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Concept of Bilayer Tablet: A Review

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ABSTRACT

Bilayer tablets present a much better choice where one layer provides an immediate dose which then maintains the plasma drug level by its controlled-release layer of the tablet. The introduction of bilayer tablets into the pharmaceutical industry has enabled the event of pre-determined release profiles of active ingredients and the incorporation of incompatible active ingredients into a one-unit dosage form. Bilayer tablets provide one among the important design approaches where incompatible drugs, with a special indication and the same drug with different release rates are often incorporated during one unit. Bilayer tablets offer definite advantages over conventional tablets of the same drug. Bilayer tablets are often a primary option to avoid chemical incompatibilities between API by physical separation and to enable the event of varied drug release profiles. Bilayer formulations carry one drug, and deliver each of them with no pharmacokinetic or dynamic interactions, with their rate of delivery. Controlled release dosage forms are extensively used to improve therapy with several important drugs. This review aims to explain the challenges that appear during the formulation of bilayer tablets, and also propose solutions for these challenges.

INTRODUCTION:

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The formulation of sustained or controlled drug delivery systems possesses momentum over the past decade because the immense specialization in the marketing of these new drug molecules has increased to counter multiple diseases that require different dosage regimens [1,2]. Usually, conventional dosage forms produce wide-ranging fluctuation in drug concentration within the bloodstream and tissues with consequent undesirable toxicity and poor efficiency. This factor such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery systems is to scale back the frequency of the dosing or to extend the effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery. The primary objective of sustained-release drug delivery is to make sure safety and to enhance the efficacy of medicine also as patient compliance. Bi-layer tablet is suitable for sequential release of two drugs together, separate two incompatible substances and also for sustained release tablet during which one layer is immediate release as initial dose and the second layer is maintenance dose. The basic goal of therapy is to achieve a steady-state drug in blood level for an extended period [3-5] the main objective of controlled drug delivery is the reduction of the dose frequency. According to these findings, a bilayer tablet has been proposed [6]. One of its layers is formed for ensuring the moment extraction of the drug and aims to succeed in a high serum concentration during a brief time. Its second layer may be a controlled release hydrophilic matrix that aims at maintaining an efficient plasma level for an extended time. The pharmacokinetic benefit depends on the very fact that the immediate release of the drug from the primary layer leads to rising blood concentration suddenly [7].

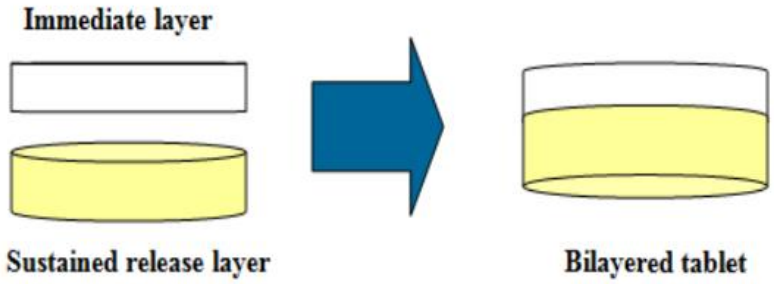

Figure No. 1: Bi-layered Tablet

NEED OF DEVELOPING BI-LAYER TABLETS [7,8]

For the supervision of fixed-dose combinations of API's, prolong the drug product life cycle, buccal/mucoadhesive delivery systems, manufacture novels drug delivery systems like chewing devices and floating tablets for gastro-retentive drug delivery systems.

1. Controlling the delivery rate of either single or two different API'S.

2. To adapt the total surface area available for the API layer either by sandwiching with one or two inactive layers to achieve swellable/erodible barriers for controlled release.

3. To separate incompatible API's from each other, to control the release of one layer by utilizing the functional property of the other layer (such as osmotic property).

ADVANTAGE OF BI-LAYERED TABLETS OVER CONVENTIONAL TABLETS: [8]

1. Blood level of a drug can be held at a consistent therapeutic level for improved drug delivery, accuracy, safety and reduce side effects.

2. Reduction of adverse effects can be accomplished by targeting the drug release to the absorption site as well as controlling the rate of release, enabling the total drug content to be reduced.

3. Patient convenience is improved because fewer daily doses are required competed to traditional systems. Patient compliance is enhanced leading to improved drug regimen efficacy.

4. Bi-layered tablets readily lend themselves to repeat action products; wherein one layer provides the initial dose, the other layer provides maintenance dose.

5. Separate physically or chemically incompatible ingredients.

DISADVANTAGES OF BI-LAYERED TABLETS [9]

1. Some drugs resist compression into dense compacts, due to their amorphous nature, low-density character.

2. Bitter-tasting drugs, drugs with an objectionable odor, or drugs that are sensitive to oxygen may require encapsulation or coating.

3. Difficult to swallow in the case of children and unconscious patients.

4. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate as a tablet that will still provide adequate or full drug bioavailability.

IDEAL CHARACTERISTICS OF BI-LAYERED TABLETS [10]:

1. A Bi-layered tablet should have an elegant product identity while free from defects like chips, cracks, discoloration, and contamination.

2. It should have sufficient strength to stand mechanical stock during its product packaging, shipping, and dispensing.

3. It should have the chemical and physical stability to take care of its physical attributes over time. The Bi-layered tablet must be ready to release the medicinal agents in a predictable and reproducible manner.

4. It must have a chemical stability shelf-life, to not follow alteration of the medicinal agents.

VARIOUS APPROACHES TO BILAYER TABLETS

FLOATING DRUG DELIVERY SYSTEM-

These are manufactured for having a lower density so that they can float over gastric contents following that if they are being administered till the system breaks down or the device absorbs the fluid until its density and buoyancy is reduced and it can easily pass from the stomach through a motility wave that causes emptying of the stomach. The bilayer tablet

is formed such one among its layers provides an instant dose of the drug, giving faster onset action and thus the other layer is that the floating layer that floats inside the stomach [11,12]. The two basic approaches to get floating dosages are Intra-gastric bilayer floating tablets, and multiple-unit type floating pills. Both of those are explained as given below:

INTRAGASTRIC BILAYER FLOATING TABLETS- These tablets contain two major layers which are in compressed form, one layer is termed as an immediate layer, which is used to quickly affect the target, whereas the second layer, is termed as the sustained release or expanded release, which affects the target after the completion of first layers occurs [13].

MULTIPLE UNIT TYPES FLOATING PILLS- These pills contain expanded/sustained release as seeds encapsulated by double layers. The inner layer is chemically composed of effervescent agents, while the outer layer has the composition of the swellable membrane layer. When such sort of pills is dissolved during a solution at normal body temperature, the primary sink to the bottom and then swell up like a balloon due to its low density, and therefore, floats on the surface [14].

POLYMERIC BIO-ADHESIVE SYSTEM- These are manufactured in such a way that they absorb the fluid after they are administered. Then, the outer layer turns vicious and tacky and sticks to the gastric layer made from mucus. This encourages gastric preservation to tilt the adhesiveness becomes weak. These contain one layer for immediate dosing and the other having the bio-adhesive property. However, this type of dosage has only been administered to animals and has been avoided to use for humans. This is due to the different physiology of the human and animal body, wherein the amount and consistency of mucous differ largely [14].

SWELLING SYSTEM- These are manufactured to be considerably small on being administered for easing the dose ingestion. After being ingested, these disintegrate, swell, or unfold rapidly to a size that stops the pylorus passage until the progression of the drug release to the desired level. It leaves the stomach after its gradual erosion or breaking down into smaller bits. The simple bilayer tablet can consist of one layer for immediate release while the second other layer provides extended or conventional release [15, 16].

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 so troll 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 below with diagrams [17–20].

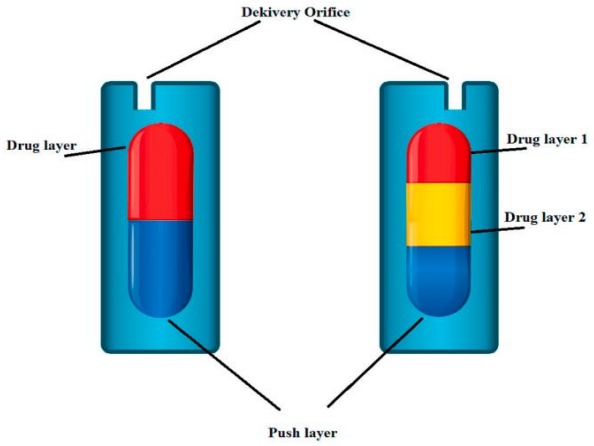

Figure No. 2: OROS push-pull technology

1. OROS ® PUSH-PULL TECHNOLOGY - This technology mostly includes two or three layers, among which the primary one or two layers contain the active pharmaceutical ingredient and therefore the last one is the push layer. The drug layers are only composed of the drug and a couple of excipients and are made from poorly soluble material. It could also additionally include a suspending and osmotic agent (Fig. 2). A semipermeable layer keeps the tablet core separate from its surroundings [21,22].

L-OROS TM TECHNOLOGY - This technology is formed by Alza and solves a serious problem of solubility. The drug was first developed within the sort of lipid soft gel in a dissolved state. It had been then covered by a barrier membrane, followed by the osmotic push layer, and then, the semipermeable membrane was punctured for an exit cavity (Fig. 3) [23–25].

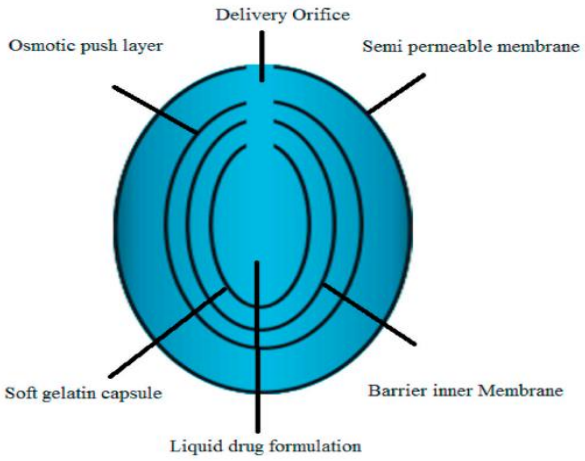

Figure No. 3: L-OROS Tm Technology

DUROS TECHNOLOGY (ALZA CORPORATION)- The Duros technology relies on the implant technique and acts as a substitute for the transmission of numerous therapeutic substances, which ranges from peptides, proteins, and various other biochemical substances. Also known as "Miniature drug dispensing technology", this system works similarly to a miniature syringe that releases drugs continuously and consistently in a concentrated form for a longer period. In the human body, the therapeutic compounds are protected due to these cylinders, hence, making them resistant to human tissues for a long period (Fig. 4). For the annual palliative treatment of advanced prostate cancer, Viadur (leuprolide acetate implant) this technology is employed [26–28].

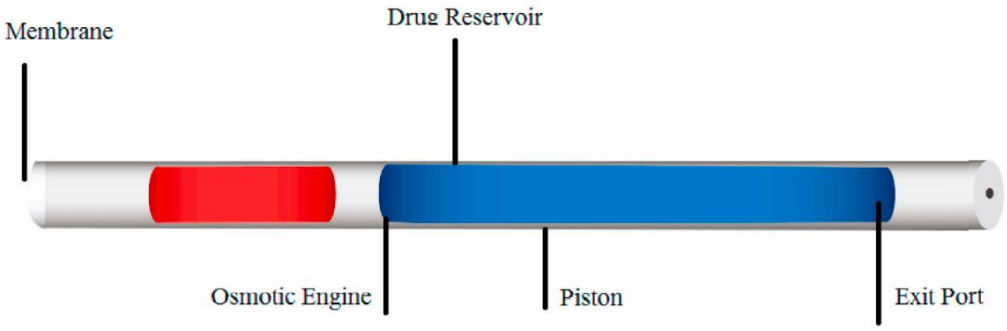

Figure No. 4: DUROS Technology

ELAN DRUG TECHNOLOGIES' DUAL RELEASE DRUG DELIVERY SYSTEM (DUREDAS TECHNOLOGY) - Dual drug delivery system (DUREDAS) is a technology employed by Elan corporations for two distinct discharge amounts or double discharge from a solo dosage. This technology provides a combination release pattern of drugs i.e.

immediate or sustained release. This technology produces a tablet through two independent direct compression steps which combine the immediate-release layer with the hydrophilic layer in a single tablet. This generates a posh controlled-hydrophilic matrix that is still compact and gradually absorbs liquid from the alimentary canal (GI tract). The hydrophilic matrix upon absorption of fluid turns in sticky, permeable gel, which acts like obstacles between the dosage and therefore the adjacent fluid, because the gel expands more the surrounding fluid, penetrates the drug, hence, dissolving it [6,10,29]. This technology offers a combined release pattern of drugs, or in simple words, sustained or immediate release. It either provides a single drug with a different release pattern or two drugs with a combined release pattern. It achieves the various release patterns through the utilization of a mixture of hydrophilic polymer. The system has several benefits, including the combined release in a tablet or two drugs combined in one dose. While the bilayer tablet is manufactured by following the DUREDAS™ Technology, the immediate release firstly grinds the compressed layer then the sustained release layer. This technology was first used for developing the OTC controlled release aesthetics [29-30]. EN SO TROL technology an integrated approach is used by the Shire laboratory for the drug delivery system by properly identifying and incorporating the enhancer to get the optimized dosage form in the controlled release system (Fig. 5). This approach helps to increase solubility [31-34].

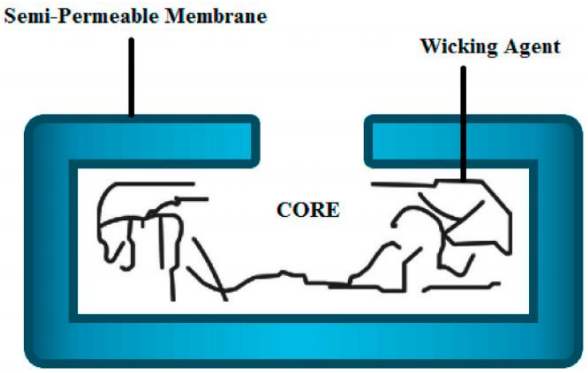

Figure No. 5: EN SO TROL technology

GEMINEX TECHNOLOGY This technology helps massively in increasing the therapeutic effectiveness of the drugs while also minimizes their side effects. It delivers one or more drugs having different release rates through a single dose. It is extremely beneficial for patients as well as the industry and is largely used by pen west for

cardiovascular diseases, CNS disorders, diabetes, cancer, and central nervous system (CNS) disorders [35].

PROGRAMMABLE ORAL DRUG ABSORPTION SYSTEM (PRODAS) - PRODAS, also known as multi particulate drug technology (Elan Corporation), encapsulates mini-tablets of controlled drug release, with sizes ranging from 1.5 to 4 mm. The technology is a combination of multiparticle and hydrophilic matrix tablet technologies and is used for providing the combined benefits of these drugs in one dose [36]. PRODAS technology is beneficial in the targeted delivery of the drugs for targeting GIT. Different release rates of the mini-tablets, like immediate, delayed, or controlled release, are combined within the sort of one dosage for providing the wanted release rate. The Minitab is sometimes combined with various APIs for forming products with anticipated release patterns [37].

Erodible Molded Multilayer Tablet - The Egalet delivery technology consists of erodible, molded, multilayered tablets. This technology is formed consistent with the quality plastic injection molding and contains a coat and a matrix. The release pattern for the Egaleterodible molded tablets is that the erosion of the matrix portion. This technique helps to deliver a zero-order or delayed-release pattern of the drug while not affecting the GI conditions [38]. The release pattern of this technology is controlled by the planning and engineering of the coat's and matrix's geometry. The drug is spread in the matrix for the zero-order release. Moreover, the coat is biodegradable and has minimal water permeability. The erosion of the matrix happens if it is in contact with the existing water or GI fluids and is promoted by the gut movements in the GI tract. The technique is highly beneficial for the drugs that having issues regarding stability if contacted by water, including chemical and physical stability issues. It also promises reproducibility, accuracy, and low production costs [39–41].

GEOMATRIX TECHNOLOGIES - Geomatrix technology generates a multilayer tablet, wherein an active ingredient is present inside a matrix core surrounded by one or more modulating layers (acting as a barrier) bonded to the central matrix in the course of the tablet generating process. The basic tasks of these obstacles are to avoid contact between core and dissolution medium [42].

TYPES OF BI-LAYERED TABLET PRESS [10, 43]

1. Single-sided tablet press.

2. Double-sided tablet press.

3. Bi-layered tablet press with displacement monitoring

SINGLE-SIDED TABLET PRESS: The only design may be a single-sided press with both chambers of the doublet feeder separated from one another. Each chamber is gravity or forced fed with different power, producing the two individual layers of tablets. When the die passes under the feeder, it's first loaded with the primary layer powder followed by the second layer powder. Then the whole tablet is compressed in one or two steps.

DOUBLE-SIDED TABLET PRESS: In most double-sided tablet presses with automated production control use compression force to watch and control tablet weight. The effective peak compression force exerted on each tablet of the layer is measured by the system at the main compression of the layer. This measured peak compression force is that the signal employed by the system to reject out of tolerance and proper the die fill depth when required.

BI-LAYERED TABLET PRESS WITH DISPLACEMENT MONITORING: The displacement tablet weight control principle is fundamentally different from the principle-based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied pre-compression force.

EVALUATION OF BI-LAYERED TABLETS

CHARACTERIZATION OF IMMEDIATE AND SUSTAINED RELEASED POWDER BLENDS

PARTICLE SIZE DISTRIBUTION - The particle size distribution was measured using the sieving method.

PHOTO-MICROSCOPE STUDY- Photo-microscope image of TGG and GG was taken (X450 magnifications) by photomicroscope.

THE ANGLE OF REPOSE - The diameter of the powder cone was measured and the angle of repose was calculated using the following equation.

$$\text{Tan } Ø = h/r$$

where h and r are the height and radius of the powder cone.

MOISTURE SORPTION CAPACITY - All disintegrates can absorb moisture from the atmosphere which affects moisture-sensitive drugs. Moisture sorption capacity was performed by taking 1 g of disintegrating uniformly distributed in Petri-dish and kept in stability chamber at 37±1°C and 100% relative humidity for 2 days and investigated for the amount of moisture uptake by the difference between weights.

DENSITY - The loose bulk density (LBD) and tapped bulk density (TBD) were determined and calculated using the following formulas.

LBD ¼ weight of the powder=volume of the packing = ð2Þ

TBD ¼ weight of the powder=tapped volume of the packing = ð3Þ

COMPRESSIBILITY - The compressibility index of the disintegrate was determined by Carr's compressibility index.

$$C = 100 \times (1 - ÞB/ÞT) \qquad [44,45].$$

HAUSNER'S RATIO- It is calculated by the formula, $H = \rho T / \rho B$ Where ρB is the freely settled bulk density of the powder, and ρT is the tapped density of the Powder (46).

EVALUATION OF FINAL BI-LAYERED TABLETS

TABLET THICKNESS AND SIZE - Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using a venire caliper.

TABLET HARDNESS - The resistance of tablets to shipping or breakage under conditions of storage, transportation, and handling before usage depends on its hardness. The hardness of the tablet of each formulation was measured by the Monsanto hardness tester. The hardness was measured in kg/cm^2.

UNIFORMITY OF WEIGHT - Twenty tablets were selected at random and the average weight was calculated. Weight Variation was calculated and was compared with I. P. [47]

FRIABILITY - Friability is the measure of tablet strength. Electrolab EF2 friabilator (USP) was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed and the percentage loss in tablet weight was determined.

$$\% \text{ loss} = [(\text{Initial wt. of tablets} - \text{Final wt. of tablets}) / \text{Initial wt. of tablets}] \times 100$$

DISSOLUTION STUDIES - Bilayer tablets were subjected to in vitro drug release studies in simulated gastric and intestinal fluids to assess their ability in providing the desired controlled drug delivery. Drug release studies were carried out using USP dissolution test apparatus I at 100 rpm, 37±0.5°C, and pH 1.2 buffer (900 ml) (i.e. 0.1 N HCl) for 2 hours since the average gastric emptying time is about 2 hours. The dissolution medium was replaced with pH 6.8 phosphate buffer (900ml) and the experiment continued for another 10 hours. At different time intervals, 5ml of the samples were withdrawn and replaced with 5ml of drug-free dissolution medium. The samples withdrawn were analyzed by UV spectrophotometer using the multi-component mode of analysis [46].

CHALLENGES IN THE FORMATION OF BILAYER TABLETS

Nevertheless, these mediums of drug delivery are mechanically difficult to manufacture and it is not easy to foretell their long-term mechanical properties because of the inferior mechanical and compression characteristics of the basic materials used in the manufacturing of the drug layers, the elastic disparity of the layers, inadequate hardness, imprecise individual mass control, cross-contamination amongst the layers, decreased yield, and their affinity of delaminating at the interface between the layers throughout and after the different production stages following the compaction process. Thus, the main issue that has to be dealt with is the proper and detailed understanding of the main sources of the issues in both macro and micro scales and the development of effective remedies for their solution during the solid dosage delivery design [48].

Among the main issues are the insufficient adhesion and bonding at the interface between the adjacent compacted layers that are mostly caused by an interfacial crack resulted in residual stresses in the tablet, spreading a finite distance in the tablet and resulting in delamination, or layer-separation, that is not visible instantly after compaction, such as during packaging, storage, or shipping. Moreover, if the compacted layers are excessively hard or soft, they

won't be able to adhere firmly which could result in negotiated mechanical integrity. Some other issues in the development process are the establishment of the layer sequence order, the elastic disparity of the adjacent layers, layer weight ratio, the damping force of the first layer, and cross-contamination between layers [48,49].

If these factors are not controlled, they will somehow affect the bilayer compression per se (uncontrolled or inefficient process) and the quality characteristics of the bilayer tablets, i.e., adequate mechanical strength for maintaining its usefulness and the weight control of the individual layer. Thus, the proper attainment of a detailed understanding of the main causes is important for enabling the design of a robust process and product [50,51]. As the adjacent compacted layers within a bilayer tablet adhere to each other mechanically, the understanding of the things influencing the stress state, the mechanical attributes of every layer and the overall bilayer tablet, and compression parameters, as well as the dedicated methods for predicting failure as a function of compression conditions and layer properties are elemental for the successful development of the bilayer tablets [48,52].

CONCLUSION:

Bilayer tablet is an improved beneficial technology to overcome the shortcoming of the single-layered tablet. There is the various application of the bilayer tablet it consists of monolithic partially coated or multi-layered matrices. Bilayer tablet is suitable and one of the important design approaches where incompatible drugs, with different indications, and same drug with different release rate (e.g. IR and SR) can be incorporated in a single unit in the immediate-release layer as initial dose and Sustained Released layer is maintenance dose. To develop a bilayer tablet a complete mechanistic understanding must be developed through the application of scientific and quality risk management tools. The main purpose of this drug delivery system is to guarantee that the drug is effective and has the least side effects, is properly manufactured keeping in view all GMP parameters to maintain its quality throughout its shelf life. To meet these criteria, different approaches are applied and different presses are used to maximize their efficacy and minimize the side effects. The manufactured tablet is evaluated both physically and chemically to ensure its effectiveness and stability throughout its shelf life. Nowadays different bilayer tablets are produced that have different APIs for combination therapy or the same API to be given in a single unit having both Immediate and Sustained released drug profiles.

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