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A Review on Bilayer Tablets and Its Technology

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ABSTRACT

Bilayer tablets are medications that combine two pharmaceuticals, either the same or different, in one dose to effectively treat a patient's condition. The purpose of this paper is to identify the difficulties encountered when making bilayer tablets and to suggest ways to overcome them. In order to accomplish regulated administration of various medications with predetermined release profiles, bi-layer tablets have been developed. The pharmaceutical industry has become more interested in creating bilayer tablets, which combine two or more API in a single dose form, in the past ten years in an effort to improve patient compliance and convenience. To further help with understanding, types including single side press, double side press, and bilayer tablet displacement press are discussed, along with uses, advantages, and disadvantages of bilayer tablets. A bi-layer tablet can be used to segregate two substances that are incompatible, release two medications sequentially in tandem, or create a sustained release tablet where the first layer is the initial dose and the second layer is the maintenance dose.

INTRODUCTION

The most common and recommended route of administering medication is orally. Because of its self-medication capabilities, patient compliance, convenience of administration, and variety of available dose forms, this route is well-known. Combination therapy is becoming more and more popular in both developed and developing nations to treat a wide range of illnesses and disorders that call for long-term care, such as diabetes, cardiovascular disease, and hypertension (2). Nowadays, more than 90% of the formulations produced are meant to be taken orally. It demonstrates that this formulation class is the most well-liked globally and that the researcher's primary focus is on this direction. Reducing the frequency of dose is the main goal of regulated medication delivery (3). By delivering the medication gradually and continuously across the whole dose interval, modified release medicinal products are designed to maximise a treatment regimen and increase patient convenience and compliance. In order to extend or sustain the release of the formulation, they disperse the drug at a specified rate and location. (4, 5)

Skye Pharma PLC used the concept of the bilayer tablet to create its Geomatrix tablet, which is made up of several layers. Multiple drugs can be added to the dose form thanks to the technology. Several types of drug delivery, such as targeted drug delivery in the GI tract using pH dependent polymers or drug release with a bolus and subsequent controlled rate, are made possible by the formulation of layers from different polymers, allowing manipulation over more than one rate-controlling polymer. (6)

Nevertheless, 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 compacted layers during and after the various production stages downstream of the compaction process. (7, 8) Therefore, the main challenge that needs to be addressed is developing solutions to address these issues during solid dose administration design by thoroughly understanding their causes on both the micro- and macro-scales.

1.1 Advantage:

- Separation of incompatible components.
- Retain potency and ensure dose accuracy.
- They are used as an extension of a conventional technology.
- Patients compliance is enhanced leading to improve drug regimen efficacy.
- Potential use of single entity feed granules.
- Patient compliance is improved because fewer daily doses are required compared to traditional delivery system.
- Maintain physical and chemical stability. (9, 10, 11)

1.2 Disadvantage:

- Adds complexity and bilayer rotary presses are expensive.
- Insufficient hardness, layer separation reduce yield.
- Cross contamination between the layers.
- Inaccurate individual layer weight control. (12, 13)

1.3 Ideal Characteristics:

- It should be elegant & free from chipping, cracking, discoloration and contamination.
- It ought to have adequate quality to with stand mechanical shock during its tablet formulation process. (14, 15)

1.4 Need of Bilayer Tablets:

- To modify the total surface available for API layer either by sandwiching with one or two in active layers in order to achieve swellable/erodible barriers for modified release.
- For the administration of fixed dose combination of different API prolong the drug product life cycle buccal/mucoadhesive delivery system; fabricate novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery.

- Controlling the delivery rate of either single or two different active pharmaceutical ingredients.

- To separate incompatible active pharmaceutical ingredients (APIs) from each other to control the release of API from one layer by utilizing the functional property of the other layer (such as osmotic property. (12, 15, 16)

1.5 Challenges Related to Bilayer Technology:

Despite the above-described benefits that bilayer technology offers, a number of problems related to the processes of compression of bilayer tablets have recently been documented in the literature. For the production process and bilayer tablet to be robust, the formulators and process scientists must solve the obstacles. Among the major obstacles are:

- Reduced production yield and the propensity to delaminate (distinct layers separation) at the non-planer interface between the adjacent compacted layers.

- Cross contamination between the layers.

- Long term physical and chemical integrity throughout shelf life.

- Elastic modulus mismatch between the adjacent layers. High elastic modulus ratio between adjacent layers could cause insufficient layer bonding and relatively low interfacial strength.

- Insufficient bilayer tablet hardness.

- Inaccurate individual layer weight control.

- Disproportionate layers weight ratio coupled with low drug load.

- Impact of high temperature and humidity on layer adhesion upon storage.

- Large tablet size, which can impact the swallowability of the unit dose. (17-24)

1.6 Bi-Layer Tablet Press

1. Single Sided Press: Different kinds of bi-layer presses have been designed up to this point. The most basic type of press is the single-sided model, in which the two chambers of the double feeder are kept apart. Two separate powders are pressed or gravity-fed into each

chamber to create the two distinct tablet layers. As the die passes beneath the feeder, the first layer's powder and then the second layer's powder are loaded. Next, either a single process or two stages (two = pre- and main compression) are used to compress the entire tablet. On a single-sided press, individual layer-weight management necessitates some kind of measurement of the first layer and of the entire tablet.

The initial control loop regulates the first layer's fill depth and indirectly keeps an eye on weight. Only the second-layer fill depth is adjusted by the second loop, which obliquely tracks the entire tablet weight. Compression force is typically employed to track tablet or layer weight. However, in order to accomplish this, the first layer must be compressed before the powder from the second layer is added. Use two different powder feeders with a compression station in between to deliver a compression force to the first layer before adding the second layer. Installing a second feeder between the pre- and main-compression stations on a single-sided press will accomplish this. Very often the precompression roller must be reduced to a much smaller size in order to create the space required for the second feeder. Limitations of single-sided press: (25-27)

- No weight monitoring/control of the individual layers.
- Very short first layer-dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping and hardness problems. This may be corrected by reducing the turret-rotation speed but with the consequence of lower tablet output.
- Mixing slightly at the interface hence no distinct visual separation between the two layers.
- Very difficult first-layer tablet sampling and sample transport to a test unit for in-line quality control and weight recalibration.

2. Doubled Sided Press:

A double-sided tablet press can overcome the drawbacks of a single-sided press. Each layer has its own fill station, precompression, and primary compression on a double-sided press. The bi-layer tablet will really undergo four phases of compression before being released from the press.

- Start the feeding granules corresponds to the end of compression of the first layer. At this stage, we obtain a density distribution that is specific to a flat-faced tablet compressed such

that the lower punch is stationary. In the present example, in order to get frictional effects, the friction coefficient was set, which is a relatively high value, specific to clean (unlubricated) die wall conditions.

- After compression of the first layer, the powder for the second layer is delivered into the die. The initial density of the second layer is uniform.

- At this stage, densification occurs in the second layer and the density distribution in the first layer has not yet changed. (25, 27)

The die wall mismatch eventually goes away as the bilayer compaction process progresses. It's also fascinating to see that the contact between the two layers becomes warped near the end.

3. Compression Force-Controlled Tablet Presses: When the bi-layer tablet is finally compressed, there is not enough bonding between the two layers, which causes the two individual layers to separate. In order for the first layer to interact with the second layer during the tablet's final compression, proper bonding can only be achieved when the first layer is compressed with a low compression force. If the first layer is squeezed with an excessively high compression force, bonding will be severely limited. Unfortunately, in tablet presses that use "compression force measurement," the low compression force needed to compress the first layer lowers the precision of the weight monitoring/control of the first layer. Compression force is used by the majority of double-sided tablet presses with automated production control to track and regulate tablet weight. The control system measures the effective peak compression force applied to each tablet or layer at the major compression of that layer.

An exponential relationship and, by extension, the compression force-controlled system are intrinsically sensitive to this decreasing degree of sensitivity. The qualities of the powder or the formulation determine how quickly the sensitivity declines. Because a larger compression force is needed to obtain appropriate sensitivity and enable a more precise control, a compression force control system is always based on the measurement of compression force at main-compression and not at pre-compression. However, in the case of protein and peptide formulations, which are more susceptible to compression force lowering the pharmacological activity of protein and peptide during compression, this will not occur. For first layer weight management in a bi-layer tableting process, a compression force monitoring-based weight

control system is not the ideal choice. A few hundred daN must be the minimum compression force needed for a system that is controlled by compression force. However, in order to maintain the ability to connect with the second layer, many bi-layer formulations require a first layer compression force of less than 100 daN. (16, 25, 28)

4. Displacement controlled tablet press: Using an alternative weight monitoring approach based on "displacement" solves the fundamental issue with the compression force monitoring concept. The advantage of "displacement measurement" over "compression force measurement" is that accuracy rises as compression force decreases. The risk of separation and capping rises with increasing production speeds, but it can be decreased with enough dwell time at each of the four compression stages. Along with good bonding between the two layers, weight monitoring based on "displacement" also offers longer dwell times, with more precise and enhanced weight monitoring/control of the first layer. Therefore, the best press to make bi-layer tablets is a double-sided tablet press with "displacement measurement."

Advantages:

- Low compression force exerted on the first layer to avoid capping and separation of the two individual layers.
- Displacement' weight monitoring/control for accurate and independent weight control of the individual layers.
- Increased dwell time at precompression of both first and second layer to provide sufficient hardness at maximum turret speed.
- Maximum prevention of cross-contamination between the two layers.
- A clear visual separation between the two layers.
- Maximized yield. (25, 28, 29)

1.7 Various Approaches to Bilayer Tablets:

i) Intra Gastric Bilayer Floating Tablets: The two main compressed layers of these tablets are called an immediate layer and are used to quickly affect the target area. The second layer, known as a sustained release or expanded release, is applied after the first layer has finished acting on the target. (30)

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 malfunctions or the device absorbs the fluid to reduce its density and buoyancy, allowing the fluid to pass easily from the stomach through a motility wave that causes the stomach to empty. The bilayer pill is designed such that the floating layer floats inside the stomach and the other layer delivers an instant dose of the medication for a quicker start to action. (31, 32) Intra-gastric bilayer floating tablets and multiple-unit type floating pills are the two main methods used to create floating dosages.

iii) Multiple Unit Types Floating Pills: These tablets are made up of double-layered seeds with expanded/sustained release. The exterior layer is made up of a swellable membrane layer, while the inner layer is chemically made up of effervescent chemicals. Due to their low density, these particular tablets sink to the bottom of solutions at room temperature before swelling up like a balloon and floating on the surface. (33)

iv) Swelling System: When delivered, these are designed to be comparatively small in order to facilitate the administration of the dose. Once swallowed, these break down, expand, or unfurl quickly to a size that halts the passage of the pylorus until the drug release reaches the appropriate concentration. It slowly erodes or fragments into tiny pieces before exiting the stomach. One layer of the straightforward bilayer tablet can be released immediately, while the second layer offers traditional or prolonged release. (34, 35)

iv) Polymeric Bio-Adhesive System: These are made in a way that allows them to absorb fluid after administration. The outer layer then becomes sticky and viscous, adhering to the mucus-containing stomach layer. This promotes the adhesiveness of stomach preservation to tilt. These have two layers: one with a bioadhesive quality and the other for instant dosage. Nevertheless, people have not been given this kind of dosage; it has only been given to animals. This is because the physiologies of the human and animal bodies are different, resulting in significant differences in mucous quantity and consistency. (36)

1.8 Techniques of Bilayer Tablets:

Various bilayer tablet techniques are employed to generate the desired quality of bilayer tablets. The techniques involved in this process include osmotic-release oral system (OROS) push-pull technology, En sotroll technique, L-OROS Tm technology, DUROS Technology, Duredas technology/Elan drug technology, Geomatrix technologies, Geminix technology,

programmable oral drug absorption system (Prodas), and erodible multilayer drug system. These are explained as below with diagrams: (36-39)

L-OROS Tm 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. Next, an exit cavity was created by puncturing the semipermeable membrane, which was then filled by a barrier membrane and the osmotic push layer. (40-42)

OROS ® push-pull technology: The active pharmaceutical ingredient is contained in the first one or two layers of this technology, which typically consists of two or three layers, with the push layer being the final layer. The drug layers are formed of poorly soluble material and only contain the drug and a small number of 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. (43, 44)

DUROS technology (Alza corporation): Based on the implant technique, Duros technology serves as an alternative means of delivering a wide range of medicinal compounds, including proteins, peptides, and other biochemical substances. This device, which is sometimes referred to as "Miniature drug dispensing technology," functions similarly to a miniature syringe and delivers pharmaceuticals continuously and reliably over an extended period of time in a concentrated form. These cylinders shield the medicinal chemicals found in the human body, extending their resistance to human tissues. This technology is used for the annual palliative treatment of advanced prostate cancer with the Leuprolide Acetate Implant (Vivadur). (45-47)

EN SO TROL technology: To obtain the ideal dose form in the controlled release system, the Shire laboratory employs an integrated strategy for the drug delivery system by correctly selecting and adding the enhancer. This method aids in improving solubility. (48)

RoTab bilayer: (49-51)

Software. It is software with a modular design that allows for the addition of new features. The sophisticated PCF system with a 15-inch touch screen allows for quick graphical evaluations and precise findings.

Working. When RoTab bilayer is employed for the manufacturing mode that is switched towards it, the system automatically adjusts. By adjusting 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.

R and D modified technique. R and D adjusted Because of the measuring points that they are present on, RoTab Bilayer aids in graphical visualisation and assessment. These perform important roles, such as modifying the punch tightness. These include R and D plus the possibility of an abrupt upgrade.

R and D plus. R and D Plus offers better standards and is an important component of tableting technology. They assist in managing important operations such as force displacement display, punch tightness, and tablet scraper force.

Elan drug technologies' dual release drug delivery system (DUREDAS™ technology): Elan firms use a technology called the dual drug delivery system (DUREDAS) to double the amount of discharge from a single dosage or to produce two different discharge amounts. With the help of this technology, drugs can be released in two ways: immediately or gradually. With the use of two separate direct compression processes, this method creates tablets that integrate the hydrophilic and immediate-release layers into one unit. This produces a sophisticated controlled-hydrophilic matrix (GI tract) that absorbs liquid from the gastrointestinal tract (GI tract) gradually while staying compact. After absorbing a fluid, the hydrophilic matrix transforms into a sticky, permeable gel that creates barriers between the dosage and the surrounding fluid. As the gel expands, the surrounding fluid seeps into the gel and dissolves the medicine. (52)

With this technology, medications can be released in a combination pattern, which can be either instantaneous or continuous. It offers two medications with a combined release pattern, or it offers one drug with a distinct release pattern. The various release patterns are accomplished by combining several hydrophilic polymers. The combination release in a tablet or two medications taken in one dose is one of the system's many advantages. The instant release grinds the compressed layer first, followed by the sustained release layer, while the bilayer tablet is made using the DUREDASTM Technology. Initially, controlled release anaesthetics for over-the-counter usage were developed using this approach. (53)

Programmable oral drug absorption system (PRODAS): PRODAS, which stands for "multi particulate drug technology" (Elan Corporation), is a technique that encapsulates controlled-release mini-tablets that vary in size from 1.5 to 4 mm. The method combines the

advantages of both medications in a single dosage by utilising hydrophilic matrix tablet technology and multiparticle technology. The targeted delivery of medications to the GIT is aided by PRODAS technology. (54) To achieve the desired release rate, various mini-tablet release rates—such as immediate, delayed, or controlled release—are blended into a single dosage. Sometimes, different APIs are used with Minitab to create products with predictable release schedules. (55)

Geminex technology: This method reduces the negative effects of the medications while simultaneously significantly boosting their therapeutic efficacy. It administers a single dosage of one or more medications with varying rates of release. Pen West uses it extensively for CNS problems, cancer, diabetes, cardiovascular diseases, and other conditions affecting the central nervous system (CNS). It is very helpful for both patients and the industry. (56)

Erodible molded multilayer tablet: Tablets with many layers that are moulded and erodible make up the Egalet delivery technology. This technology comprises a matrix and a coat, and it is manufactured in accordance with typical plastic injection moulding procedures. The erosion of the matrix section is the release pattern for Egalet erodible moulded tablets. This method aids in the delivery of drugs with zero-order or delayed-release patterns without compromising gastrointestinal health. The geometry of the matrix and coat (57) are engineered and designed to regulate the technology's release pattern. For the zero-order release, the medication is dispersed throughout the matrix. In addition, the coat has a low water permeability and is biodegradable. The GI tract's stomach movements encourage the matrix to erode if it comes into contact with the water or other fluids already there. This method works very well for medications that have stability problems when they come into touch with water, such as chemical and physical stability problems. Accuracy, repeatability, and low production costs are further promises. (58-59)

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 (60). This technology is used in the sale of medications like diclofenac sodium, nifedipine, and diltiazem hydrochloride. The eight Geomatrix methods, which aim to achieve a wide range of therapeutic goals, include:

- Zero-order release Geomatrix technology is employed for a constant medicine discharge rate over a long duration of time.

- Binary-release geomatrix technology is utilized for the measured discharge of two distinct drugs present in a particular dosage.

- Quick-slow release geomatrix technology involves a fast discharge of dosage tailed by a continual discharge for a specific period.

- ➢ Slow-quick release geomatrix technique, this is anti-parallel to the quick-slow release technique. It involves a slow constant release of drug followed by an immediate discharge at a fixed time.

- ➢ Positioned released geomatrix technique involves the transport of the medicine to a specific location in the gastrointestinal tract earlier to the discharge of the main dosage.

- ➢ Accelerated release geomatrix technology includes the constant accelerating release of the core drug.

- ➢ The delayed-release geomatrix technique is utilized when a prearranged time delay of the actual dosage is required.

- ➢ Multiple pulse geomatrix technology is employed whereby a prior quick burst is required followed by a prearranged time of no release.

1.9 Application:

- Separate two incompatible substances.

- Bilayer tablet is suitable for sequential release of two drug in combination.

- Bilayer tablet is used to deliver the loading dose and sustained dose of the same or different drugs.

- Sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose.

- Bilayer tablet is improved beneficial technology to overcome the short coming of the single layer tablet.

- Bilayer tablets are used for bilayer floating tablets in which one layer is floating layer another one is immediate release layer of the drug.

- Bilayer tablets are used to deliver the two different drugs having different release profiles. (61, 62, 63)

CONCLUSION

A bilayer tablet is a technologically advanced solution that addresses the shortcomings of a single-layered tablet. A bi-layer tablet can be used to segregate two substances that are incompatible, release two medications sequentially in tandem, or create a sustained release tablet where the first layer is the initial dose and the second layer is the maintenance dose. Tablets prepared in the multilayer form are utilised to give incompatible drug delivery methods and to provide control release tablet preparations through the employment of surrounding or multiple swelling layers. GMP regulations and the quality of bilayer tablets can differ greatly. This explains why a wide variety of presses, from straightforward single-sided presses to extremely complex devices, are utilised to make bilayer tablets.

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