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Review Article

REVIEW ON FORMULATION AND INVITRO EVALUATION OF BILAYER TABLETS

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ABSTRACT:
Bilayer tablets have emerged as a viable strategy in drug delivery systems, with the ability to combine two unique layers with varied release patterns or drug combinations in a single dosage form. This method is particularly useful for administering incompatible medications, sequential drug release, and controlled distribution of a single active medicinal component. This paper includes a thorough discussion of formulation methodologies, bilayer tablet designs, and the issues encountered during development, such as layer separation, inadequate hardness, and cross contamination. Various approaches to addressing these issues are described, including the use of modified granulation methods and improved compression equipment. The study also emphasizes essential assessment factors including as hardness, friability, weight fluctuation, drug content homogeneity, and in vitro dissolving investigations, which are critical for ensuring the quality and efficacy of bilayer tablets. Advances in bilayer tablet technology, regulatory issues, and future prospects for pharmaceutical development are all discussed. This study intends to be a beneficial resource for academics and formulators working on bilayer tablets to improve therapeutic results.

INTRODUCTION

The most frequent and recommended method of delivering medicine is orally. This method is well-known for its self-medication capabilities, patient compliance, ease of administration, and diversity of possible dosage forms.Nowadays, more than 90% of formulations are designed to be taken orally. It shows that this formulation class is the most popular worldwide, and that the researcher's principal attention is in this direction. The primary purpose of controlled medicine distribution is to reduce the frequency of the dosage[1]. Modified release pharmaceutical goods are intended to optimize a treatment regimen while also increasing patient comfort and compliance by administering the medicine gradually and continuously over the whole dosing interval. To extend or sustain the formulation's release, they spread the medicine at a certain pace and place.[2,3]

The design and manufacturing of these drug delivery devices are mechanically complex, and it is more difficult to predict their long-term mechanical properties because of the constituent materials' poor mechanical and compression characteristics, elastic mismatch between the layers, insufficient hardness, inaccurate individual mass control, cross contamination between the layers, reduced yield, and tendency to delaminate at the interface between the adjacent [4,5] As a result, the primary problem that must be addressed is establishing solutions to these challenges during solid dosage administration design by properly understanding their origins at both the micro and macro levels.

Merits: [6,7,8]

- ✓ Separate incompatible components.
- ✓ Maintain potency and guarantee dosing accuracy.
- ✓ They are employed as an extension of existing technologies.
- ✓ Improved patient compliance leads to better effectiveness of medication regimens.
- ✓ Consider using single-entity feed granules.
- ✓ Reduced daily dosages lead to increased patient compliance compared to traditional administration systems.
- ✓ Ensure physical and chemical stability.

Demerits:[9,10]

- ✓ Bilayer rotary presses are more complicated and costly.
- ✓ Insufficient hardness and layer separation decrease yield.

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- ✓ Cross contamination of layers.
- ✓ Inaccurate weight control for individual layers.

Challenges Related to Bilayer Technology:[11-18]

Despite the benefits that bilayer technology provides, a number of issues with the compression processes of bilayer tablets have lately been reported in the literature. Formulators and process scientists must overcome the challenges in order for the manufacturing process and bilayer tablet to be successful. Among the main hurdles are:

- ✓ Lower production yield and increased delamination at the non-planer interface between compacted layers.
- ✓ Cross contamination of layers.
- ✓ Ensures long-term physical and chemical integrity during shelf life.
- ✓ Mismatch in elastic modulus between neighboring layers. A high elastic modulus ratio between neighboring layers may result in inadequate bonding and low interfacial strength.
- ✓ Insufficient hardness in bilayer tablets.
- ✓ Inaccurate weight control for individual layers.
- ✓ Low drug load and disproportionate layer weight ratio.
- ✓ How high temperatures and humidity affect layer adhesion during storage.
- ✓ Large pill size may affect swallowability of the unit dosage.

Method for Preparing Bilayer Tablets:

1. Single Sided Press:

Various types of bi-layer presses have been developed up to this time. The most basic sort of press is the single-sided model, which separates the two chambers of the double feeder. The two unique tablet layers are created by pressing or gravity-feeding two separate powders into each chamber. As the die passes beneath the feeder, the first layer of powder is loaded, followed by the second layer of powder. The whole tablet is then compressed using either a single procedure or two phases (pre- and main compression). On a single-sided press, individual layer-weight management entails measuring the first layer as well as the entire tablet.

The first control loop manages the first layer's fill depth and indirectly monitors weight. The second loop, which follows the total tablet weight obliquely, only adjusts the second layer fill depth. Compression force is commonly used to measure tablet or layer weight. To do this, the first layer must be compacted prior to the addition of the second layer's powder.

Use two distinct powder feeders with a compression station in the middle to provide compression force to the first layer before adding the second layer. This can be accomplished by installing a second feeder between the pre- and main-compression stations of a single-sided press. Often, the precompression roller must be lowered in size to make room for the second feeder.

Limitations of the single-sided press:[19,20,21]

The tiny compression roller may cause poor de-aeration, capping, and hardness issues owing to its short first layer dwell time. This may be addressed by slowing down the turret rotation speed, however this will result in reduced tablet output.

The interface blends somewhat, making it difficult to distinguish between the two levels.

Difficulty in sampling and transporting first-layer tablets to a test facility for quality control and weight calibration.

2. Doubled Sided Press:

A double-sided tablet press helps mitigate the disadvantages of a single-sided press. On a double-sided press, each layer is assigned its own fill station, precompression, and primary compression. The bi-layer tablet will go through four stages of compression before being released from the press.

- ✓ Begin feeding grains after the first layer's compression is complete. At this point, we have obtained a density distribution particular to a flat-faced tablet squeezed so that the lower punch remains stationary. In the current example, the friction coefficient was set to a rather high value, which is appropriate for clean (unlubricated) die wall circumstances.
- ✓ Following compression of the first layer, the powder for the second layer is introduced into the die. The initial density of the second layer is uniform. At this point, densification occurs in the second layer, but the density distribution in the first layer has not altered.

Merits

- To prevent chapping and layer separation, the initial layer is compressed with low force.
- Provided appropriate hardness at maximum turret speed by increasing dwell time during precompression for both the first and second layers.
- Prevents cross-contamination between layers to the maximum extent possible.
- Clear visible distinction between layers.
- Monitoring displacement weight ensures accurate and independent weight management for each layer.
- Maximized yields.
- Insufficient bonding between layers causes separation during final compression of bi-layer tablets.

Limitations

- ✓ Correct bonding occurs when the first layer is squeezed at a low force, allowing for interaction with the second layer during final compression.
- ✓ High compression forces impede bonding.
- ✓ The low compression force required for compressing the first layer lowers the precision of weight monitoring/control in tablet presses using compression force measurement.

3. Compression Force-Controlled Tablet Presses:

When the bi-layer tablet is eventually squeezed, there is insufficient bonding between the two layers, causing them to split. Proper bonding is only possible when the first layer is squeezed with a modest compression force. If the first layer is crushed with an abnormally high compression force, bonding will be severely restricted. Unfortunately, in tablet presses that employ "compression force measurement," the low compression force required to compress the first layer reduces the accuracy of weight monitoring/control of the first layer. Most double-sided tablet presses with automated production control employ compression force to track and manage tablet weight. The control system monitors the effective peak compression force delivered to each tablet or layer during its major compression.

4. Displacement controlled tablet press:

Using an alternate weight monitoring technique based on "displacement" resolves the basic problem with the compression force monitoring paradigm. The benefit of "displacement measurement" over "compression force measurement" is that the accuracy increases as the compression force diminishes. The danger of separation and capping increases with higher production speeds, but it can be reduced by allowing ample dwell time at each of the four compression stages. Along with appropriate bonding between the two layers, weight monitoring based on "displacement" allows for longer dwell durations, as well as more precise and improved weight monitoring/control of the first layer. As a result, the ideal press for producing bi-layer tablets is a double-sided tablet press with "displacement measurement.

Various Types to Bilayer Tablets:

i) Intra Gastric Bilayer Floating Tablets:

The tablets' two major compressed layers are referred to as the immediate layer, and they are employed to swiftly effect the target region. The second layer, sometimes known as a sustained or extended release, is applied after the first layer has finished operating on the target. [22]

ii) Floating Drug Delivery System:

These are designed to be less dense, so that if taken as directed, they will float over the contents of the stomach until the system fails or the device absorbs the fluid to reduce its density and buoyancy, allowing the fluid to pass easily from the stomach via a motility wave that causes the stomach to empty. The bilayer pill is constructed such that the floating layer floats inside the stomach while the other layer provides an immediate dosage of the drug for a faster onset of effect. [23,24] The two most common ways for creating floating doses are intra-gastric bilayer floating tablets and multiple-unit floating pills.

iii) Multiple Unit Types Floating Pills:

These tablets are composed of double-layered seeds with expanded/sustained release. The outside layer is constructed of a swellable membrane layer, while the inner layer is chemically composed of effervescent substances. Because of their low density, these tablets sink to the bottom of room-temperature fluids before expanding like a balloon and rising to the surface.[25]

iv) Swelling System:

When supplied, they are meant to be tiny in order to make dosage administration easier. Once eaten, they swiftly break down, inflate, or unroll to a size that prevents the pylorus from passing until the medication release concentration is appropriate. It gradually erodes or fractures into little bits before leaving the stomach. The first layer of the simple bilayer tablet can be released instantly, while the second layer provides typical or extended release. [26,27]

iv) Polymeric Bio-Adhesive System:

These are designed in a way that permits them to absorb liquids after delivery. The outer layer subsequently becomes sticky and viscous, clinging to the mucus-rich stomach layer. This increases the adhesion of stomach preservation to tilt. These have two layers: one with bioadhesive properties and the other for immediate administration. Nonetheless, people have not received this dose; only animals have. The physiologies of the human and animal bodies differ, resulting in considerable variances in mucous amount and consistency. [28]

Techniques of Bilayer Tablets:

L-OROS Tm technology:

Alza developed this technique, which tackles a severe solubility issue. The drug was originally developed as a dissolved lipid soft gel. Next, an exit cavity was produced by puncturing the semipermeable membrane, which was then filled with a barrier membrane and the osmotic push layer.

OROS ® push-pull technology:

The active pharmacological component is incorporated in the first one or two layers of this technology, which is commonly made up of two or three layers, the push layer being the last. The drug layers are composed of poorly soluble material and contain only the drug and a few excipients. It may also contain an osmotic and suspending agent. The tablet's core is separated from its surroundings by a semipermeable layer.

DUROS technology (Alza corporation):

Duros technology, which is based on the implant technique, provides an alternate method of delivering a variety of pharmaceutical chemicals such as proteins, peptides, and other biochemical components. This device, also known as "Miniature drug dispensing technology," works similarly to a small syringe, delivering drugs continuously and consistently over a lengthy period of time in a concentrated form. These cylinders protect the pharmaceutical substances contained in the human body, increasing their resistance to human tissue. The Leuprolide Acetate Implant (Vivadur) is used annually as a palliative therapy for advanced prostate cancer.

EN SO TROL technology:

To get the optimal dosage form in the controlled release system, the Shire laboratory uses an integrated drug delivery approach that includes accurately choosing and administering the enhancer. This approach helps to improve solubility.

Geminex technology:

This technique mitigates the unwanted effects of the drugs while considerably increasing their therapeutic efficacy. It delivers a single dose of one or more drugs at different rates of release. Pen West widely utilizes it to treat CNS issues, cancer, diabetes, cardiovascular disease, and other CNS-related illnesses. It is extremely beneficial for both patients and the industry. Erodible, molded multilayer tablet: Egalet delivery technique consists of tablets with many layers that are molded and erodible. This technique consists of a matrix and a coat, which are created using standard plastic injection moulding processes. Egalet erodible molded tablets have a release pattern that is caused by matrix erosion. This approach facilitates the distribution of medications with zero-order or delayed-release patterns while preserving gastrointestinal health. The shape of the matrix and coat is tailored to control the technology's release pattern. For zero-order release, the drug is distributed across the matrix. In addition, the coat has minimal water permeability and is biodegradable. The stomach motions of the GI system cause the matrix to dissolve if it comes into touch with the existing water or fluids. This approach is particularly effective for drugs that exhibit stability issues when exposed to water, such as chemical and physical stability issues. Accuracy, reproducibility, and low production costs are further promises.

Geomatrix Technologies:

Geomatrix technique produces a multilayer tablet containing an active substance by connecting one or more modifying layers (which act as a barrier) to the core matrix during the tablet-making process. These barriers' principal role is to prevent the core and dissolving medium from coming into contact. The eight Geomatrix approaches attempt to achieve a wide range of therapeutic aims, including:

- Zero-order release. Geomatrix technology is used to maintain a steady medication discharge rate over an extended period of time.
- Binary-release geomatrix technology measures the release of two medicines at a certain dose.
- Quick/slow release. Geomatrix technique features a rapid dose discharge followed by a continuous discharge over a set length of time.
- The slow-quick release geomatrix approach works in the opposite direction as the quick-slow release technique. It entails a steady, consistent release of medication followed by an instantaneous discharge at a predetermined period.
- The positioned released geomatrix technology transports medicine to a specified area in the gastrointestinal system before the main dosage is released.
- Geomatrix technology accelerates the release of the main medication.
- Use the delayed-release geomatrix technology to postpone dose delivery.
- Multiple pulse geomatrix technique involves a fast burst followed by a timed no-release period.

Evaluation of BilayerTablets[29,30]

1. General Appearance

The general look of a tablet, its visual identity, and overall elegance are critical for customer adoption. Tablets' size, shape, color, odor presence or absence, taste, surface texture, physical faults, consistency, and readability of any identifying marking are all included.

2. Size and Shape

The tablet's size and form may be dimensioned, monitored, and adjusted.

3. Tablet thickness

Tablet thickness is a crucial factor in recreating appearance and counting when utilizing filling equipment. Some filling machinery counts pills based on their uniform thickness. Ten pills were ingested, and their thickness was measured using a micrometer.

4. Weight variation[31]

Standard processes are followed, as outlined in the official publications.

5. Friability

Friction and stress are the most common causes that cause the tablets to chip, slice, or shatter. The friability test is closely connected to tablet hardness and is intended to evaluate the tablet's ability to withstand abrasion during packaging, handling, and shipment. It is commonly assessed using the Roche friabilator. A number of pills are weighed and placed in the device, where they are subjected to rolling and repeated shocks, falling 6 inches in each revolution. After four minutes of treatment, or 100 rotations, the pills are weighed and compared to their starting weight. The loss due to abrasion is an indicator of tablet friability. The value is represented as a percentage. A maximum weight loss of no more than 1% of the weight of the tablets being evaluated during the friability test is regarded typically acceptable, and any broken or shattered tablets are not collected. When capping happens, friability ratings are often not calculated. A thick tablet may have fewer tendencies to cap, whereas thin tablets of large diameter frequently show extensive cupping, indicating that tablets with greater thickness have lower internal stress. The loss in tablet weight is the measure of variability and is expressed as a percentage.

$$\%\text{Friability} = 1 - \frac{\text{loss in weight}}{\text{Initial weight}} * 100$$

2. Hardness [32]

Tablets' resistance to capping, abrasion, or breaking during storage, transit, and handling before use is determined by their hardness.Monsanto produced and released the tiny and portable hardness tester in the mid-1930s. It's currently known as either the Monsanto or Stokes hardness tester. The gadget measures the force necessary to shatter the tablet when a coil spring is applied diametrically to it. The strong-Cobb Pfizer and Schleuniger equipment, which were later invented, measures the diametrically applied force necessary to shatter a pill. Hardness, also known as crushing strength, is measured during tablet manufacture and used to assess the requirement for pressure adjustments on the tablet machine. If the tablet is too hard, it may not dissolve in the time necessary to fulfill dissolving criteria; if it is too soft, it may be unable to endure additional processing such as coating, packaging, and shipping procedures. The force necessary to shatter the tablet is measured in kilograms, and a crushing strength of 4 kg is typically regarded the minimum for good tablets. Oral tablets typically have a hardness of 4 to 10 kg; however, hypodermic and chewable tablets are much softer (3 kg), and certain extended release tablets are significantly harder (10-20 kg). Tablet hardness has been linked to other tablet qualities, such as density and porosity. Hardness typically rises with tablet size and is determined by the form, chemical characteristics, binding agent, and compression pressure.

Stability Study

The bilayer tablets are put in appropriate packaging and kept under the following conditions for the duration specified by the ICH guideline for accelerated research.After 15 days, the tablets were extracted and examined for physical characteristics such as visual flaws, hardness, friability, and dissolution, as well as drug content. The collected data is fitted into the first or derequations to calculate the degradation kinetics. Accelerated stability data are plotted according Arrhenius equation to determine the shelf life at 25°C

CONCLUSION

Bilayer tablets are a flexible and efficient platform for modern pharmaceutical drug delivery, allowing for the combination of rapid and sustained release profiles, as well as the inclusion of several medicines with different physicochemical features. Their capacity to increase patient compliance, manage drug release, and minimize dose frequency makes them ideal for chronic therapy and combo treatments. Despite formulation and production concerns such as layer separation, weight homogeneity, and cross-contamination, advances in tablet press technology and formulation processes have made these issues more manageable. A full grasp of formulation principles and assessment parameters is required to guarantee that bilayer tablets are of high quality, safe, and effective. Continued innovation and research in this field will most likely result in more complex and patient-friendly medication delivery systems in the future..

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