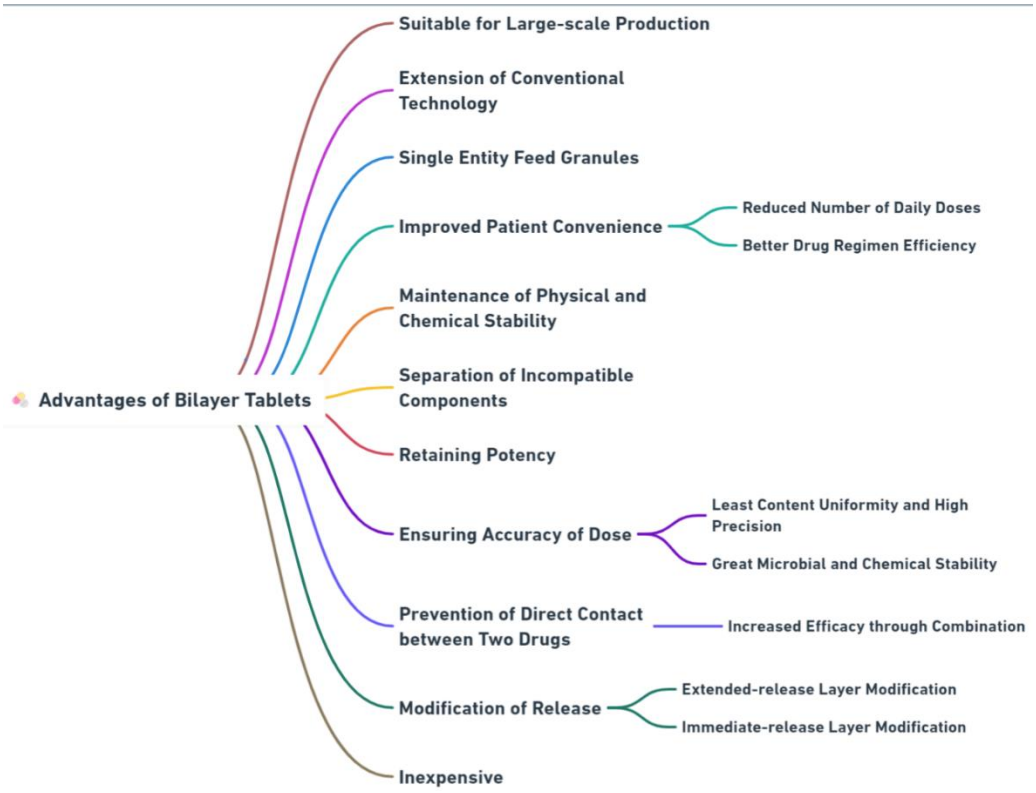

Figure 1. Advantages of Bilayer Tablet [7].

Figure 2. Disadvantages of bilayer tablet [7].

Types of bilayer tablets

Heterogeneous or homogeneous bilayer tablets are both possible.

Homogenous type: Although the two layers of a bilayer tablet contain the same medication, their drug release profiles differ. These bilayer tablets have an immediate release layer on one side and an extended-release layer on the other.

Heterogeneous type: A bilayer tablet can be used to separate two chemicals that are incompatible while releasing two medications continuously [8].

Techniques of bilayer tablets

OROS® push pull technology

Alza Corporation developed the OROS (Osmotic Controlled Released Oral Delivery System) Pull-Push technique to get around the problem of inadequate osmotic pressure in poorly soluble medicines, which prevents full drug release. The majority of this technology consists of two or three layers, the push layer being the final one and the active medicinal ingredient being present in the first one or two layers. The drug layers are formed of poorly soluble substance and consist simply of the drug and a few excipients. It might also contain an osmotic and suspending agent. The core of the tablet is kept apart from its surroundings by a semipermeable layer [1].

L-OROS™ technology

Alza is the maker of this technology, which addresses a significant solubility issue. The medication was initially created as a dissolved lipid soft gel. The semipermeable membrane was then pierced to create an exit cavity, and it was then filled by a barrier membrane, the osmotic push layer, and so on [9, 10].

DUROS technology

Peptides, proteins, and other biological compounds are among the many medicinal chemicals that can be transmitted by the Duros technology, which is based on the implant procedure. This device, which is also referred to as "miniature drug dispensing technology," functions similarly to a tiny syringe and delivers medications constantly and reliably in a concentrated form over an extended length of time. These cylinders shield the drugs in the human body, extending their long-term resistance to human tissues. It is used as a palliative measure to treat prostate cancer patients with advanced stages every year using the Viadur (leuprolide acetate implant).

DUREDAS ™ Technology

Elan Corporation's Dual Release Drug Delivery System (DUREDAS) is a system that enables a medicine to release in two different ways from a single dosage. It can deliver a drug's release either immediate or sustained. This is accomplished by using two separate direct compression procedures to create a tablet consisting of two layers: an immediate-release layer and a hydrophilic layer. The hydrophilic layer transforms into a permeable gel that regulates the drug's release after absorbing liquids from the digestive system. One or two medications can have distinct release patterns thanks to this technology. Initially,

controlled release anaesthetics for over-the-counter usage were developed using it [11].

EN SO TROL technology

To obtain the ideal dosage form in the controlled release system, the Shire laboratory employs an integrated strategy for the drug delivery system by correctly identifying and adding the enhancer, Usually, a wicking agent is utilized. This method aids in boosting solubility.

Ro Tab bilayer

It is one of the reliable and versatile tools for compressing mono- and bilayer tablets. It is simple to operate because it comes with software. It is more useful in R&D because of its flexibility and range of modifiable factors. Changes in monolayer versus bilayer properties affect its appeal.

Working. When Ro Tab bilayer is employed for the manufacturing mode that is switched towards it, the system automatically adjusts. By modifying the filling speed and die table, it facilitates the automatic management of the dose and compression force. Additionally, it aids in controlling the hardness as needed [12].

Geminex technology

Bilayer tablet development employs Geminex technology. Using this technique, a single dosage form can include one or more drugs with varying rates of release. Because it can greatly boost the therapeutic effects of drugs and reduce adverse effects, it is advantageous for both the pharmaceutical industry and patients. In a single tablet, for example, two distinct actives or the same active can be administered at various rates. Cardiovascular problems are among the therapeutic areas in which this technology is actively being used [1].

Programmable oral drug absorption system (PRODAS)

The advantages of both tablet and capsule dose forms are provided by the multiparticulate drug delivery technology known as the PRODAS®. The primary objective is to integrate tablet technology into a capsule as a multi-particulate device to regulate drug release.

Here are a few of PRODAS's salient attributes:

Mini Tablets: The drug is loaded into hard gelatine capsules

Target Multiple Sites: The drug can be targeted at multiple sites within the gastro intestinal tract.

Higher Doses: The drug can be loaded at higher doses.

Different Sizes: The mini tablets can be incorporated into the capsule in different sizes.

This technology is helpful because it enables controlled drug release, which may lessen adverse effects and increase pharmaceutical effectiveness [12].

Erodible molded multilayer tablet

A particular kind of drug delivery method that makes use of erosion-based technology is called Erodible Molded Multilayer Tablets. One benefit of this technique is that it can provide zero-order or delayed release with little to no effect on gastrointestinal disorders.

The process is as follows:

Eaglet technology is used to prepare the tablets using injection moulding. It consists of a matrix and a coat.

These tablets erodible quality enables a gradual, controlled release of the medication.

Over time, the release rate may vary due to the shrinkage caused by the erosion of the tablet.

As a result, the release of drugs can be precisely controlled, this technique is especially helpful to the pharmaceutical industry, where it may improve medicine effectiveness and minimize negative effects [12].

Geomatrix technologies

By bonding one or more modulating layers (which function as a barrier) to the central matrix during the tablet-generating process, geomatrix technology creates a multilayer tablet with an active ingredient inside. These barriers' primary functions are to keep the core and dissolving medium from coming into contact. The eight Geomatrix methods, which aim to achieve a wide range of therapeutic goals, include:

A steady release of medication is achieved through zero-order release Geomatrix technology.

Two different medications given in a specific dosage are released gradually thanks to binary-release geomatrix technology.

Rapid-slow discharge with geomatrix technology, a quick dosage release is followed by a continuous release for a set period of time.

A counter-method to the quick-slow-release technique is the slow-quick release geomatrix technique. The drug is released bit by bit over time, with an immediate release occurring at a predetermined period.

By using the positioned released geomatrix technology, the medication is delivered to a certain area of the gastrointestinal tract prior to the main dosage being released.

The main medication is constantly released at a faster pace because to the technique known as "accelerated release geomatrix."

When a prearranged time delay of the real dosage is needed, the delayed-release geomatrix approach is applied.

Multiple pulse geomatrix technology is used, requiring an immediate burst beforehand and a predetermined period of no release [13].

Manufacturing process of bilayer tablet

Drugs are manufactured as bi-layer tablets so that one layer releases the drug immediately and the other releases it gradually over time, either as an extended-release version or as a second dose. To minimize the area of interaction between the two layers, Individual layers of each drug can be compressed to create bi-layer tablets containing two incompatible pharmaceuticals. It is also feasible to add one more layer of inert material [13].

Bilayer tablet: quality and GMP requirement

Bilayer tablet quality and Good Manufacturing Practice (GMP) criteria are essential to guaranteeing their effectiveness and safety.

A) Prevent the bi-layer tablets from splitting into their layers and capping.

B) A clear visual division is used to accomplish the two layers' separation.

C) Ensuring the proper hardness of tablets.

D) Preventing contamination between the two layers.

E) Accuracy, high yield, and weight control of individual layers [7].

Types of bilayer tablet press

Single-sided press

Two distinct tablet layers are created in the most basic configuration of a single-sided press by filling two chambers, either by force or gravity. The drug powder for the first layer is first loaded into the die, which is passing beneath the feeder, and then the second layer. After that, the tablet is assembled in one or two phases. The two films form a tight bond and reduce layer separation as they somewhat mix at their interface as they go through the die.

Limitations of the single-sided press

1. There isn't a control mechanism accessible for the individual levels.
2. There is no visual separation between the layers
3. A small compression roller may cause poor deaeration, capping, and hardness issues because the initial layer dwell time is very short [8].

Double-sided tablet press

In most automated production control double-sided tablet presses, tablet weight is monitored and controlled using compression force. The control system measures the effective peak compression force applied to each tablet or layer at major compression. The control system rejects out-of-tolerance die fill depths and makes necessary adjustments based on this recorded peak compression force [15].

Dwell time

The period of time during which the compression force exceeds 90% of its maximum value is known as the "dwell time." High-quality tablets are produced via long dwell durations, especially when a complicated formulation is compressed [14].

Bilayer tablet press with displacement

Displacement pill weight management and compression force principles are very different. The applied pre-compression force, not the tablet weight, determines the sensitivity of the control system while monitoring displacement [14].

Various approaches for formulation of bilayer tablets

Floating drug delivery system

Floating drug delivery system are intended to float above the contents of the stomach until they disintegrate or absorb liquid, which lessens their buoyancy and permits passage through the stomach. One of these products is the bilayer tablet, which consists of two layers: one floating in the stomach and the other giving an immediate dose for fast effect.

Intra-gastric bilayer floating tablets and multiple-unit type floating pills are the two primary approaches of floating dosages. The former has two compacted layers: a sustained release layer that activates after the first layer fades, and an immediate layer for a rapid effect.

The latter kind, known as multiple unit type floating pills, are double-layered seeds that have a swellable membrane layer on the outside and an interior layer of effervescent chemicals. These pills sink when dissolved, then swell and float due to their low density [15].

Polymeric bio-adhesive system

These are made in a way that allows them to absorb liquid after administration. The outer layer then becomes sticky and viscous, adhering to the mucus-containing stomach layer. This promotes the tilting of the stomach preservation such that the adhesiveness weakens. These have two layers: one for immediate dosage and the other for bio adhesive qualities. Nevertheless, this particular dosage has only been given to animals; it has not been used on people. This is because the physiologies of the human and animal bodies are different, with respect to the quantity and composition of mucus [15].

Swelling system

When administered, these are designed to be significantly smaller in order to facilitate the ingestion of the dosage. Ingestion of these materials results in their disintegration, swelling, or unfolding to a size that halts pylorus passage until the required amount of drug is released. It gradually erodes or fragments into tiny pieces before exiting the stomach. One layer of the simple bilayer tablet may be for rapidly release, while the other layer may be for prolonged or conventional release [16].

Characterization of bilayer tablet [7]

Particle size distribution

Sieving was used to measure the particle size distribution.

Photo microscope study

With the use of a photomicroscope, we have taken a photo of TGG and GG (X450 magnification).

Angle of repose

To calculate the angle of repose, we measured the diameter of the powder cone and used the following equation:

Tan Ø=h/r,
where **h** and **r** are the height and radius of the powder cone, respectively.

Hausner's ratio
A fixed funnel method was used to find the angle of repose of powder blends in each layer of the formulations. Every layer was passed via the funnel separately until the funnel's tip was touched by the apex of the pile that had developed at the tip. The angle of repose was then calculated according to a formula.

Hausner's ratio = Tapped density / Bulk density

Moisture sorption capacity
Disintegrates are capable of absorbing moisture from the atmosphere, which can adversely affect moisture-sensitive drugs. The degree of absorption of moisture was determined by measuring the difference in weight between 2 grams of disintegrating uniformly distributed in Petri dishes kept in a stability chamber at 37°C and 100% relative humidity for two days and measured by the amount of moisture absorbed.

Density
Bulk density: A bulk density calculation was carried out utilizing a formula that was derived from the subsequent calculation:

Bulk density (BD) = weight of powder/volume of bulk.

The bulk density is calculated by placing the powder blend into a measuring cylinder; the total volume

Tapped density: Tapped the cylinder 100 times to get the tapped density, which was then calculated using a formula. After 100 taps, the tapped volume was measured, and the following formula was used to determine the tapped density

Tapped density (TD)= weight of powder / Tapped volume.

Compressibility
We can determine the powder's compressibility index by applying Carr's compressibility index.

Carr's index (%) =Tapped density – bulk density/tapped density ×100

Evaluation of bilayer tablets [16]

General Appearance
A product's visual identity, such as its size, colour, shape, Odor, taste, texture, physical flaws, and legibility of identifying marks, is what attracts consumers.

Size and Shape
Dimensionally, we are able to specify, monitor, and manage the tablet's size and appearance.

Tablet Thickness
One of a tablet's most important visual attributes is its thickness. A portion of the filling machinery counts by using tablets with consistent thickness. For this, a micrometre or Vernier caliper is used to record the average thickness of ten tablets.

Uniformity weight
Select twenty tablets at random, and then compare their weight with the mean weight. Weighing each tablet and comparing its weight to the average allowed us to achieve this. The USP standard for weight uniformity is shown in table 1.

Table 1. USP standard for Uniformity weight.

Sr. no.	As per USP standards	Max.% deviation allowed	As per IP/BP standards
1	130 mg or less	10%	84 mg or less
2	130 -324 mg	7.5%	80-250 mg
3	More than 324 mg	05%	More than250mg

Hardness
We measured the tablet's hardness using Monsanto's hardness tester; it has a high level of impact resistance throughout handling, shipping, and storage. The unit of hardness is kg/cm^2.

Friability
The friability test gauges a tablet's robustness to shock and friction during handling, packing, and transportation. Using a Roche Friabilator, the machine is supposed to run at 25 RPM for roughly 100 revolutions. tablets are weighed, repeatedly rolled and shocked for approximately four minutes, and then weighed one more. The tablet's friability is represented by the weight differential, expressed as a percentage. Generally, tablets that allow for a maximum 1% weight loss following the test are approved. It can be inferred that thicker tablets have less internal tension than small, large-tablets, which are more likely to cap.

% friability = [initial weight – final weight/initial weight] × 100

Determination of drug content
Standard calibration curve for drug
Prepare the standard calibration curve of the standard drug by solubilising them into a suitable solvent. Diluting at different concentrations i.e. 2, 4, 6, 8, 10, and 20 µg/ml. Measuring the absorbance by a UV-VIS spectrophotometer at a suitable λmax. Determine the mean weight after choosing 20 tablets at random. Use a mortar to crush the tablets. Measure an accurately weighed quantity of the average tablet weight from the crushed blend. Transfer the measured amount into a volumetric flask with a capacity of 100 ml. Add a small quantity of solvent to dissolve the drug. Make up the final volume to the mark with the respective

medium. To make certain that the drug dissolves thoroughly, shake the contents occasionally and set it aside for one hour. Perform filtration and suitable dilutions. Determine the dilutions using a UV-VIS spectrophotometer to find out the percent drug content. The drug's content needs to be between 90 and 110% of the recommended dose. If two drugs are present in the formulation, determine the contents by the simultaneous equation method [16].

Simultaneous equation method

Select two wavelengths for the two drugs present in the formulation. Perform serial dilutions of the stock solutions separately with the dissolved solvent to obtain a series of standard solutions of serial concentrations for both drugs. Determine the concentrations in the samples using the following equations:

For drug 1 (CX): $A2ay1-A1ay2 \ / AX2ay1-aX1ay2$

For drug 2 (CY): $A1\ ax2-A2ax1 \ / AX2ay1-aX1ay2$

Where:

The absorbance values are A1 and A2. of the mixture at X nm (λ1) and Y nm (λ2).

The absorptivity of drug 1 at λ1 and λ2 are ax1 and ax2.

The absorptivity of drug 2 at λ1 and λ2 are ay1 and ay2.

CX is the concentration of drug 1.

CY is the concentration of drug 2.

Drug loading

The percentage for drug loading is to be calculated by utilizing the subsequent formula

Drug loading (%) = (*Amount of drug recorded / Amount of formulation taken*) *x*100

Drug entrapment efficiency

The percent drug entrapment efficiency is calculated by utilizing the subsequent formula.

Entrapment efficiency (%) = (*Practical drug content / theoritical drug conten*t) *x*100

Infra-red Spectroscopy (IR)

IR spectra show the distinct peaks of each functional group in a sample. The active pharmaceutical components and their physical combinations were to be exposed to FTIR investigations in order to determine the compatibility study. An IR spectrophotometer operating in the 500 cm-1 to 4000 cm-1 range should be used to obtain FTIR spectra.

Differential Scanning Calorimetry (DSC)

To determine whether the drugs employed in the formulations and the active pharmaceutical ingredients are compatible, DSC research should be conducted. DSC instruments that needed to be calibrated with indium were to be utilized to undertake DSC analysis of the pharmaceuticals used and physical combinations of the formulations. The analysis should be carried out at rates of 20ºC per minute and a heating range of 50–300ºC.

Disintegration time

One tablet needs to be placed in each of the basket's six tubes. Hold the assembly in water that is kept at 370°C ± 20°C while you run the apparatus. Use a stopwatch to record the amount of time it takes for the assembly to fully disintegrate.

***Release kinetics of bilayer tablets* [16]**

To determine the drug release mechanism from the produced bilayer tablet, data from the in vitro drug release investigations were fitted to a variety of kinetic models, including zero order kinetics, first order kinetics, Hixson-Crowell, Korsmeyer-Peppas, and Higuchi.

The drug's release was examined using the following mathematical formulas.

Zero-Order Mode: Mt = M0+K0t

Where,

Mt = Quantity of drugs released at a given time t.

K0=Apparent dissolution rate or zero-order release constant.

M0 = Initial quantity of drug into the solution in result of a burst effect.

In this case, drug release is independent of its concentration, it run at a constant rate.

First-Order Model: ln Mt = ln M0 + K1t

Where,

K1 = first-order release rate constant. In this case, the release is dependent on its concentration. each time the drug is released, it is proportional to the residual drug inside the dosage form.

Higuchi Model: Mt = M0 + KHt1/2

Where,

Mt = Quantity of drug discharged at given time t.

KH = Higuchi release rate constant.

The most popular model for explaining how drug release from an insoluble matrix formulation depends on Fickian diffusion and is linearly associated with the square root of time.

Hixson-Crowell equation:

To ascertain the data, the Hixson-Crowell equation (Hixson and Crowell, 1931) was utilized.

Q 1/3 0 – Q 1/3 t = kst

Where,

Q0 = is the initial drug amount in the matrix tablet.

Qt = is the quantity of drug remaining in the dosage form at particular time interval t.

ks = is a constant involving the surface/volume ratio.

Korsmeyer-Peppas Model: Mt/M1 = M0/M1 + KKPtn
Where,
KKP is a constant incorporating geometric and structural characteristic of the drug-dosage form and 'n' is the exponent of release. representing drug release mechanism. Determination coefficient (R2) and rate constants for zero order kinetics (K0), first order kinetics (K1), Higuchi model (KH), Hixon-Crowell model (KHC) and release component for Korsemeyer-Peppas model were determined to understand drug release.

Interpretation of diffusion mechanism

Interpretation of diffusion mechanism is presented in table 2.

Table 2. Interpretation of diffusion mechanism.

Release Exponent (n)	Drug Transport Mechanism	Rate as Function of Time	Drug Release Mechanism
<0.5	Quasi-s diffusion	t^{n}	Non swellable matrix diffusion
0.5	Fickian diffusion	$t^{0.5}$	
0.5<n	Anomalous (non-Fickian transport)	t^{n-1}	For both diffusion and relaxation (erosion)
1.0	Case-II transport	Time dependent	Zero order release
Higher than 1.0	Super Case-II transport	t^{n-1}	Relaxation/erosion

In vitro dissolution studies

The process of dissolving a solid into a solution is known as dissolution. In the pharmaceutical sector, it is defined as the quantity of drugs material dissolved in a unit of time under controlled parameters such as temperature, solvent composition, and liquid/solid interface. The crucial Quality Control (QC) tests for pharmaceutical formulations is dissolution. It is becoming known as a method for bioavailability prediction. It is recommended to investigate the drug release from various batches of manufactured tablets by utilizing the USP dissolving apparatus type II. The site of action may affect the choice of dissolving agent. For the sustained release layer, it could be either phosphate buffer pH 6.8 with 0.5% w/v sodium lauryl sulfate (SLS) for up to 12 hours, or simulated stomach juice with a pH of 1.2. Samples should be taken out at regular intervals, and new medium should be added to replace the volume taken out. Whatman filter paper should be used to filter the extracted samples. A spectrophotometer should be used to observe the samples at each λmax in comparison to a blank (corresponding medium). The stirring rate and temperature should be kept at 50 rpm and 37 ± 0.5°C, respectively [16].

Stability study

As required by ICH rules, the bi-layer tablets would be placed in suitable packaging and maintained under the following conditions for the length of the accelerated study, The tablets would be taken out after 15 days and examined for drug content in addition to physical characteristics like hardness, friability, dissolution, and visual flaws. The kinetics of deterioration are ascertained by fitting the data into first-order equations. The shelf life is calculated by plotting accelerated stability data at 25°C and using the Arrhenius equation [16]. Storage condition is mentioned in table 3.

Table 3. Storage condition.

Study	Storage Condition	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

Buoyancy determination

Floating lag time is the amount of time it takes for the dosage form to appear on the medium's surface; total floating time (TFT) is the amount of time it takes for the dosage form to appear on the medium's surface continuously. In a dissolving unit filled with 900 cc of dissolution media, one tablet from each formulation batch would be put and rotated at the necessary RPM. The temperature of the medium would be maintained at 37±0.5°C. Both the duration that the tablet remains on the medium's surface and the time it takes for it to appear there would be noted [16].

Swelling study

Each tablet would be weighed exactly and kept in a 50-millilitre water container. The tablets would be carefully taken out after 60 minutes, blotted using filter paper to remove any leftover water, and accurately weighed [16]. To determine the proportion of swelling, use the formula.
Swelling study = Wet weight - Dry weight / Dry weight x 100.

Different marketed examples of bilayer tablets

Different marketed examples of bilayer tablets are presented in table 4.

Marketed formulations of multilayered tablets FDA- and EMA-approved FDC products with multilayer technology (Table 5).

Conclusion

In summary, the report Bilayer tablets are a type of modern pharmaceutical that effectively treats illnesses by bonding various chemicals together. This drug delivery system's primary goal is to make certain that the medication is both effective and has the fewest possible side effects. It is also made according to GMP guidelines, ensuring that its quality is maintained for the duration of its shelf life. In order to optimize effectiveness and avoid adverse effects, several approaches and presses are utilized to achieve these requirements. To guarantee the produced tablet's efficacy

and stability during the course of its shelf life, it is assessed chemically and physically. The first loading dose of API should be administered, then the maintenance dose of API to maintain an effective plasma level for an extended period of time. Currently, several bilayer tablets with distinct APIs may be used for combination therapy or to maintain an effective plasma level for an extended period of time.

Table 4. Example of bilayer tablets.

Drug	Dosage Form	Rationale	References
Atorvastatin, Atenolol	Bilayer gastro retentive matrix tablet.	Treatment of hypercholesterolemia and hypertension.	(17)
Nifedipine	Gastro retentive floating bilayer tablets.	Treatment of angina pectoris and hypertension.	(18)
Aspirin, Isosorbide 5 mononitrate.	Sustained tablets.	Treatment of fever, pain and other inflammatory condition.	(19)
Pioglitazone HCL, Gliclazide	Bilayer tablets.	Treatment of type 2 diabetes.	(20)
Losartan. Potassium	Bilayer tablets.	Treatment of hypertension.	(21)
Trimetazidine HCL Clopidogrel Bisulphate,	Bilayer tablets.	Cytoprotective anti-ischemic, platelet inhibitor in acute coronary syndromes,	(22)
Diclofenac, Cyclobenzaprine	Bilayer tablets.	Synergistic effect in pain.	(23)
Granisetron HCL.	Bilayer buckle tablets.	To overcome bio availability problem.	(24)
Indomethacin,	Bilayer floating tablets	Bilayer drug release.	(25)
Metformin HCL, Glimepiride	Bilayer tablets	Synergistic effect in diabetes.	(26)
Metformin HCL, Atorvastatin calcium	Bilayer tablets	To develop polytherapy as a means of treating hyperlipidemia and NIDDS.	(27)
Cefixime trihydrate Dicloxacillin sodium	Bilayer tablets	Synergistic effect in bacterial infection.	(28)
Piracetam, Vinpocetine,	Bilayer tablets	Synergistic effect in Alzheimer disease.	(29)
Atenolol,	Bilayer buckle tablets	To overcome bioavailability problems, reducing the number of times a dose is given and adverse effects.	(30)
Cefuroxime Axetil, Potassium clavulanate	Bilayer tablets.	A synergistic effect on microbial infections and to minimise dose dependent side effects.	(31)
Amlodipine Bisylate, Metoprolol succinate	Bilayer tablets.	Synergistic effect in hypertension.	(32)
Diclofenac sodium, Paracetamol	Bilayer tablets.	Synergistic effect in pain.	(33)
Ibuprofen, Methocarbamol	Bilayer tablets.	Synergistic effect of drugs in back pain.	(34)
Atorvastatin calcium	Bilayer buckle tablets.	In order to address the issue of bioavailability, lowering adverse effects and dosage frequency.	(35)
Salbutamol, Theophylline	Bilayer tablets.	Synergetic effect of drugs in asthma.	(36)
Montelukast, levocetirizine	Bilayer tablets.	To improve the stability of drugs in combination.	(37)
Telmisartan, Simvastatin	Bilayer tablets.	To reduce contact between simvastatin and telmisartan.	(38)

Atenolol, Lovastatin	Bilayer floating tablets.	Hypertension and biphasic release profile synergistic effect	(39)
Tramadol, Acetaminophen	Bilayer tablets.	Synergistic effect for pain	(40)

Table 5. Various commercialized examples of bilayer tablets.

Product Name	Chemical Name
Alprax Plus	Sertraline/ Alprazolam
Glycomet-GP2Forte	Metformin hydrochloride /Glimepiride
Lopressor HCT	Metoprolol/Hydrochlorothiazide
Diovan HCT	Valsartan/ Hydrochlorothiazide
Lotensin HCT	Benazepril/Hydrochlorothiazide
Clarinex-D	Desloratadine/Pseudoephedrine sulphate
Treximet	Sumatriptan/Naproxen sodium
Atripla	Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate

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Conflicts of interest
The authors report no conflicts of interest in this work.

Ethical approvals
This study does not involve experiments on animals or human subjects.

Data availability
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References

1. Abebe A, Akseli I, Sprockel O, Kottala N, Cuitiño AM. Review of bilayer tablet technology. International journal of pharmaceutics. 2014; 461(1-2):549-58.
2. Akhtar M, Jamshaid M, Zaman M, Mirza AZ. Bilayer tablets: A developing novel drug delivery system. Journal of Drug Delivery Science and Technology. 2020; 60:102079.
3. Singh A, Das S, Gupta S, Ghosh S. The Challenges of Producing Bilayer Tablet: A Review. Journal of Drug Delivery and Therapeutics. 2021; 11(4-S):171-5.
4. Simão J, Chaudhary SA, Ribeiro AJ. Implementation of Quality by Design (QbD) for Development of Bilayer Tablets. European Journal of Pharmaceutical Sciences. 2023; 106412.
5. Kottala N, Abebe A, Sprockel O, Bergum J, Nikfar F, Cuitiño AM. Evaluation of the performance characteristics of bilayer tablets: Part II. Impact of environmental conditions on the strength of bilayer tablets. AAPS PharmSciTech. 2012;13(4):1190-6.
6. Kottala N, Abebe A, Sprockel O, Bergum J, Nikfar F, Cuitiño AM. Evaluation of the performance characteristics of bilayer tablets: Part I. Impact of material properties and process parameters on the strength of bilayer tablets. AAPS PharmSciTech. 2012;13(4):1236-42.
7. Kale PS, Ghadge PS, Bobde MN, Shahi SR. Overview of bilayer tablet: A Review. International Journal for Research Trends and Innovation.2022; (6):697-707
8. Chapagain B, Vandana S, Patil S. Review on Bilayer Oral Dosage Form with Immediate and Sustained Release Layers. Latin American Journal of Pharmacy: A Life Science Journal. 2023; 42(5):169-79.
9. Ahuja N, Kumar V, Rathee P. Osmotic-controlled release oral delivery system: An advanced oral delivery form. The Pharma Innovation. 2012; 1(7):116-24.
10. Liu L, Xu X. Preparation of bilayer-core osmotic pump tablet by coating the indented core tablet. International journal of pharmaceutics. 2008; 352(1-2):225-30.
11. Sarma A, Deb P, Dash S. Bilayer tablet and duredas technology–a review. International Journal of Pharmacy and Biological Sciences. 2013; 3(2):554-63.
12. Kale SS, Saste VS, Ughade PL, Baviskar DT. Bilayer tablet. International Journal of Pharmaceutical Sciences Review and Research. 2011; 9(1):25-30.
13. Sarma A, Deb P, Dash S. Bilayer tablet and duredas technology–a review. International Journal of Pharmacy and Biological Sciences. 2013; 3(2):554-63.
14. Chakka PG, Bindu VH, Nischala M. An Overview on Bilayered Tablet Technology. Journal of Global Trends in Pharmaceutical Sciences. 2013; 4(2).
15. Deshpande RD, Gowda DV, Mahammed N, Maramwar DN. Bi-layer tablets-An emerging trend: a review. International journal of pharmaceutical sciences and research. 2011; 2(10):2534.
16. Kumar Verma N, Roshani K, Panda P, Vishwakarma DK. A brief review on bilayer floating tablet. 2017; 06(03):1077-1085.
17. Jyoti Das R, Pathak K, Mazumder B. Chapter-3 Advancement in Bilayer Tablet Technology as a Novel Drug Delivery System. 2023; 1(7):41-63.
18. Dey S, Chattopadhyay S, Mazumder B. Formulation and evaluation of fixed-dose combination of bilayer gastroretentive matrix tablet containing atorvastatin as fast-release and atenolol as sustained-release. BioMed Research International. 2014; 2014.
19. Maddiboyina B, Hanumanaik M, Nakkala RK, Jhawat V, Rawat P, Alam A, Foudah AI, Alrobaian MM, Shukla R, Singh S, Kesharwani P. Formulation and evaluation of gastro-retentive floating bilayer tablet for the treatment of hypertension. Heliyon. 2020; 6(11).
20. Hu L, Hu Q, Kong D. formulation and in vitro evaluation of aspirin and isosorbide 5-mono-nitrate sustained bilayer tablets. International Journal of Pharmacy & Life Sciences. 2014; 5(3).
21. Sharma SK, Mohan S, Jaimini M, Chauhan BS, Chatterjee A. Formulation and in-vitro evaluation of Bilayer tablets containing Pioglitazone HCl and Gliclazide for type II

diabetes. International Journal of PharmTech Research. 2014; 6(2):607-22
22. Todicherla VKS, Parimi N, Cherukuri M. Development of formulation and in-vitro evaluation of buccoadhesive tablets of losartan potassium. International Journal of PharmTech Research. 2013; 5(4). 828-1838.
23. Saif AA, Alburyhi MM, Noman MA, Almaktari A. Formulation and evaluation of trimetazidine hydrochloride and clopidogrel bisulphate multi-unit solid dosage forms. Journal of Chemical and Pharmaceutical Research. 2014; 6(2):421-6.
24. Jamunadhevi V, Sahoo PK, Kailasam P. Formulation and in vitro evaluation of bi-layer tablet of cyclobenzaprine hydrochloride ER and diclofenac potassium IR-A novel fixed dose combination. Int J Res Pharm Sci. 2011; 2(2):170-8.
25. Pv Swamy, Kinagi M, Biradar S, Gada S, Shilpa H. Formulation design and evaluation of bilayer buccal tablets of granisetron hydrochloride. Ind J Pharm Edu Res. 2011; 45(3):242.
26. Jain J, Marya BH, Mittal RP, Patel M. Formulation and evaluation of indomethacin bilayer sustained release tablets. Int J PharmTech Res. 2011; 3(2):1132-8.
27. Pattanayak DP, Dinda SC. Bilayer tablet formulation of metformin hydrochloride and glimepiride: A novel approach to improve therapeutic efficacy. Int. J. Drug Discov. Herb. Res. 2011;1:1-4.
28. Mohindeen S, Jyothi B, Pavani S, Satyanarayana T, Kumar SP, Krishna NS. Formulation and evaluation of bilayered tablets of metformin hydrochloride and atorvastatin calcium. Int J Pharm Sci Rev Res. 2011; 10(2):130-4.
29. Kumar GV, Babu KA, Ramasanay C. Formulation and evaluation of bilayered tablets of cefixime trihydrate and dicloxacillin sodium. Int J PharmTech Res. 2011; 3(2):613-8.
30. Jadhav RT, Patil PH, Patil PR. Formulation and evaluation of bilayered tablet of Piracetam and Vinpocetine. J Chem Pharm Res. 2011; 3(3):423-31
31. Shirsand SB, Swamy PV, Keshavshetti GG. Design and evaluation of atenolol bilayer buccal tablets. RJPS. 2011; 1(1):1.
32. Dhumal RS, Rajmane ST, Dhumal ST, Pawar AP. Design and evaluation of bilayer floating tablets of cefuroxime axetil for bimodal release. J Sci Ind Res (India). 2006; 65(10).
33. Jayaprakash S, Halith SM, Pillai KK, Balasubramaniyam P, Firthouse PM, Boopathi M. Formulation and evaluation of bilayer tablets of amlodipine besilate and metprolol succinate. Der Pharmacia Lettre. 2011; 3(4):143-54.
34. Gohel MC, Parikh RK, Nagori SA, Jethwa BA. Fabrication and evaluation of bi-layer tablet containing conventional paracetamol and modified release diclofenac sodium. Indian journal of pharmaceutical sciences. 2010; 72(2):191.
35. Remya PN, Damodharan N, Kumar CV. Formulation and evaluation of bilayered tablets of Ibuprofen and methocarbamol. Int J PharmTech Res. 2010; 2(2):1250-55.
36. John AS, Sathesh BP, Divakar G, Jangid MK, Purohit KK. Development and evaluation of Sachin S. Kale*, Viraj S. Saste, Prajkta L. Ughade, Dheeraj T. Baviskar drug delivery system for atorvastatin calcium. Journal of current pharmaceutical research. 2010; 1:31-8.
37. Nagaraju R, Kaza R. Formulation and evaluation of bilayer sustained release tablets of salbutamol and theophylline. International Journal of Pharmaceutical Sciences and Nanotechnology (IJPSN). 2009; 2(3):638-46.
38. Rathod RT, Misra D. FDC of montelukast with levocetirizine: focus on bilayer technology. Journal of the Indian Medical Association. 2009; 107(8):562-4.
39. Kohlrausch A, inventor; Boehringer Ingelheim International GmbH, assignee. Bilayer tablet of telmisartan and simvastatin. United States patent application US 11/236,911. 2006 Apr 13.
40. Kulkarni A, Bhatia M. Development and evaluation of regioselective bilayer floating tablets of Atenolol and Lovastatin for biphasic release profile. Iranian J Pharm Res. 2009;8(1): 15-25.