EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 2
Issue: 6
92-98
Year: 2015

BI LAYER TABLET

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Article Received on 04/09/2015 **Article Revised on 24/09/2015** **Article Accepted on 14/10/2015**

ABSTRACT
Tablets are the most convenient and mostly preferred for drug administration as compared to the other techniques by the patients since a long duration of time. With the increase in time various modifications in the doses forms were made. Bi layer tablets are the new era drug that is developed for control release formulation. Bi layer dosage form has two different incompatible drugs in a single unit dosage form with different release pattern.

KEY WORDS: Tablets are the most convenient and mostly preferred for drug.

INTRODUCTION

The goal of drug delivery system is to provide a therapeutic amount of drug to a proper site in the body to achieve and maintain the desired drug concentration. That is the drug delivery system should delivery drug at a rate dictated by the needs of the body over a specified period of treatment. Delivery of drug by idealized objectives is divided into two drug delivery system-

1. Spatial placement
2. Temporal drug delivery

Spatial placement -relates to targeting a drug to a specific organ or tissues Temporal drug delivery -relates to controlling the rate of drug delivery to the target tissues. Sustained release, sustained action, controlled release, extended action, timed release dosage forms are the terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after the administration of single dose. The term "Controlled release" has become associated with those systems from which therapeutic agents may be automatically delivered at predefined rates over a long period of time. Based on the technical sophistication of the controlled-release drug delivery systems (**CrDDSs**) can be classified as follows-

I. Rate preprogrammed drug delivery system
II. Activation-modulated drug delivery system
III. Feedback-regulated drug delivery system
IV. Site targeting drug delivery system.

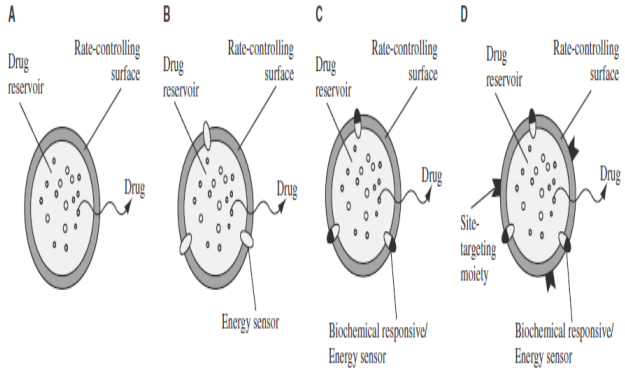

Fig 1: Four major classes of drug delivery system (A) Rate Pre-Program DDS, (B) Activation modulated DDS, (C) Feed Back Regulated DDS, (D) Site Targeting DDS.

Rate-Preprogrammed Drug delivery Systems[1]

In this group of CrDDSs, the release of drug molecules from the delivery systems has been preprogrammed at a specific rate profile. This is accomplished by system design, which controls the molecular diffusion of drug molecules in and/or across the barrier medium within or surrounding the delivery system. Fick's laws of diffusion are often followed. These CrDDSs can further be classified as follows:

1. Polymer membrane permeation-controlled drug delivery systems.
2. Polymer matrix diffusion-controlled drug delivery systems.
3. Polymer (membrane/matrix) hybrid-type drug delivery systems.
4. Micro reservoir partition-controlled drug delivery systems.

- **Polymer Membrane Permeation-Controlled Drug Delivery Systems**

In this type of CrDDS, a drug formulation is either totally or partially encapsulated in a drug reservoir compartment whose drug-releasing surface is covered by a rate-controlling polymeric membrane. The drug reservoir can be drug solid particles, a dispersion of drug solid particles, or a concentrated drug solution in a liquid- or solid-type dispersing medium. The polymeric membrane can be fabricated from a homogeneous or a heterogeneous non-porous polymeric material or a microporous or semipermeable membrane. The encapsulation of drug formulation inside the reservoir compartment can be accomplished by molding, capsulation, microencapsulation, or other techniques. Different shapes and sizes of drug delivery systems can be fabricated.

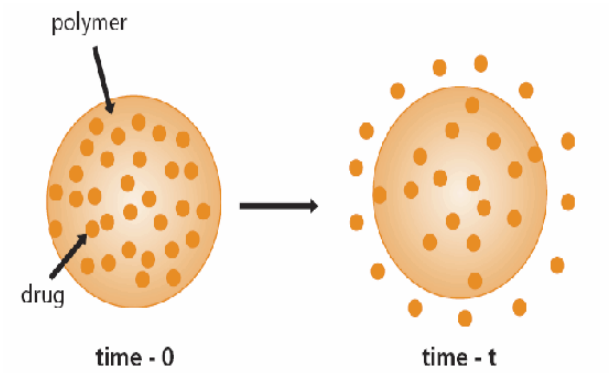

Fig 2: Polymer Membrane Permeation-Controlled Drug Delivery Systems.

- **Polymer Matrix Diffusion-Controlled Drug Delivery Systems**

In this type of CrDDS, the drug reservoir is produced from the homogeneous dispersion of drug particles in either a lipophilic or a hydrophilic polymer matrix. The drug dispersion in the polymer matrix is accomplished by either 1) Blending a dose of finely ground drug particles with a viscous liquid (or a semisolid) polymer, followed by a cross linking of polymer chains.

2) Mixing drug solids with a melted polymer at an elevated temperature. The resultant drug-polymer dispersion is then molded or extruded to form drug delivery devices of various shapes and sizes designed for a specific application.

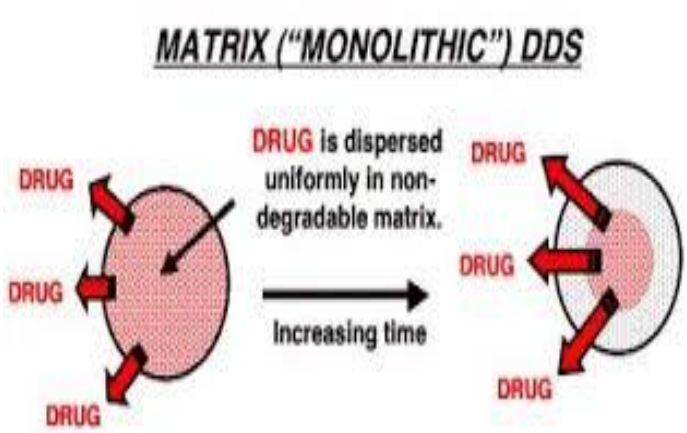

Fig 3: Polymer Matrix Diffusion-Controlled Drug Delivery Systems.

- **Polymer (Membrane/Matrix) Hybrid-Type Drug Delivery Systems**

This type of CrDDS is developed with the objective of combining the constant drug release kinetics of polymer membrane permeation-controlled drug delivery systems with the mechanical superiority of polymer matrix diffusion-controlled drug delivery systems.

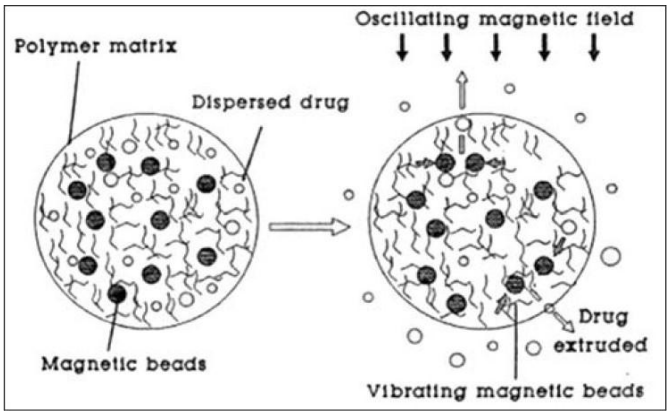

Fig 4: Polymer (Membrane/Matrix) Hybrid-Type Drug Delivery Systems.

- **Micro reservoir Partition-Controlled Drug Delivery Systems**

In this type of CrDDS, the drug reservoir is a suspension of drug solid particles in an aqueous solution of a water-miscible polymer, like polyethylene glycols. This forms a homogeneous dispersion of many discrete, microscopic drug reservoirs in a biocompatible polymer, like silicone elastomers. The micro-dispersion is achieved by applying a high-energy dispersion technique. Different shapes and sizes of drug-delivery devices can be fabricated from this microreservoir-type CrDDS by molding or extrusion techniques. Depending upon the physicochemical properties of drugs and the desired rate of drug release, the device can be further coated with a layer of biocompatible polymer to modify the mechanism and the rate of drug release.

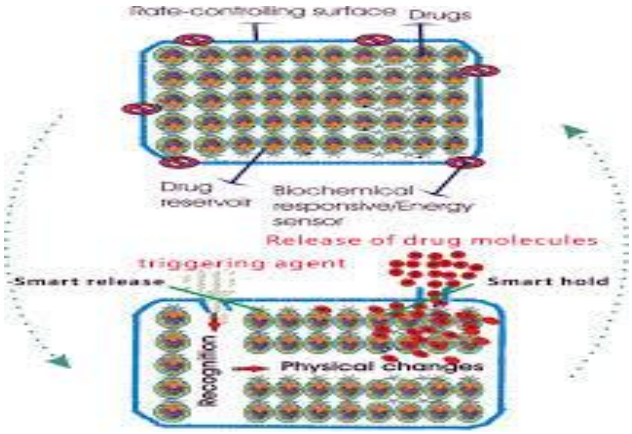

Fig 5: Micro reservoir Partition-Controlled Drug Delivery System.

Activation-Modulated Drug Delivery Systems

In this group of CrDDSs, the release of drug molecules from the delivery systems is activated by some physical, chemical, or biochemical processes and/or facilitated by an energy supplied externally. The rate of drug release is then controlled by regulating the process applied or energy input.

Feedback-Regulated Drug Delivery Systems

In this group of CrDDSs, the release of drug molecules is activated by a triggering agent, such as a biochemical substance, in the body via some feedback mechanisms. The rate of drug release is regulated by the concentration of a triggering agent detected by a sensor built into the CrDDS.

Site-Targeting Drug Delivery Systems

Delivery of a drug to a target tissue that needs medication is known to be a complex process that consists of multiple steps of diffusion and partitioning. The CrDDSs outlined above generally address only the first step of this complex process. Essentially, these CrDDSs have been designed to control the rate of drug release from the delivery systems, but the path for the transport of drug molecules from the delivery system to the target tissue remains largely uncontrolled. Dosage form produces a large fluctuation in concentration within the systemic circulation. This variation was the basic need for the development of the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery systems is to reduce patient compliance by either reducing the frequency of drug administration or reducing the amount of drug that is to be administered to produce desired pharmacological effect in a patient. 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. There is various application of the bi-layer tablet it consist of monolithic partially coated or multilayered matrices. In the case of bi-layered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper non-adhesive layer its delivery occurs into the whole oral cavity.

Advantages of the Bi-Layer Tablet Dosage Form[2-4]

- Used for extended or immediate release drugs that can produce the desired level of action.
- Maximize the efficacy of two different drug by producing synergetic action as two drugs are simultaneously present in a single dosage form.
- Separation of incompatible component of a drug in a single dosage form as by forming different layer of drug.
- Low cost of a single drug as compared to cost of two different drug.
- Greater stability of drug.
- Single entity feed granules are used in the preparation of the drug.
- Patient compliance as the dosing reduced.
- Easy consumption of the drug by the patient.

Disadvantages of Bi-Layer Tablet Dosage Form[2-4]

- Difficult to swallow in case of children and unconscious patients.
- Poor wetting and dissolution property.
- Difficult to be administered in the patients are unconscious.
- Production cost is relatively high.
- Cross contamination between different layers is the common problem.
- Hardness is insufficient.

Various Techniques for Bilayer Tablet[5]

A. OROS® push pull technology

This system consist of mainly two or three layer among which the one or more layer are essential of the drug and other layer are consist of push layer (Fig.6). 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.

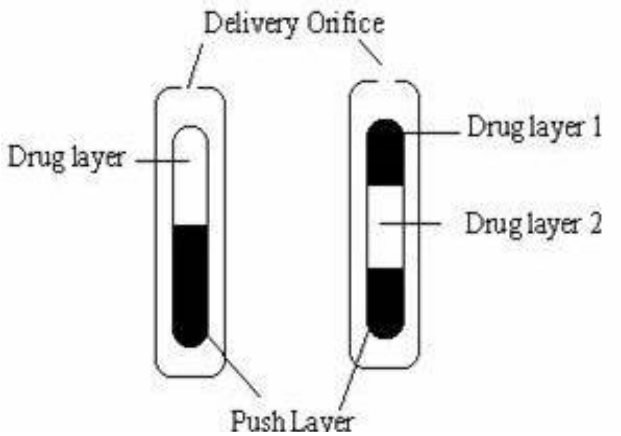

Fig. 6: OROS Push pull technology.

B. OROS TM Technology[5]

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.

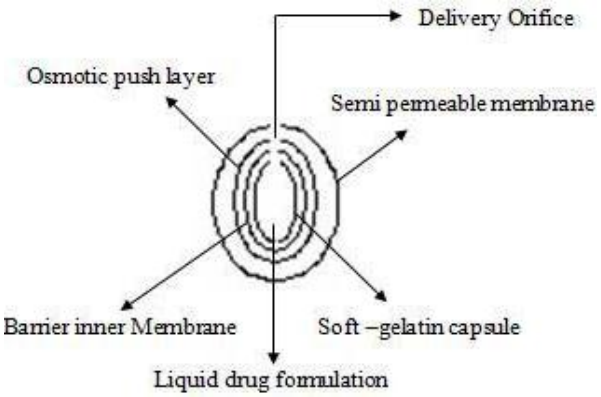

Fig. 7: L – OROS TM technology.

C. 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.

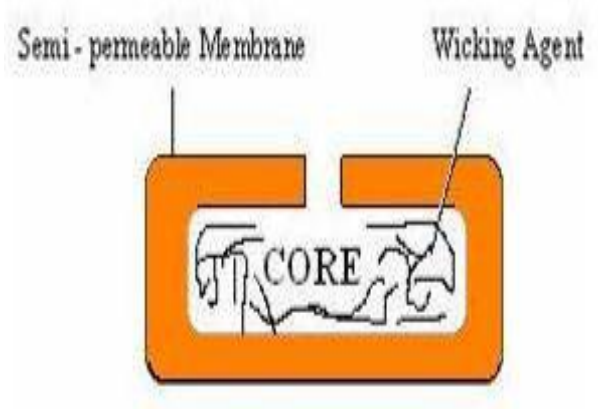

Fig 8: EN SO TROL TECHNOLOGY.

D. DUROS TECHNOLOGY

The system consists from an outer cylindrical titanium alloy reservoir. This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the miniature drug dispensing system that opposes like a miniature syringe and release minute quantity of concentrated form in continues and consistent from over months or year.

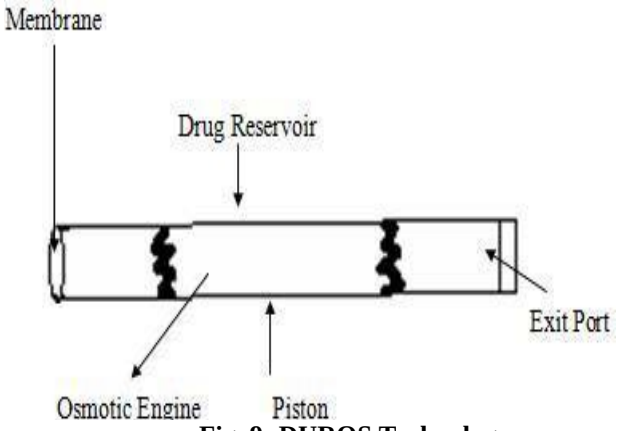

Fig. 9: DUROS Technology.

E. 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 tabletting 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.

Method of Preparation of Bi-Layer Tablets[6-9]

1. Bi layer tablets are prepared using two different active ingredients with different release patterns.
2. One layer of drug show immediate release profile while the other drug is released later as second dose or extended release dose.
3. The bilayer tablets with two incompatible drugs can also be prepared by compressing separate layers of each drug so as to minimize area of contact between two layers.
4. An additional intermediate layer of inert material may also be included. To produce adequate tablet formulation, certain requirements such as sufficient mechanical strength and desired drug release profile must be met.
5. At times, this may be difficult task for formulator to achieve these conditions especially in bilayer tablet formulation where double compression technique is involved, because of poor flow and compatibility characteristic of the drug which will result in capping and/or lamination.
6. The compaction of a material involves both the compressibility and consolidation. Compression: it is defined as reduction in bulk volume by eliminating voids and bringing particles into closer contacts.

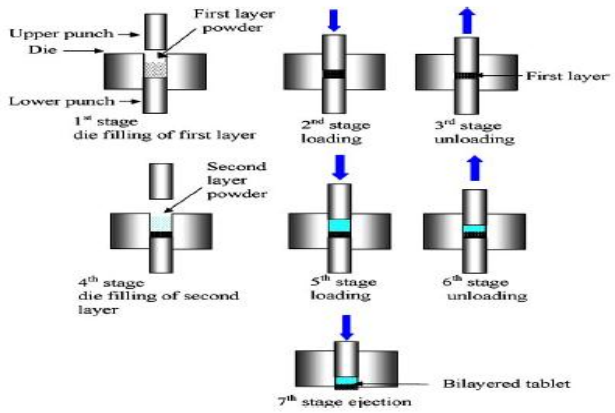

Fig 10: Preparation of bilayer tablet Compact.

Quality and GMP-requirements[9]

To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the Selected press is capable of 5:

1. Preventing capping and separation of the two individual layers that constitute the bi-layer tablet
2. Providing sufficient tablet hardness
3. Preventing cross-contamination between the two layers
4. Producing a clear visual separation between the two layers
5. High yield Accurate and individual weight control of the two layers. These requirements seem obvious but are not so easily accomplished.

Need of Bilayer Tablets[10-11]

1. For administration of fixed dose of different active ingredients combination for prolong action, mucoadhesive delivery system; novel drug delivery as chewing devices, floating tablets.
2. Controlling the delivery rate of same or different drugs.
3. To modify the total surface area available for the active drug layer either by sandwiching with one or two in active layers in order to achieve swellable/erodible barriers for modified release.
4. 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).

Evaluation Of Sustain Release Bilayer Tablet[12-13]

Tablet Thickness and Size

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter was measured using 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 tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured I kg/cm^2.

Friability

Friability is the measure of tablet strength. 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.

% loss = [(Initial wt. of tablets – Final wt. of tablets)/ Initial wt. of tablets] ×100

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. standards.

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 2hours. 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.

Recent Developments in the Field Of Bilayer Tablets

The introduction of bilayer tablets into the pharmaceutical industry has enabled the development of pre-determined release profiles of active ingredients and incorporation of incompatible active ingredients into the single unit dosage form. Large number of work has been done in this field. Some of the recent findings are explained in the preceding table-1.

Table- 1: Various advancement in the field of bilayer tablet[14-35]

Drug(s)	Dosage form	Rationale
Diclofenac, Cyclobenza-prine	Bilayer tablet	Synergistic effect in pain
Granisetron HCl	Bilayer buccal tablet	To overcome bioavailability problem, reducing side effect
Metformin HCl, Glimipride	Bilayer tablet	Synergistic effect in diabetes

Indomethacin	Bilayer floating tablet	Biphasic drug release
Metformin HCl, Atorvastatin Calcium	Bilayer tablet	To develop polytherapy for the treatment of NIDDS& hyperlipidemia
Cefexime Trihydrate Dicloxacilline sodium	Bilayer tablet	Synergistic effect in bacterial infections
Piracetam, Vinpocetin	Bilayer tablet	Synergistic effect in Alzheimer disease
Metformin HCl pioglitazone	Bilayer tablet	Synergistic effect in bacterial infection
Atenolol	Bilayer buccal tablet	To overcome bioavailability problem, reducing side effects and frequency of administration.
Cefuroxime axetil potassium, Clavulanate	Bilayer tablet	Synergistic effect against microbial infections and to minimize dose dependent side effects
Amlodipine Besilate Metoprolol Succinate	Bilayer tablet	Synergistic effect in hypertension
Diclofenac sodium, paracetamol	Bilayer tablet	Synergistic effect in pain
Atorvastatin, calcium	Bilayer buccal tablet	To overcome bioavailability problem, reducing side effects and frequency of administration
Guaifenesin	Bilayer tablet	Biphasic release profile
Losartan	Bilayer tablet	Biphasic release profile
Tramadol, acetaminophen	Bilayer tablet	Synergistic effect in pain
Atenolol, Lovastatin	Bilayer tablet	Synergistic effect in hypertension and biphasic release profile
Montelukast, levocetrazine	Bilayer floating tablet	To improve the stability of drugs in combination
Salbutamol, theophylline	Bilayer tablet	Synergistic effect in asthma
Ascorbic acid, cyano-cobalamine	Double layer suppositories	To avoid interaction between incompatible vitamins
Rifampicin, Isniazid	Capsule and tablet	To avoid interaction between incompatible drugs
Misorostol, Diclofenac	Bilayer tablet	Minimize contact b/w drugs46

CONCLUSION

Bilayer tables is a advance form of the simple tablet that prove more efficient and effective form of drug delivery system. The drugs used in the formulation are the different drugs with different release pattern. The basic consideration and standards of the bilayer tablets vary widely. This explains why many different types of presses are being used to produce bi-layer tablets, ranging from simple single sided presses to highly sophisticated machines such as the Courtoy-R292F. So use of bilayer tablets are very different aspect for anti-hypertensive, diabetic, Anti-inflammatory and analgesic drugs where combination therapy is often used.

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