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Recent Advancement and Challenges in Bilayer Tablet Technology: An Overview

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ABSTRACT

Bilayer tablets were developed recently for the effective production of controlled release formulations in various quality levels to give a method of successful drug delivery. Over the last three decades, as the cost and complexity of developing novel pharmacological entities have increased and as the therapeutic benefits of controlled drug administration have been recognized, considerable attention has been focused on developing sustained or controlled release drug delivery systems. It is utilized to produce a variety of antihypertensive formulations. Bilayer tablets allow for the predetermined release of two drugs in combination, separating two incompatible substances, and sustained-release tablets with one layer serving as the loading dose and the second layer serving as the maintenance dose. Bilayer tablets are advancing helpful technologies to overcome the disadvantages of single-layered tablets. However, bilayer tablet technology is resource-intensive. A thorough selection of excipients and manufacturing conditions for each technical stage is also required. The purpose of this paper is to summarize the state of art in bilayer tablet technology and to highlight the difficulties encountered during bilayer tablet manufacture, as well as the possible solutions for these obstacles.

Keywords: *Bilayer tablet, Conventional release, controlled release, Sustained release, maintenance dose.*

1. INTRODUCTION

Oral administration is the most common and preferred method of drug administration. This method is widely recognized due to its ease of administration, self-medication, patient compliance, and versatility with various dosage forms available. Tablets are the most convenient oral dosage form of all the solid oral dosage forms and are chosen by both patients and physicians.[1] Novel formulations with changed drug release profiles are being investigated to meet current requirements. Controlled release formulations are one of them. They administer the drug at a predetermined rate and to a specified place to prolong or sustain the formulation's release. [2]

The limited stomach residence period complicates the oral continuous drug administration mechanism. Rapid gastrointestinal transit can limit complete drug release in the absorption zone, decreasing the efficacy of the provided dose, as most pharmaceuticals are absorbed in the stomach or upper section of the small intestine. Several strategies have been proposed to increase the gastric residence time of drug delivery systems in the upper gastrointestinal tract to address these limitations. These strategies include floating drug dosage systems, swelling or expanding systems, mucoadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices. [3-5]

Nowadays, several pharmaceutical companies are developing combination therapies for hypertension, multiple sclerosis, and cardiovascular disease conditions. Bilayer tablet technology enables the incorporation of many drugs into a single dosage form. The formulation of bilayer tablets from various polymers allows manipulation of more than one type of drug delivery for one or more drugs, i.e., the drug may be released in a bolus and then at a controlled rate, or it may be delivered to the GIT via targeted drug delivery using the polymers' pH development. Numerous difficulties were encountered with the manufacture of bilayer tablets. [6]

Conventional dosage forms frequently create broad fluctuation in drug concentration in blood and tissues resulting in undesired toxicity and low efficiency. Repetitive dosing requirements and unpredictable absorption in conventional methods led to the concept of controlled medication delivery systems. The primary goal in designing sustained or controlled delivery systems is to lower the dosing frequency with greater effectiveness of the drug. Site-specific localization of drug or reducing the dose to achieve uniform drug concentration may be another purpose of controlled release dosage forms. A controlled release drug delivery device delivers the drug locally or systemically at a predetermined rate for a specified period.[7] Controlled release drug delivery systems are devised to ensure the safety and increased efficacy of medications with higher patient compliance.

Drug release through matrix system can be modulated by adding different polymers and can be measured by water penetration, polymer swelling, drug dissolution, drug diffusion, matrix erosion techniques. It gets increasingly challenging to distribute two or more drugs within a single delivery mechanism. Formulation of layers from different polymers allows manipulation over more than one rate-controlling polymer, thus enabling different types of drug delivery of one or more drugs, i.e., where the drug may be released as immediate and then at a controlled rate or by targeted drug delivery in the GI tract using pH-dependent polymers. [8]

Controlled release dosage form delivers one or more drugs continuously in a predetermined pattern for a fixed length of time, either systemically or locally, to the selected target organ. Sustained release dosage forms allow better management of plasma drug levels, reduced dosing frequency, fewer side effects, higher efficacy, and consistent delivery. Drug release is based on polymer properties, so the use of these properties can provide well-defined and reproducible dosage forms. [9] To control the release of the drug, which have different solubility qualities, the drug is dispersed in swellable hydrophilic polymers, an insoluble matrix of rigid non-swellable hydrophobic materials or plastic materials. [10]

The concept of floating tablets is usually connected with bilayered tablets, including one immediate layer and another sustained layer. The prolonged release of the drug is achieved by using a matrix-type drug delivery method. The drug remains embedded in the matrix and swells up after coming in touch with the gastric fluid, followed by the slow erosion of the drug without disintegration the tablet takes place. Floating of the tablet can also be performed by applying an effervescent or gas-producing agent. Floating matrix tablets retain in the stomach for a long time, increasing the sustained oral administration of drugs with an absorption window in a particular region of the GIT. [11]

2. RATIONALE OF DEVELOPING BILAYER TABLETS [12]

- To deliver fixed dose combinations of different APIs, prolonging the drug product life cycle, developing buccal/ mucoadhesive delivery systems or development of floating tablets for gastro-retentive drug delivery.
- Controlled release drug delivery of either single or two different active pharmaceutical ingredient(s).
- To achieve modified drug release either by sandwiching drug with one or two inactive layers with swellable/erodible barriers.
- To separate incompatible drugs 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).

2.1 Advantages of the Bilayered tablets [13]

- It helps in avoiding chemical incompatibilities between API's by physical separation.
- Suitable for sequential release of two drugs Repetitive dosing is required in conventional dosage forms which can be avoided by bilayer tablet.
- Decreases the dosing frequency. Drug delivery is uniform.
- Chemical & microbial stability is more compared to other oral dosage forms.
- In case of drugs having a low half life, each of the two layers of the tablet respectively content a loading dose and maintenance dose of the same and thus increase the bioavailability of the drug.
- Taste & odor can be masked by coating technique.
- They show highest dose precision & low content variability.
- Cost is lower compared to all other oral dosage form.
- Easy to swallowing with least tendency for hangup.
- Suitable for large scale production.

2.2 Limitations of Bilayer tablet [13]

- Drugs with objectionable odour & with bitter taste cannot be formulated.

- Swallowing is difficult for children & for unconscious people.
- Formulation is difficult for drugs with poor wettability, slow dissolution rate & high absorption in the GIT.
- Lack of sufficient bonding and adhesion at the interface between the adjacent compacted layers which is often the result of an interfacial crack and layer separation.
- Sustained release bilayer tablet does not permit the prompt termination of therapy.
- Cross contamination may occur between the 2 layers.
- Individual layer weight is inaccurate.
- Less flexibility on adjusting the dose regimens
- Low yield, insufficient hardness & the layers gets separated.

2.3 Types of bilayer tablets

Bilayer tablets may be identical (homogeneous) or dissimilar (heterogeneous).

2.3.1 Homogenous type

Bilayer tablets having same drug in two layers but drug release profile is different from one another. These bilayer tablets contain one layer of the immediate release and second layer is extended release manner [14].

2.3.2 Heterogeneous type

Bilayer tablet is suitable for continuous release two drugs in combination, separate two incompatible substances.

To produce a quality bi-layered tablet, in a validated and GMP way, it is important to select a bi-layer tablet press capable of:

- High yield.
- Preventing capping and separation of the two individual layers that form the bilayer tablet.
- Preventing cross-contamination between the two layers.
- Producing a clear visible separation between the two layers.
- Accurate and individual weight control of the two layers.

2.4 Applications

- Mostly bilayer tablets used in combination therapy.
- Bilayer tablets are used to transport the loading dose and maintenance dose of the same or different drug.
- Bilayer tablets are used to provide the two different drugs having different release profile.
- Bilayer tablets are used for bilayer floating tablets in which one layer is floating layer another one is immediate drug release layer.

3. ADVANCED TECHNIQUES USED IN PREPARATION OF BILAYER TABLET

- OROS Push Pull Technology
- L-OROS Technology
- EN SO TROL Technology
- DUROS TROL Technology
- Elan Drug Technology' Dual release Drug Delivery System

3.1 OROS Push Pull Technology

This approach comprises mainly two or three layers, one or more of which must contain the drug, and the other is a push layer. Generally, it consists of a drug and two or more agents utilized in the drug layer such as suspending and osmotic agents. A semipermeable membrane surrounds the core of the tablet [15]

3.2 L-OROS Technology

This system is used to resolve the solubility problem associated with the drug. L-OROS system contains a lipid soft gel product holding drug in a dissolved state and an osmotic push layer with semi permeable membrane and a drilled for exit orifice. [16]

3.3 EN SO TROL Technology

Increased solubility by an order of magnitude or creation of an optimal dose form Shire's drug delivery laboratory takes an integrated strategy, concentrating on the identification and implementation of discovered enhancers into controlled release technologies. [17]

3.4 DUROS Technology

The system is comprised of an outer cylindrical titanium alloy reservoir and an inner cylindrical titanium alloy reservoir. This reservoir is extremely robust and effectively protects the drug molecules from enzymes. The DUROS technology is a small medicine delivery system that resembles a miniature syringe and continuously and consistently releases minute amounts of concentrated medication over months or years. [17]

3.5 DUREDAS™ Technology

This system is also known as Elan drug technologies' Dual release drug delivery system. DUREDAS™ Technology is a bilayer tablet which can provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form. The tableting process can provide an immediate release granulate and a modified release hydrophilic matrix complex as separate layers within the one tablet. The modified-release properties of the dosage form are provided by a combination of hydrophilic polymers. [18]

4. CHALLENGES INVOLVED IN MANUFACTURING OF BILAYER TABLET

During the production of bilayer tablets, difficulties may arise due to insufficient hardness, layer sequence, layer weight ratio, and elastic mismatch between neighbouring layers, as well as tamping force on the first layer and cross contamination between layers. If these elements are not appropriately regulated, they will have a detrimental effect on bi-layer compression pressure, as well as qualitative features such as mechanical strength and regulation of individual layer weight. As a result, caution must be exercised to enable the design of a robust product and process. [19]

Bilayer tablets can be thought of as two single-layer tablets compacted into one but in practicality there are several manufacturing problems associated.

4.1 Material Properties

The physicochemical qualities of the active pharmaceutical ingredient (API) and excipients are critical to the success of bilayer tablet manufacture [20]. The composition of materials has a significant effect on the strength and fracture mode of multi-layer tablets. Plasticity, brittleness, and visco-elasticity of the material all have a substantial effect on the compression process. The deformation of the material's plasticity and brittleness play a vital influence in the compression process. This indicates that as long as the elasticity of the plastic material does not exceed the bond limit, plasticity has no effect on the compression process. Additionally, particle deterioration is stronger in the middle area of the die than in the outer layer; thus, it is vital to consider the material qualities of a substance before utilizing it to manufacture bilayer tablets. Each layer in a multi-layer tablet formulation must display a suitable volume decrease and the capacity to solidify mechanically strongly and coherently. As a result, they should exhibit high compressibility (a substance's capacity to shrink in volume when compressed) and compatibility (ability of powdered substances to convert into tablets). When using layered tablet manufacturing, it is critical to tune the particle size distribution, flow properties, and compression capabilities of the material to enable exact control of each layer's weight.

4.2 Compression force

According to previous research, the most critical parameter in the manufacturing process of a multi-layer tablet is the assessment of the compression force used for the first layer, as this parameter affects the interfacial strength and adhesion between the two layers, resulting in mechanical attraction between the layers in the tablet. As a result, if the initial layer of the bilayer tablet is more elastic, the stress and strain generated throughout the system degrades the strength of the bilayer tablet. This can result in the breakdown of the link between the two layers at the bilayer tablet's interface, compromising the layers' adhesion. Compression pressure and punch speed both have a major impact on the compactability and resistance to compression within the die. The initial layer of compression forces (usually between 2 and 18 KN) is responsible for compacting the powder/granulated substances, reducing their volume, smoothing the first layer's surface, and creating a space for depositing the second layer.

In general, increasing compression force results in an increase in tensile strength and a decrease in surface roughness. Smoothing the initial layer's surface may facilitate delamination by reducing intermolecular adhesion between adjacent layers. Proper bonding is only obtained when the first layer is compressed at a low compression force so that this layer can still interact with the second layer during final compression of the tablet. Bonding is severely restricted if the first layer is compressed with high compression force. [20]

4.3 Lubricant

Research has indicated that substance which is having better lubricity will have reduced friction between its particles and with die when it comes into contact since all the matter will be uniformly distributed. Conversely, when it comes to bilayers formulation to achieve higher interaction and strength between the two layers' low lubricant level is obligatory. Because lubricant levels have a bigger impact than brittle substances, this characteristic of the material should be considered while dealing with the development of Bilayer tablet.

As part of the product development process, the amount of lubricant essential to avoid picking and sticking of the first layer must be calculated. When the granules come into contact with dies and punches during compression, the blended lubricant in the granular bulk distributes throughout the mixture, or "coats" on the surface of the granules, providing lubrication and reducing friction. Lubrication can also lessen inter-granular adhesion, which can have an effect on critical quality measures such tablet breaking force and dissolving. Thus, the influence of lubricant on the critical quality parameters of the tablet has been examined by adding it to the dies and punches rather than directly to the granules. This approach is known as external lubrication in the literature. External lubrication, in which the lubricant is sprayed over the die and punches for each compression cycle rather of being introduced to the bulk powder combination, has been demonstrated to boost crushing strength by 40 percent without lengthening tablet disintegration time. The existence of a layer of magnesium stearate on the pill was confirmed using a scanning electron microscope. Though this novel technique tends to be helpful for monolayer tablets, it may be applied to better comprehend the influence of lubricant on bilayer tablet quality aspects.

4.4 Layer ratio and layer sequence

This section contains the least amount of research. The weight of the two layers in a bilayer tablet is not necessarily equal during the design process. In the majority of circumstances, the ratio of their weights will vary significantly. However, it has been demonstrated that in the majority of cases, the ratio between the first and second layers is 1:1, 1:2, or even 1:3. However, maintaining the second layer's weight constant with the first layer, which is normally heavy, is difficult, and thus presents a problem during the development of bilayer medications.

4.5 Environmental condition

While formulating the bilayer tablet, environmental conditions such as humidity and moisture have a considerable effect on the compactness of bilayer tablets. Despite the fact that just a few researchers have investigated the effect of moisture on bilayer tablet strength. In reaction to the relative humidity of the surrounding air, bilayer tablets made of hygroscopic material will absorb/desorb moisture into/out of their pore structure.

Additionally, if the compacts are formed of starches, microcrystalline cellulose, crospovidone, hydroxypropyl methylcellulose, polyvinylpyrrolidone, sodium starch glycolate, and colloidal silicon dioxide, moisture can infiltrate the majority of the particles. When porous compacts and/or particles absorb moisture, layer expansion occurs. Any change in the thickness of the layers decreases the contact between them, which may result in time-dependent delamination. It was recommended that the materials be pre-conditioned to achieve equilibrium with the moisture content of the air in the producing area and that the compacts be packaged in airtight, moisture-resistant blisters.

Along with formulation design and manufacturing process issues, physical stability of bilayer tablets is critical to address during product development since it can affect quality features such as tensile strength, layer adhesion, friability, and dissolution. After storage, the strength of bilayer tablets composed of plastic/brittle, brittle/plastic, and brittle/brittle was compared. The interfacial strength of bilayer tablets created with MCC in the first layer and lactose in the second layer decreased with increasing humidity and storage duration, whereas those prepared with lactose/lactose enhanced tablet strength due to the creation of solid bridges during storage.

4.6 Layer weight control

To ensure the uniform distribution of active drug components in bilayer tablets, several antecedents are critical, including material flow properties, particle size distribution, and the bilayers' ability to press properly. Each vendor's instrumented bilayer press has its own weight control method. Existing development and commercial presses include the capability to measure the weight of the first layer and the second bilayer. However, there is currently no commercially available bilayer press equipped with a mechanism for separately sampling the weight of the second layer. This creates a significant production challenge for the bilayer tablets.

4.7 Bilayer tablet compression machine:

Several commercially available bilayer presses to formulators and process development scientists working on bilayer tablets are the Kilian, Oystar Manesty, Hata, Korsch, Courtoy, Fette, Kilian, and Piccola. The majority of instrumented bilayer presses include control systems that automatically calculate compression forces and punch displacements. Recent improvements in compression machine design and accessory technology have enabled product-specific characteristics (initial layer sampling, sealed feeders, precompression rolls, layer strain gauge sensitivity, and maximum upper punch penetration) to be customised. Consider the precompression force, punch velocity, consolidation time, dwell time, and relaxation. Since a result, compression machines are crucial in the manufacture of bilayer tablets, as they can either help achieve the desired dose quality or impair the tablet's quality. As a result, this region should receive considerable attention throughout the construction of the bilayer tablet. [21]

4.8 Bilayer tablet characterization:

It is one of the most critical points that should never be overlooked when contemplating bilayer tablets. While it is theoretically preferable to have a material that can be compressed without deformation and compacts independently when compressed, resulting in a stronger bond between the two layers of a bilayer tablet, there are additional factors that influence the formation of bilayer tablets with the desired quality. Characterization includes the particle size distribution, angle of response, photomicroscopic examination, density, compressibility, and moisture sorption capacity. [22]

The following are some of the advantages of bilayer tablet characterization in early formulation development:

- Determination of the interfacial strength of bilayer tablets using quantitative methods.
- Unusual or severe characteristics of compacted layers must be detected.
- Ensure that the bilayer tablets produced are consistent from batch to batch.

- To create a rationale strategy in order to guide formulation development and the selection of suitable product formulations and manufacturing process.
- Explain material failure mechanisms during tablet manufacturing.
- Understand the effect of the factors specific to tableting equipment (e.g., speed of operation, applied forces, etc.).
- Reduction in energy utilization by minimization of faulty tablet production.
- Environmental issues and concerns related to the waste management of materials.

5. CONCLUSIONS

Bi-layer tablets enable the combination of incompatible drugs with several indications and the same drug with varying release rates in a single unit. The bilayer tablet is an advanced technology that overcomes the constraints associated with single-layered tablets. Both bilayer and monolayer tablet manufacturing share numerous comparable technological characteristics, as both of these pharmaceutical formulations are created by compacting powdered/granulated active pharmaceutical ingredient (API) with or without excipients. In comparison to typical immediate-release monolayer tablets, multilayer tablets offer a number of significant advantages. Significant advancements in the manufacture of tablets have been made recently. This has resulted in an improvement of the tablets' physicochemical qualities and the capability of generating tablets with modified/controlled release. However, a number of technological difficulties must be solved before a multilayer tablet with the same level of reliability as monolayer tablets can be achieved. The variability of adjacent layers is a significant source of design and production issues for multilayer tablets. Even small changes in one of the compression parameters (e.g., compression strength, layer ratio, layer arrangement, or excipients utilised) can have a considerable effect on the properties of each layer and the interfacial strength. However, by adjusting the manufacturing parameters of multi-layer tablets, the desired release profile can be achieved. Bilayer formulations are a convenient dose form, are safe, and offer additional benefits to both the patient and clinician due to the fact that they can be taken as a single tablet once daily.

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