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REVIEW ARTICLE

A REVIEW ON BI-LAYER TABLETS - AN EMERGING TREND

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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. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose. 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). There is various application of the bilayer tablet it consist of monolithic partially coated or multilayered matrices.

Keywords: Bilayer Tablets, Immediate release, Chemical incompatibilities

INTRODUCTION

Bi-layer tablets have been developed to achieve controlled delivery of different drugs with pre-defined release profiles. Bi-layer 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.

The most common controlled delivery system has been the matrix type such as tablets and granules where the drug is uniformly dissolved or dispersed throughout the polymer, because of its effectiveness, low cost, ease of manufacturing and prolonged delivery time period[1,2]. Bi-layer tablets have some key advantages compared to conventional monolayer tablets. For instance, such tablets are commonly used to avoid chemical incompatibilities of formulation components by physical separation.

The bi-layer tablet is a concept which 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 dependant polymers[5].

MULTI-LAYER TABLET DOSAGE FORMS ARE DESIGNED FOR VARIETY OF REASONS-

- To control the delivery rate of either single [6] or two different active pharmaceutical ingredient(s)[7,8].
- To control the delivery rate of either single or two different active pharmaceutical ingredient(s).
- 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 (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.
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ADVANTAGES OF THE BI-LAYER TABLET

- Bi-Layer execution with optional single-layer conversion kit.
- Cost is lower compared to all other oral dosage form.
- Greatest chemical and microbial stability over all oral dosage form.
- Objectionable odor and bitter taste can be masked by coating technique.
- Flexible Concept.

DISADVANTAGES OF BI-LAYER TABLET DOSAGE FORM ARE

- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
- Bitter testing drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating.
- Difficult to swallow in case of children and unconscious patients.
- Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.

GENERAL PROPERTIES OF BI-LAYER 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 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 large influence on the manufacture of multilayer tablets. Bilayer tablets are composed of two layers of granulation compressed together. 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 second layer design to release drug, later, either as second dose or in an extended release manner[9].

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. 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. 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.

VARIOUS TECHNIQUES FOR BILAYER TABLET

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. So this drug layer comprises of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core[10].

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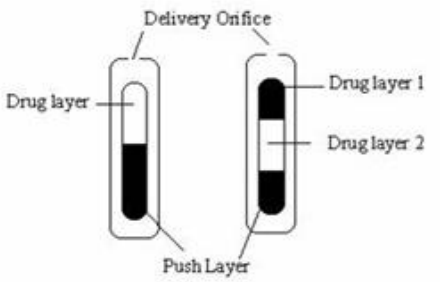

Figure 1: Oros® Push Pull Technology

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[11].

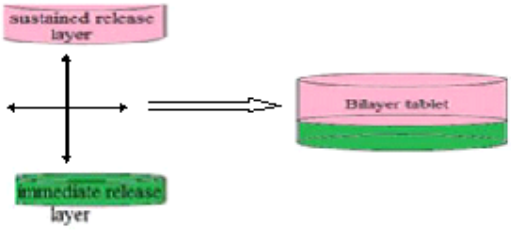

Figure 2: Bi-layer And Trilayer Oros Push Pull Technology

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, than osmotic push layer and than a semi permeable membrane, drilled with an exit orifice[12].

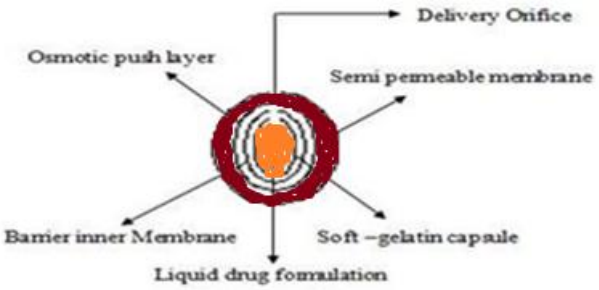

Figure 3: L – Oros Tm Technology

EN SO TROL TECHNOLOGY

Solubility enhancement of an order of magnitude or to create optimized dosage form Shire laboratory use an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies[13].

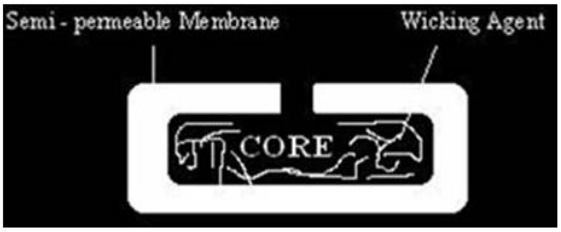

Figure 4: En So Trol Technology

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[14].

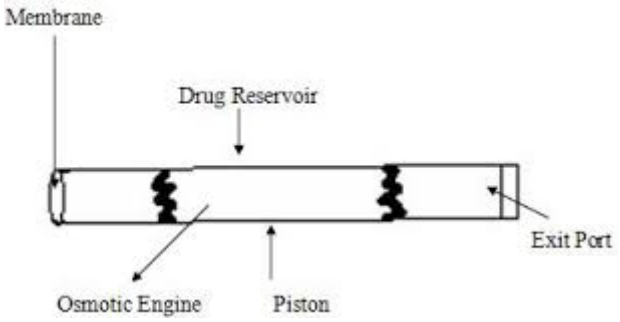

Figure 5: Duros Technology

VARIOUS ASPECTS OF BILAYER TABLET

- **FLOATING DRUG DELIVERY SYSTEMS (FDDS) [15,16]**

From the formulation and technological point of view, the floating drug delivery systems are considerably easy and logical approach in the development of Gastro retentive dosage forms (GRDFs).

- **APPROACHES TO DESIGN FLOATING DRUG DELIVERY SYSTEM**

The following approaches have been used for the design of floating dosage forms of singleand multiple-unit systems.

- **INTRA GASTRIC BILAYERED FLOATING TABLETS**

These are also compressed tablet as shown in figure and contain two layers i.e.

- Immediate release layer and
- Sustained release layer.

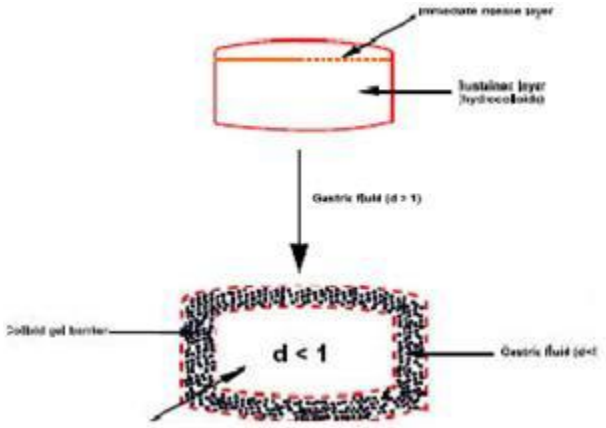

Figure 6: Intra Gastric Bilayered Floating Tablets

❖ MULTIPLE UNIT TYPE FLOATING PILL

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density.

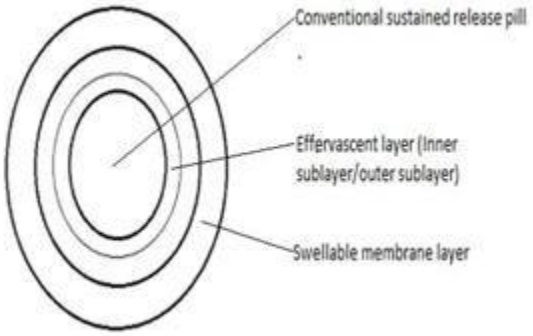

Figure 7: Multiple Unit Type Floating Pill

EVALUATION OF BI-LAYER TABLETS

- Thickness
- Hardness
- Size and shape
- Uniformity of weight
- Friability
- Wetting time
- Water absorption ratio
- Dissolution study

Thickness-

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter was measured using venire calliper[17].

Hardness-

The limit of hardness of MDT is usually kept in lower range to facilitate early disintegration in mouth. The hardness of MDTS may be measured using hardness tester (Monsanto Hardness tester). It is expressed in kg or pound[18].

Size and shape-

Size and shape of the tablet can be dimensionally described, monitored and controlled.

Uniformity of weight-

Weight variation test is done as per standard procedure. Ten tablets from each formulation are weighed using an electronic balance and the average weigh are calculated.

Friability-

Friability is the measure of tablet strength. 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. % loss = [(Initial wt. of tablets – Final wt. of tablets)/ Initial wt. of tablets] ×100[19].

Wetting time-

Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. Ten millimeters of water-containing Eosin, a water-soluble dye, is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time[20].

Water Absorption Ratio-

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper & the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio (R), was determined using following equation,

$R = 10 (Wa /Wb)$

Where- Wb is weight of tablet before water absorption & Wa is weight of tablet after water absorption[21].

DISSOLUTION STUDY-

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 (900 ml) and 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 multi component mode of analysis[22].

COMMERCIALLY MARKETED BI-LAYER TABLETS

Product Name	Chemical Name	Developer
Glycomet®-GP2Forte	Metformin hydrochloride, Glimepiride	USV Limited
ALPRAX PLUS	Sertraline, Alprazolam	Torrent Pharmaceutcals Ltd.
DIAMICRON®XRMEX500	Gliclazide, Metformin hydrochloride	Sedia® Pharmaceuticals (India) Pvt. Ltd.
Newcold Plus	Levocetrizine hydrochloride, Phenylpropanolamine, Paracetamol	Piramol Healthcare Ltd.
TRIOMUNE 30	Nevirapine, Lamivudine, Stavudine	Cipla Ltd.
DIUCONTIN-K®20/250	Furosemide, Potassium chloride	T.C. Health Care Pvt. Ltd.
Tribet-1	Glimepiride, Pioglitazone hydrochloride, Metformin HCl	Abbott Healthcare Pvt. Ltd.
PIOKIND®-M15	Pioglitazone, Metformin HCl	Psychotropics India Ltd.
Revelol®-Am 25/5	Metoprolol succinate, Amlodipine besilate	Ipca Laboratories Ltd.

CONCLUSION

Bi-layer tablet is improved beneficial technology to overcome the shortcoming of the single tablet. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second is maintenance dose. The preparation of tablets in the form of multi layers is used to provide systems for the administration of drugs, which are incompatible and to provide controlled release tablet preparations by providing surrounding or multiple swelling layers.

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