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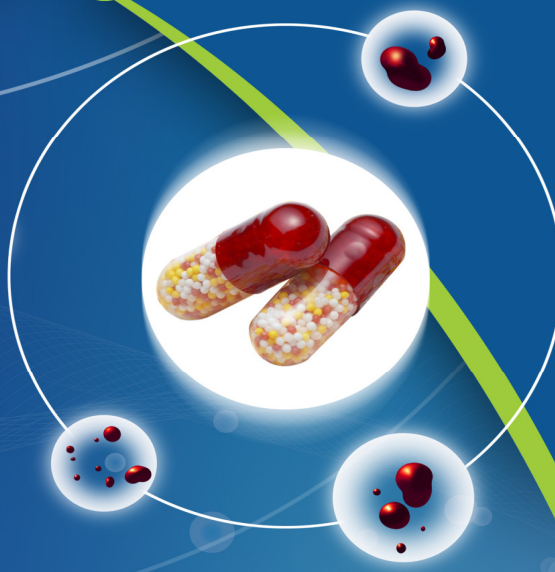

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Review Article

REVIEW ON: BILAYER FLOATING TABLET

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ABSTRACT

Bi-layer tablets have been developed to achieve controlled delivery of different drugs with pre-defined release profiles. In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bilayer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance. Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles (immediate release with extended release). Despite their advantages, due to the use of different materials and complex geometric boundaries between the adjacent layers, the mechanical structures of this drug delivery system have become quite intricate, requiring complicated tablet architectures as well as patient-friendly. GRDDS prolongs the retention time of dosage forms in the stomach or upper gastrointestinal tract, as to improve solubility, bioavailability and the therapeutic efficacy of the drugs. Several pharmaceutical companies are currently developing bi-layer tablets. For a variety of reasons: patent extension, therapeutic, marketing to name a few. To reduce capital investment, quite often existing but modified tablet presses are used to develop and produce such tablets. . This review is an attempt to illustrate the application of Bilayer tablet by releasing the medicaments immediately for patient relief and also maintaining the therapeutic level to a extended period of time by controlling the release of drug in a sustained manner for better patient compliance and acceptability.

KEY WORDS*: - Bilayer tablet, Biphasic drug delivery, Fast release layer, Sustained release layer*

INTRODUCTION

From the last few years, there are some pharmaceuticals companies developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (Bilayer tablet), promoting patient convenience and compliance. Bilayer tablets can be use to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles (immediate release with extended release). Despite their advantages, due to the use of different materials and complex geometric boundaries between the adjacent layers, the mechanical structures of this drug delivery system have become quite intricate, requiring complicated tablet architectures as well as patient-friendly administration which pose serious challenges to the pharmaceutical scientists/engineers. This oral presentation details the major challenges associated with Bilayer compression and rational strategy to deliver the desired Bilayer tablet performance. Bilayer tablet have some key advantages compared to conventional monolayer tablet. In addition Bilayer tablet have enabled the development of controlled delivery of API with predetermined release profile by combining

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layers with various release patterns or by combining slow release with immediate-release layers. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustain release tablet, in which one layer is immediate release as a initial dose and second layer is maintenance dose. [1, 2, 3]

Need of Bilayer tablet

- Multi-layer tablet dosage forms are designed for variety of reasons:
- To control the delivery rate of either single or two different active pharmaceutical ingredients.
- To separate incompatible Active pharmaceutical ingredient (APIs) from each other, to control the release of API from one layer by utilizing the functional property of the other layer (Example- 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. [4, 5, 6, 7, 8, 9]

Advantages of Bilayer tablet

Before explaining the advantages of Bilayer tablet, here are the advantages of the tablet dosage form over the dosage form are as follows:

- Tablet is a unit dosage form and they offer the greatest compatibilities of all oral dosage forms for the greatest dose precision and the least content variability.
- The cost is approximately lower than any other oral dosage form.
- These are very compact in nature.
- In genera the packaging procedure for tablets are easier and cheaper.
- Swallowing of tablets is very easy.
- They are better suited to large scale production.
- Chemically, mechanically and microbiologically tablets are very stable.

The advantages of the 'Bilayer tablet' over the other conventional preparations of oral solid dosage forms include:

- When the two different layers of the tablet content two different drugs, then the tablet can be easily used in combination therapy.
- This formulation can be use to deliver separate two incompatible substance.
- In case of drags 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.
- Frequency of the dose administration is reduced which ultimately improve the patient compliance.
- In case of a conventional dosage form due to fluctuation of the dose interval the plasma drug concentration may differ (under medication or over medication), but in this dosage form the plasma drug concentration is always constant, which ultimately provide a more effective action of the drug.
- Better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of high availability drug can be reduced by formulation in an extended action form. The safety margin of high potency drugs can be increased and the local and systemic adverse effects can be reduced in sensitive patients.

Limitations of Bilayer tablet

From the above mentioned advantage of Bilayer tablets it is quite clear that in pharmaceutical industry it is a great revolution, but there are certain limitations in the formulation and use of Bilayer tablets, such as:

- One of the major challenges in Bilayer formulation is 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.

- If the compacted layers are too soft or too hard, they will not bind securely with each other which can lead to compromised mechanical integrity and also the separation of the layers.
- Other challenges during development include establishing the order of layer sequence, layer weight ratio, elastic mismatch of the adjacent layers, first layer tamping force, and cross contamination between layers.
- The adjacent layers of a Bilayer tablet are bonded together by mechanical means, so the factors influences the stress state is very important. The mechanical properties of each layer and the tablet, and compression parameters along with specialized techniques and compression condition plays a very important role for the same.
- Administration of sustained release Bilayer tablet does not permit the prompt termination of therapy.
- The physician has a less flexibility on adjusting the dose regimens.[10]

The major requirements for floating drug delivery system

- It should release contents slowly to serve as reservoir.
- It must maintain specific gravity lower than gastric contents (1.004 – 1.01 gm/cm3).
- It must form a cohesive gel barrier.[11]

General properties of Bilayer tablet dosage forms

- A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration, and contamination.

- Should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
- Should have the chemical and physical stability to maintain its physical attributes over time. The bi-layer tablet must be able to release the medicinal agents in a predictable and reproducible manner.
- Must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

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. Thus, the tablet breaking force and the tablet's propensity for delamination/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 large influence on the manufacture of multilayer tablets. The level of pre-compression force, punch velocity, consolidation time (time when punches are changing their vertical position in reference to the rolls as the distance between the punch tips are decreased), dwell time (time when punches are not changing their vertical position in reference to the rolls), relaxation time (time when both punches are changing their vertical position in reference to the rolls as the distance between the punch tips increases before losing contact with the rolls), and the applied force can have significant effect on the critical quality attributes of the tablet. For instance, the extent of compact densification and resistance to compressibility within the die cavity was impacted by compaction pressure and the punch velocity. It was demonstrated that increase in the punch velocity between of 50 and 500mm/s decreased the porosity reduction on individual layers. [12]

Drug release mechanism

Normally the drug release from hydrophilic swellable matrices depends on the polymer macromolecular coupling, relaxation and the drug diffusion and all of these are responsible on the rate at which water may penetrate into the device. Hydration rate, swelling of the polymer and modification of the polymer matrix are the basics for the multilayered drug delivery design. These factors are very effective at the primary or initial phase of the drug dissolution but with the respect of time as swelling proceeds linearization of the release profile occurs. To

achieve this objective, coating of the matrix tablets with an inert impermeable film has been performed. Coating plays a very important role in the drug release from the multilayered preparations and a number of combinations of coating materials are used that is schematically represented by Figure 3. The release rate of the drug from tablets is observed by *in vitro* release rate study. The release rate of the drug is inversely proportional to the extent of coating. The release of the drug is primarily dependant on the swelling of the polymer which is again controlled by reducing the drug release surface by the coating material.

When a tablet is coated partially, it does not swell and retain its initial size and shape and maintain the release retardation continuously through the entire dissolution process. On the other hand, when the tablet is subjected to water immersion the polymer barrier which is inert in nature have a tendency to crack and separated out from the core within hours. This effect is resulted from volume expansion of core upon water immersion due to polymer swelling. The outer barrier layer does not expand while the core is swelling as a result a stress is generated in the outer barrier layer. When the outer barrier is sellable polymer then the both barrier and core swell simultaneously without any internal stress during the dissolution process. Multilayer compression process can be used for the application of barriers. One notable example of this phenomena is the double layer or three layer tablets in which only one layer contains the active ingredient (active core), while other layers are barrier layers.[13]

The multi-layer design allows for the production of different tablet designs by varying the geometry of the device or modulating layers characterized by specific release properties to achieve various dissolution patterns (not limited to a constant release) such as delayed, pulsatile or multi modal delivery profiles. The section below deals with various tablet possibilities based on this proposed design. [13]

Various techniques for Bilayer tablet

Osmotic-controlled release oral delivery system

In this technology the system is consist of mainly two or three layer among which one or more layer are of the drug and other layers are consist of push layer. The drug layer mainly consists of poorly soluble drug along with diluents, low molecular weight polymer, suspending agent and osmotic agent. The push layer is constructed of a higher molecular weight osmopolymer and an osmagent. A semi permeable membrane surrounds the tablet core. In this technology the medication is sandwiched with an osmotic agent that swells when it takes up water. The sandwich is then coated with a semi permeable membrane .Then a laser is used to drill a tiny hole through the membrane. In the stomach, water passes through the membrane into the pill, causing the osmotic material to swell, which pushes the drug out of the hole. This delivers the drug to the body at a constant rate instead of all at once, as happens when a traditional pill dissolves. Products manufactured using this technology are Glucotrol Xl and procardia XL both of which are composed of a bilayer tablet core and Concerta is compose of a trilayer tablet core.

Elan drug technology (DUREDUS technology)

DUREDAS or Dual Release Drug Absorption System (Elan Corporation) utilizes Bilayer-tabletting technology, which has been specifically developed to provide two different release rates or dual release of a drug from a single dosage form. The tablets are prepared by two separate direct-compression steps that combine an immediate-release granulate (for rapid onset of action) and a controlled-release hydrophilic matrix complex within one tablet. The immediate release layer, release the drug immediately after going into the GIT (stomach or intestine) in a diffusion and dissolution manner and the controlled-release matrix remains intact and slowly absorbs fluid from the GI tract, which causes the matrix to expand and transforms the hydrophilic polymers into a porous, viscous gel that serves as a barrier between the drug and the surrounding fluid. As the gel continues to expand, fluid penetrates further into the dosage form, dissolving the drug and allowing the resulting solution to diffuse out in a controlled manner. A further extension of the Duredus technology is the production of controlled-release combination dosage forms whereby two different drugs are incorporated into the different layers, and the drug release of each is controlled to maximize therapeutic effect

of the combination. Again both immediate release and controlled release combinations of the two drugs are feasible. The DUREDAS™ technology was initially employed in the development of a number of over the counter controlled release analgesics. [14]

Evaluation of Bilayer floating tablet

Weight variation test

Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variations allowed in the weight of a tablet by USP. The following percentage deviation in weight variation is allowed. In all formulations, the tablet weight was more than 324 mg, hence 5% maximum difference allowed.

Thickness

The thickness of the tablets was determined by using micrometer meter screw gauze. Five tablets from each formulation were used, average values and standard deviation were calculated.

Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of (kg/cm²) tablet was determined by using Monsanto tester. In all the cases, mean of five replicate determinations were taken.

Friability test

As per IP, this was determined by weighing 26 tablets after dusting, placing them in the Roche friabilator and rotating the plastic cylinder vertically at 25 rpm for 4 min. After dusting, the total remaining weight of the tablets was recorded and the percent friability was calculated according to following equation.

% Friability = Initial wt of tablets – Final wt of tablets / Initial wt of tablets × 100

% Friability of tablets less than 1% are considered acceptable.

In vitro buoyancy study

The time between introduction of dosage form and its buoyancy on the SGF and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TET). Floating behavior study were carried out in a USP XXIII dissolution

Apparatus type II (Paddle) at a speed 50 RPM in 900 ml SGF at 37±0.50C for 12 hr to mimic *in vivo* conditions.

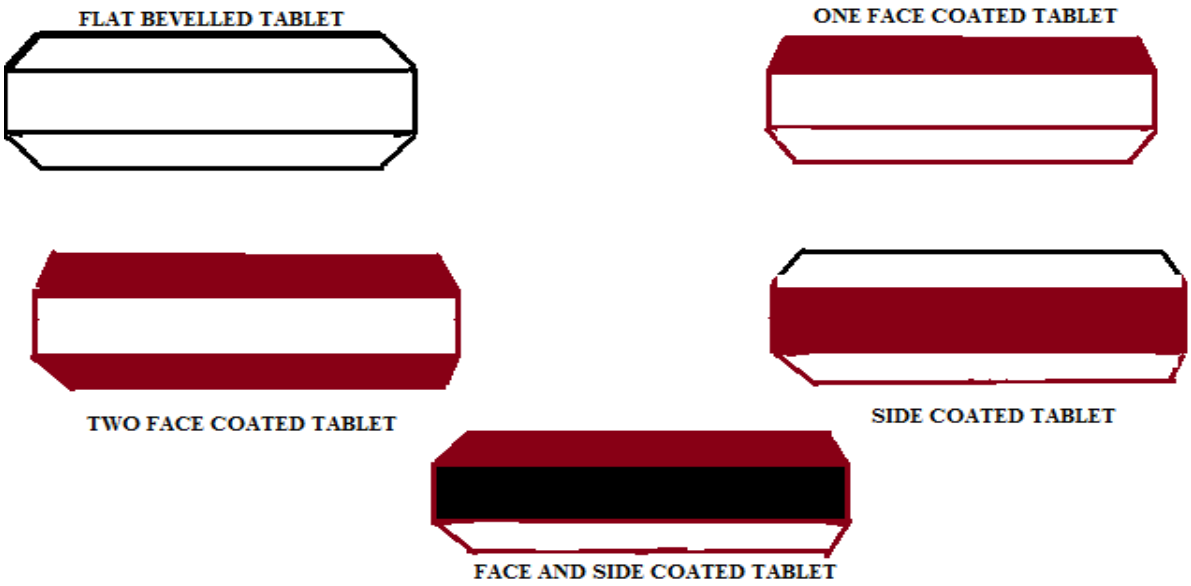

Figure 1: Schematic representation of the matrix tablet (a) and of the four partially Coated designs

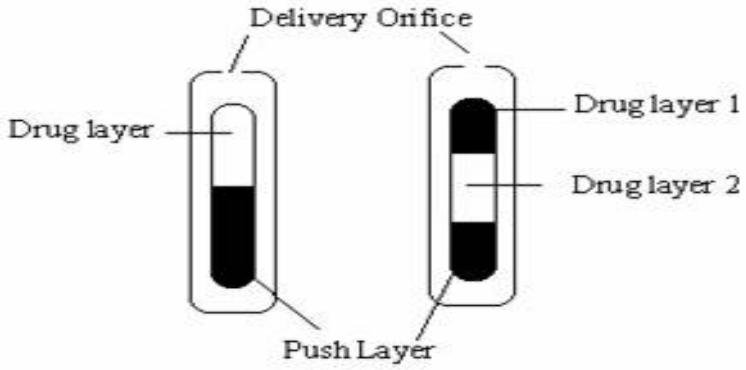

Figure 2: Preparation of bilayer and trilayer tablet by OROS push

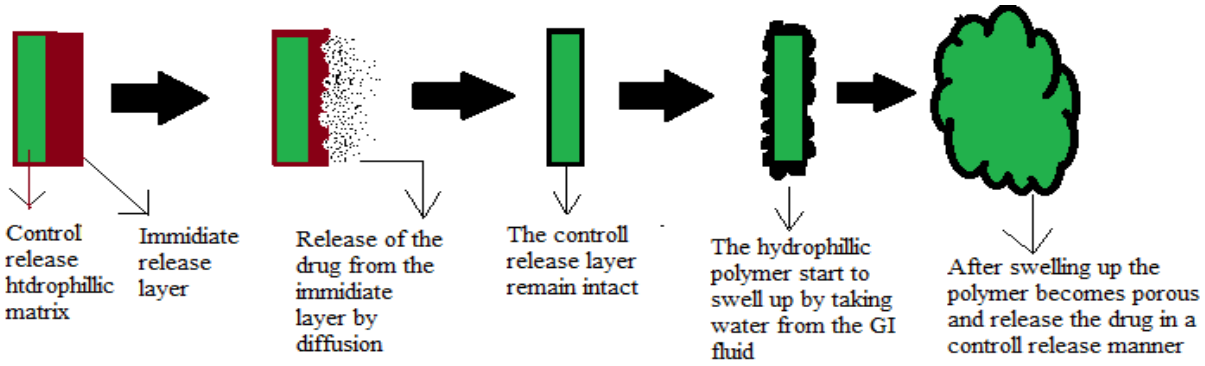

Figure 3: DUREDAS technology consists of control release and immediate release layer.

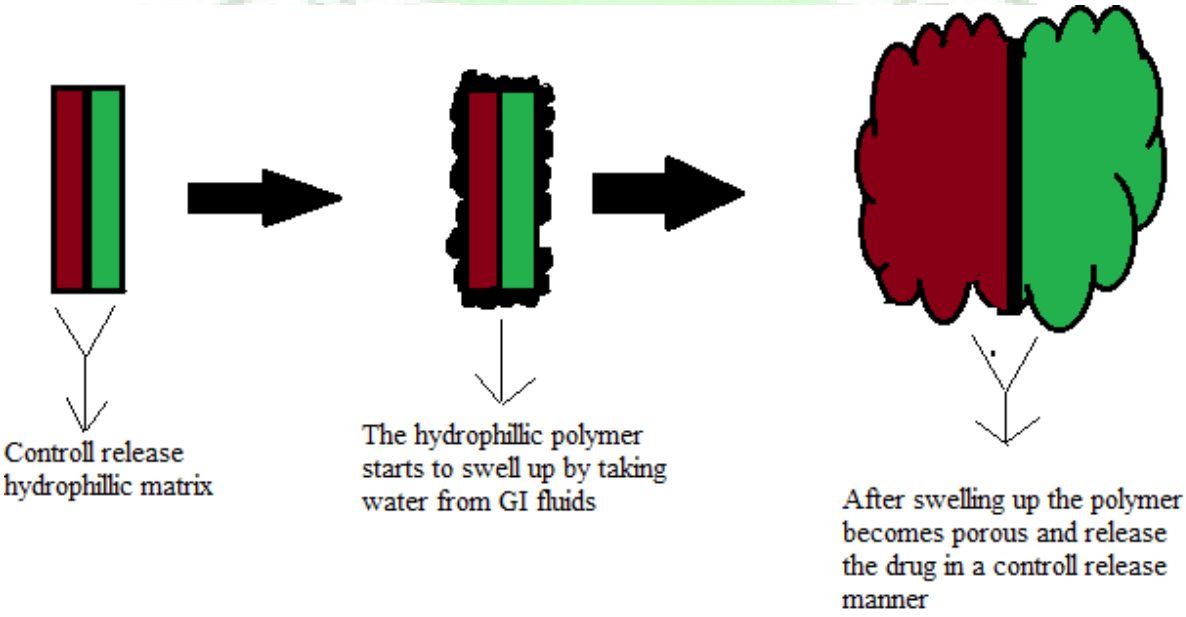

Figure 4: DUREDAS technology consist of two control release layers.

Content uniformity

Ten tablets were finely powdered, quantities of the powder equivalent to 50 mg of API were accurately weighed and transferred to a 100 ml of volumetric flask containing methanol and mixed thoroughly. The solution was made up to volume and filtered. Appropriate dilutions were done using methanol and absorbance of the resulting solution was measured at the maximum at 271 nm using a UV spectrophotometer.

Swelling Index

The individual tablets were weighted accurately and kept in 50 ml of 0.1 N HCl. Tablets were taken out carefully after each hour upto 12 hours, blotted with filter paper to remove the water present on the surface and weighed accurately. Percentage swelling (swelling index) was calculated by using following formula.

Swelling index = (Wet weight of tablet – Dry weight of tablet) / Dry weight of tablet × 100

In vitro dissolution study

In vitro dissolution study was performed for the prepared tablet formulations. The following conditions were maintained for the dissolution process:

Instrument: TDT-06T Veego VDA-63 USP Standards
Apparatus: IP Type-I paddle apparatus
Temperature: 37 ± 0.50C
RPM: 50
Sample: BILAYER FLOATING TABLET
Dissolution medium: 0.1 N HCL
Volume of medium: 900 ml
Sampling interval : 15 min, 30 min, 45 min, 1 hr, 2 hr, 3 hr,……, 12 hr

Sample volume: 10 ml withdrawn and replaced with 10 ml of fresh 0.1 N HCL10 ml of the sample withdrawn was filtered through what Mann filter paper. Appropriate dilutions were made to get the absorbance in linearity range of medium. The absorbance of the samples was determined at wavelength of 271 nm by using UV spectrophotometer against 0.1 N HCL as a blank. The amount of drug present in the filtrate was calculated from the calibration curve equation and cumulative percent of drug release was calculated. [15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25]

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