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A Review of Bilayer Oral Drug Delivery System

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ABSTRACT

Bi-layer tablet is a new era for successful development of controlled release formulation along with various features to provide successful drug delivery. Bi-layer tablets can be primary option to avoid chemical incompatibilities between APIs by physical separation and to enable the development of different drug release profiles. Bi-layer tablet is suitable for sequential release of two drugs in combination and also for sustained release of tablet in which one layer is for immediate release as loading dose and second layer is maintenance dose. So use of bi-layer tablets is a very different aspect for anti-hypertensive, diabetic, anti-inflammatory and analgesic drugs where combination therapy is often used. Several pharmaceutical companies are currently developing bi-layer tablets, for a variety of reasons: patent extension, therapeutic, marketing to name a few. General tablet manufacturing principles remain the same, there is much more to consider because making multi-layer tablets involves multiple often incompatible products, additional equipment and many formulation and operation challenges. The present article provides an introduction to bi-layer tablet technology, challenges in bi-layer tablet manufacturing, various tablet presses used, quality and GMP requirements for their production various techniques used for bi-layer tabletting and recent developments in the field of bi-layer technology.

INTRODUCTION:

Oral dosage forms are the most favored than the other route of administration as there is ease of administration when compared with the others.(1,2) The bi-layer tablet is a concept that is composed of different layers. The system allows the incorporation of more than one drug into the dosage form (3,4). 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 with a bolus and then at a controlled rate or by targeted drug delivery in the GI tract using pH dependent polymers.

Bi-layer tablets have been developed to achieve controlled delivery of different drugs with pre-defined release profiles. In addition, bilayer tablets have enabled the development of controlled delivery of active pharmaceutical ingredients with predetermined release profiles by combining layers with various release patterns, or by combining slow-release with immediate-release layers(4).

Multi-layer tablet dosage forms were designed for a variety of reasons; to control the delivery rate of either single or two different active pharmaceutical ingredients (API), to separate incompatible 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), to modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release, to administer fixed dose combinations of different APIs, prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device, buccal/mucoadhesive delivery systems, and floating tablets for gastro-retentive drug delivery(2).

CHALLENGES INVOLVED IN MANUFACTURING OF BILAYER TABLET:

Challenges during the development of bilayer tablets might include inadequate hardness, the order of layer sequence, layer weight ratio, and elastic mismatch of the adjacent layers, first layer tamping force and cross contamination between layers. If these elements are not adequately regulated in some way, they will have an adverse effect on bi-layer compression pressure, as well as qualitative characteristics such as mechanical strength and individual layer weight control. Therefore, care must be taken to enable design of a vigorous product and process (5, 6). Bilayer tablets can be thought of as two single-layer tablets compacted into one but in practicality there are several manufacturing problems associated.

MANUFACTURING PROCESS

Manufacturing processes such as wet granulation/roller compaction and addition of binders increases the level of complexity in understanding the critical factors governing compression and tablet breaking force.(7) Thus, the tablet breaking force and the tablet's propensity for de-lamination/capping either during manufacturing or during storage need to be carefully observed. Apart from the critical material attributes of individual components and final blend, the tablet press has a large influence on the manufacture of multilayer tablets. Bilayer tablets are composed of two layers of granulation compressed together. (8) They have appearance of a sandwich because the edges of each layer are exposed. They have the appearance of a sandwich because the edges of each layer are exposed. Bi-layer tablets are prepared with onelayer of drug for immediate release with a second layer design to release drug, later, either as second dose or in an extended-release manner(9).

TECHNIQUES FOR BILAYER TABLET

OROS® PUSH PULL TECHNOLOGY:

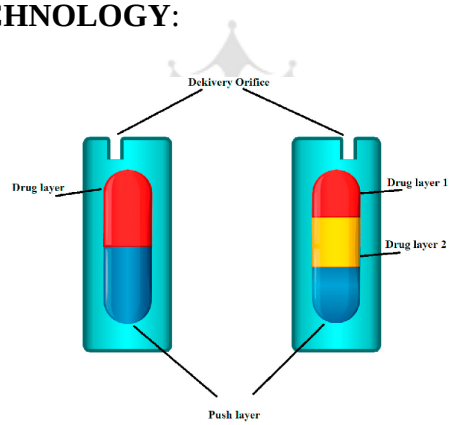

Figure 1: OROS® Push Pull Technology

This system consist of mainly two or three layers among which one or more layers are essential of the drug and other layers are consist of push layer. The drug layer mainly consists of drug along with two or more different agents as shown in figure 1(10,11) So this drug layer comprises of drug which is in poorly soluble form.(12,13) There is further addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core.(14,15)

L – OROS TM TECHNOLOGY:

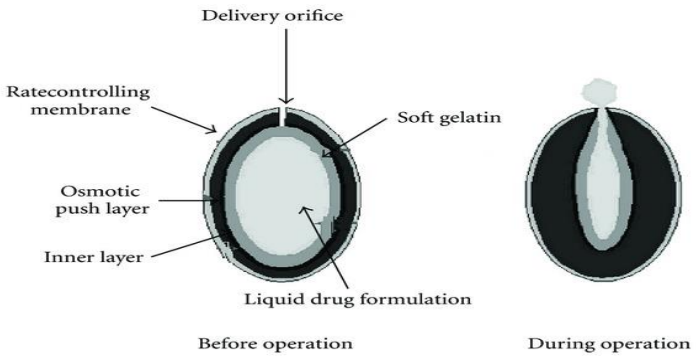

Figure 2: L – OROS TM Technology

This system used for the solubility issue Alza developed the L-OROS system where a lipid soft gel product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, than osmotic push layer and than a semi permeable membrane, drilled with an exit orifice as given in figure 2 (16,17).

BILAYER AND TRILAYER OROS PUSH PULL TECHNOLOGY:

L-OROS tm technology This system used for the solubility issue Alza developed the L-OROS system where a lipid soft gel product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, then osmotic push layer and then a semi permeable membrane, drilled with an exit orifice.(18,19)

DUROS TECHNOLOGY:

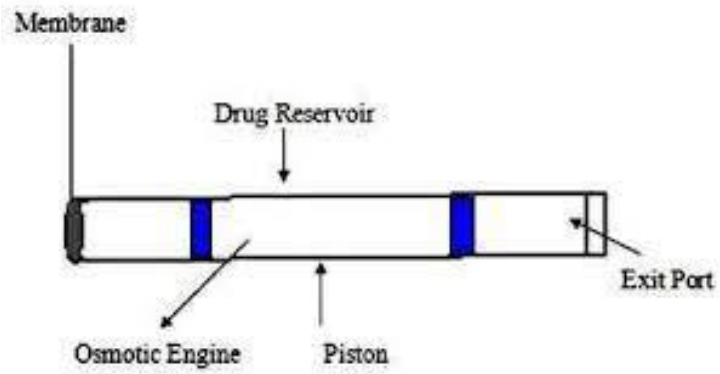

Figure 3: Duros Technology

DUROS (Alza Corporation) is based on implant technology,which provides an alternative for the delivery of a wide range of therapeutic compounds, including peptides, proteins, and other bioactive macromolecules as shown in figure 3 (20,21).

DUREDAS™

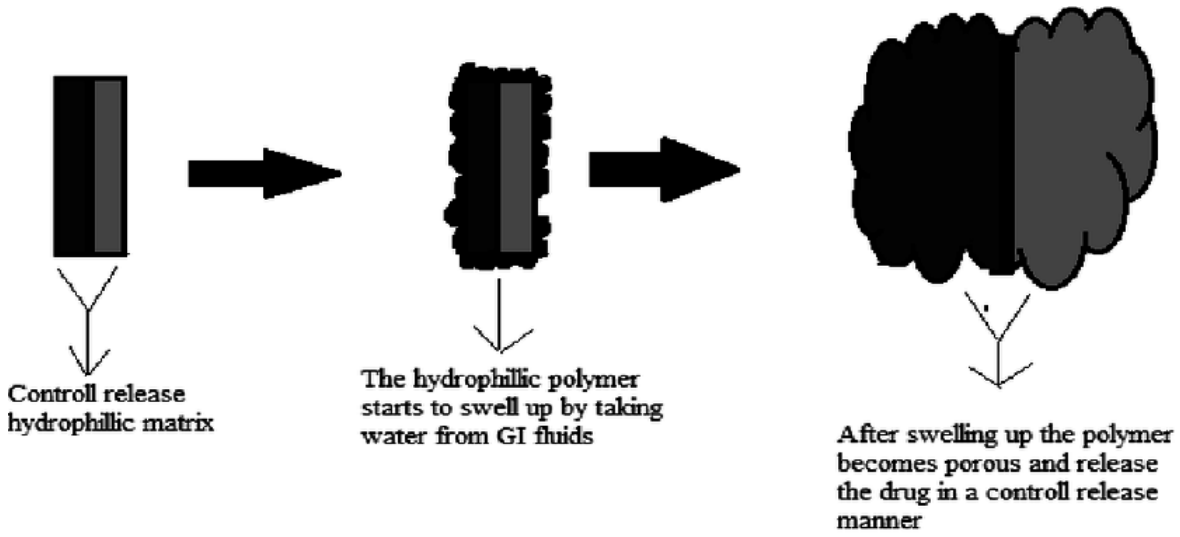

Figure 4: DUREDAS Technology (22)

Technology This system is also known as Elan drug technologies' Dual release drug delivery system. DUREDAS™ Technology is a bilayer tablet that can provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form as given in figure 4. (23,24) The tableting process can provide an immediate release granulate and a modified release hydrophilic matrix complex as separate layers within one tablet. The modified-release properties of the dosage form are provided by a combination of hydrophilic polymers.(25)

BILAYER TABLET CHARACTERIZATION:

It is one of the most important areas which should not be ignored in any case while discussing the bilayer tablets.(26,27) While it is theoretically preferable to have a material that can be compressed without deformation and compact on its own when compressed, resulting in a stronger bond between the two layers of a bilayer tablet, there are other factors that influence the formation of the desired quality of bilayer tablets (28). Particle size distribution, angle of response, photomicroscopic examination, density, compressibility, and moisture sorption capacity are all included in characterization.(29,30)

The following are some of the advantages of bilayer tablet characterization in early formulation development: (31)

(i) Determination of the interfacial strength of bilayer tablets using quantitative methods.

(ii) Unusual or severe characteristics of compacted layers must be detected.

(iii) Ensure that the bilayer tablets produced are consistent from batch to batch.

(iv) To create a rationale strategy in order to guide formulation development and the selection of suitable product formulations and manufacturing process.

(v) Explain material failure mechanisms during tablet manufacturing.

(vi) Understand the effect of the factors specific to tableting equipment (e.g., speed of operation, applied forces, etc.).

(vii) Reduction in energy utilization by minimization of faulty tablet production.

(viii) Environmental issues and concerns related to the waste management of materials.

CONCLUSION:

Bi-layer tablets offer one of the most significant design methods is to combine incompatible drugs with various indications and the same drug with varied release rates in a single unit. The bilayer tablet is an upgraded technology that overcomes the limitations of single-layered tablets. Bilayer and monolayer tablet production share several common features of technology as both of these pharmaceutical formulations are prepared by compacting powdered/ granulated API with or without excipients. Multi-layer tablets have many key benefits compared to conventional immediate-release monolayer tablets. Recently, significant advancement in the manufacturing of tablets has been achieved. This has contributed to the improvement of the physicochemical properties of tablets, as well as the possibility of producing tablets with modified/controlled release. However, there are nevertheless, a number of technological obstacles that need to be overcome in order to achieve a multilayer tablet with parallel levels of reliability as found in monolayer tablets. A key source of design and manufacturing problems of the multilayer tablets is heterogeneity of adjacent layers. Fluctuations of even one of the compression parameters (e.g. the compression strength, ratio of the layers, arrangement of layers, the used excipients) can significantly have an effect on the properties of each layer and the interfacial strength. However, considering the different

parameters of the manufacturing process of multi-layer tablets, it is possible to attain the desired release profile. Bilayer formulations are convenient dosage forms, safe and possess greater advantages to both patient and clinician that it may be administered as a single tablet once a day.

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