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A REVIEW ON NOVEL APPROACH TO BILAYER TABLETS

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ABSTRACT

Bilayer tablets is a novel method for successful development controlled release formulation to obtaine a desired therapeutic concentration of active pharmaceutical ingredient (API) at site of action thus providing way for successful drug delivery system. Bilayer tablet is advantageous in sequential release of two drugs used in combination, used in sustained release tablet in which one layer is immediate release as intial dose and second layer is maintenance dose. Bilayer tablets have various beneficial effects as masking bad odour and taste preventing gastro intestinal tract from irritation decreasing number of drugs in prescription and making it cost effective for patient's compliance.

INTRODUCTION

From past 30 years many pharmaceutical industries greater attention has been focused on development of sustained or controlled release drug delivery systems. The aspiration of any drug delivery system is to allocate a therapeutic amount of the drug to the proper site of action in the body to maintain the desired drug concentration. Oral route is most commodious route of the administration dosage form. Tablet is a convenient dosage form acceptable by patients and physicians. Sequential release of two drugs in which one is immediate release and another is sustained release can be attained through dosage form in the form of bilayer tablet. The fixed-dose Combinations of two or more active drugs produced in a single dosage form.

The advantage of such combination therapy is to reduce the number of dosage form in prescription, maintain administrative cost along with improving patient compliance and obtaining synergistic effect in treatment [1].

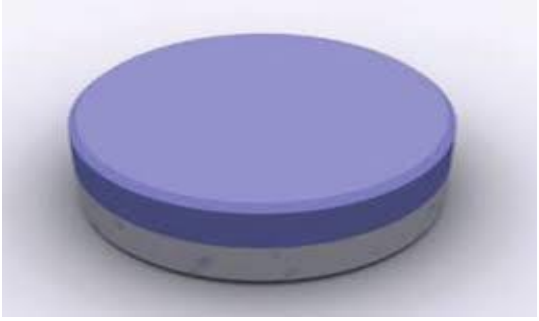

***Figure 1 Bilayer tablet*[35]**

Key advantages of bilayer tablets compared to conventional monolayer tablets. For instance, such tablets are commonly used to avoid chemical incompatibilities of formulation components by physical separation. In addition, bilayer tablets have enabled the development of controlled delivery of active pharmaceutical ingredients with pre-determined release profiles by combining layers with various release patterns, or by combining slow-release with immediate-release layers. Bilayer tablets can be a first hand opinion to avoid chemical incompatibilities between active pharmaceutical ingredients by physical separation, and to encourage burgeon of different drug release profiles. [2,3,4,5]

BILAYER TABLETS:

Ideal characteristics of bilayer tablets

1. Should be at liberty from defects like chips, cracks, discoloration and contamination.
2. Should have adequate strength during its production, packaging, shipping and dispensing
3. Should have the chemical and physical stability overtime.
4. Should releases the agents in a predictable and reproducible manner.
5. It must have a chemical stability and shelf-life.

Need of bilayer tablets:

1. Control delivery rate of single or two different Active Pharmaceutical Ingredients (APIs).
2. Modification of surface area available for active pharmaceutical ingredient by swellable /erodible barriers for modified release.
3. Controlling the release of API from one layer by exploiting the functional property of the other layer.
4. Administration of fixed dose combinations of different APIs.

Advantages:

1. Maximum chemical and microbial stability compare to other oral dosage form.
2. Cost is subordinate contrast to all other oral dosage form.
3. This technique is helpful in masking offensive odour and bitter taste.
4. Easy to swallowing with least tendency for hang up.
5. They offer greatest dose accuracy and least content variability.
6. Flexible Concept.
7. Befitted for large scale production

Disadvantages:

1. Some drugs resist compression into dense compacts due to low density character.
2. Bitter tasting drugs or drugs that are sensitive to oxygen may require coating.
3. Difficult to swallow in case of children and unconscious patients.
4. Drugs with poor wetting, slow dissolution properties may be difficult to formulate. [6]

TYPES OF BILAYER TABLET PRESS:

Single sided tablet press: Simplest design is a single sided press with both chambers of the doublet feeder separated from each other. Every chamber is gravity or forced fed with different power, producing the two individual layers of tablets. When die passes under the feeder, it is first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps [7].

Figure 2 Single sided tablet presses [36]

Limitations of the single sided press

1. No weight monitoring / control of the individual layers.
2. No distinct visual separation between the two layers.
3. Capping and hardness problems.

Double sided tablet press:

Double sided tablet presses with automated production control use compression force to monitor and control tablet weight. The compression force exerted on each individual tablet or layer is measured by the control system at main compression of the layer [8]. This compression force is the signal used by the control system to reject out of tolerance and correct the die fill depth when required.

Figure 3 Double sided tablet press[37]

Bilayer tablet press with displacement monitoring:

Displacement tablet weight control principle is fundamentally different from the principle based upon compression force. While measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied precompression force [9].

Figure 4 Bilayer tablet press with displacement monitoring [38]

MANUFACTURE OF BILAYER TABLETS:

The manufacture of multilayer tablets has been successful for over 50 years. Bilayer tablet are manufactured with one layer of drug for and second layer designed to release drug either as a second dose or in an extended release form[10,11].

CHALLENGES IN BILAYER TABLET MANUFACTURING:

Bilayer tablets can be seen as two single-layer tablets compressed into one. In Practice, there are some manufacturing challenges [12].

Delamination: Tablet falls apart when the two halves of the tablet do not bond completely.

Cross-Contamination: When the granulation of the first layer fraternize with the granulation of the second layer results in cross contamination. Proper dust collection goes a long way toward preventing cross contamination.

Production yields: Dust collection during manufacturing leads to losses. Thus, bilayer tablets have lower yields than single layer tablets.

Cost: Bilayer tableting is more expensive than single layer tableting for several reasons. First, the tablet press costs more.

Second, the press generally runs more slowly in bilayer mode. Third, development of two compatible granulations is must, which means more time spent on formulation development, analysis and validation [13].

VARIOUS TECHNIQUES FOR BILAYER TABLET:

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.1). 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.

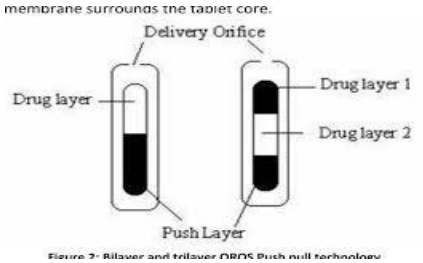

Figure 5 OROS push pull technology[39]

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 followed by a semi permeable membrane, drilled with an exit orifice.

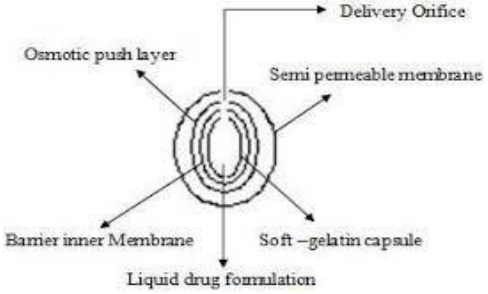

Figure 6 L- OROS tm technology[39]

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.

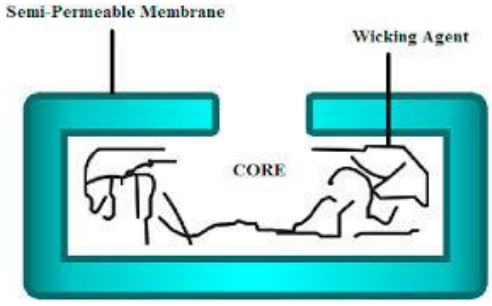

Figure 7 EN SO TROL technology[40]

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 reglious minute quantity of concentrated form in continues and consistent from over months or year.

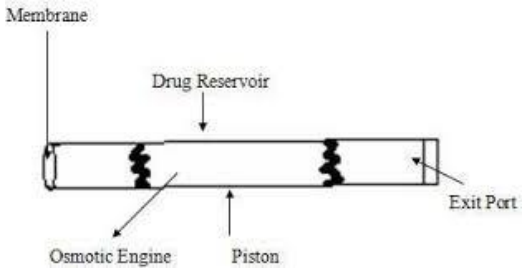

Figure 8 DUROS techlonogy[41]

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[14].

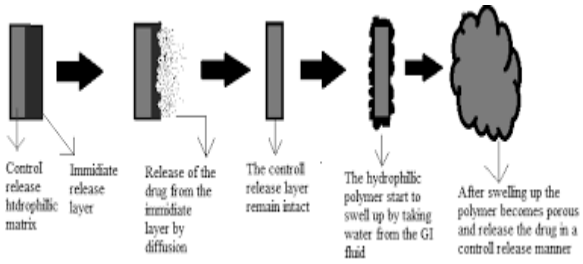

Figure 9 DUREDAS technology consists of control release and immediate release layer[42]

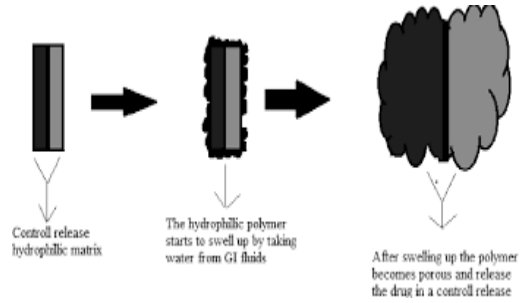

Figure 10 DUREDAS technology consist of two control release layers[43].

VARIOUS APPROACHES USED IN THE BILAYER TABLET :

Floating Drug Delivery System:

Floating drug delivery systems are considerably easy and logical approach in the development of Gastro retentive dosage forms (GRDFs) with respect to formulation and technological point of view. Following approaches have been used for the design of floating dosage forms o f single and multiple-unit systems.

1. *Intra gastric bilayered floating tablets*
2. *Multiple unit type floating pills* [15].

Polymeric Bio adhesive System:

It is designed to imbibe fluid following administration such that the outer layer becomes a viscous, tacky material that adheres to the gastric mucosa/mucus layer.. These are prepared as one layer with immediate dosing and other layer with bio adhesive property [16].

Disadvantages:

The success is seen in animal models with such system has not been translated to human subjects due to differences in mucous amounts, consistency between animals and humans.

Swelling System:

It is designed to be sufficiently small on administration so as not to make ingestion of the dosage form difficult. On ingestion they rapidly swell or disintegrate and passage through the pylorus until after drug release has progressed to a required degree. The simple bilayer tabletmay contain an immediate release layer with the other layer as extended release [17].

EVALUATION OF BILAYER TABLETS:

Following are evaluations done for bilayer dosage form after its formulation

General appearance: General appearance of a tablet, its visual identity and overall "refinement" is essential for consumer acceptance. Includes in are tablet's size, shape, colour, presence or absence of an odour, taste and surface texture.

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

Tablet thickness: Using micrometer thickness of ten tablets are recorded.

Weight variation: Standard procedures are followed as described in the official book.

Friability: The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator [18].

% Friability = 1- (loss in weight / Initial weight) X 100

Table-1: Various Advancements in the Field of Bilayer Tablets

Drug(S)	Dosage Form	Rationale
Diclofenac, Cyclobenza-prine	Bilayer tablets	Synergistic effect in pain
Granisetron HC1	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects
Metformin HC1. Glimipiride	Bilayer tablets	Synergistic effect in diabetes
Metformin HC1 Atorvastatin Calcium	Bilayer tablets	To develop polytherapy for the treatment of NIDDS & hyperlipidemia
Cefixime Trihydrate Dicloxacilline Sodium	Bilayer tablets	Synergistic effect in bacterial infections
Piracetam, Vinpocetin	Bilayer tablets	Synergistic effect in Alzheimer disease
Cefuroxime Axetil Potassium Clavulanate	Bilayer tablets	Synergistic effect against microbial infections and to minimize dose dependent side effects
Telmisartan, Simvastatin	Bilayer tablets	To minimize contact between Simvastatin & telmisartan
Montelukast, Levocetrizine	Bilayer tablets	To improve the stability of drugs in combination
Salbutamol, Theophylline	Bilayer tablets	Synergistic effect of drugs in asthma
Tramadol, Acetaminophen	Bilayer tablets	Synergistic effect of drugs in pain
Guaifenesin	Bilayer tablets	Biphasic release profile
Atorvastatin, Calcium	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects and frequency of administration
Losartan	Bilayer tablets	Biphasic release profile
Indomethacin	Bilayer floating tablets	Biphasic drug release

Hardness (Crushing strength): Tablet resistance against capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The small and portable hardness tester Monsanto or Stokes hardness testers are used to measure the hardness of the tablet.

Dissolution: Standard procedures are followed as described in the official book.

Stability study: The bilayer tablets are packed in suitable packaging and stored under different temperature conditions for a period as prescribed by ICH guidelines for accelerated studies [19].

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.

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