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Review Article

NOVEL APPROACH OF BILAYER TABLET TECHNOLOGY –A REVIEW

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ABSTRACT

Bilayer tablet is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. Bilayer tablet is better than the traditionally used mouthwash, sprays, gels. So use of bilayer tablet is a very different aspect for anti-inflammatory and analgesic. 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 tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. There is various application of the bilayer tablet it consist of monolithic partially coated or multilayered matrices. In the case of bilayered 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.

Keywords: Bilayer tablets, API, OROS push pull technology, DUROS technology.

INTRODUCTION

Pharmacological therapies either require or benefit from the administration of drugs in a sequential manner. These combined formulations function from a single dosage form, which simplifies the therapy and reduces or eliminates the chances of improper administration. Bilayer formulations carry more than one drug and deliver each of them without any pharmacokinetic or dynamic interactions, with their individual rate of delivery (immediate, timed or sustained). Bilayer tablet technology is improved beneficial technology to overcome the shortcoming of the single layered tablet. Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance. Bilayer 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.[1]

Multi-layer tablet dosage forms are designed for variety of reasons

1) To control the delivery rate of either single [2] or two different active pharmaceutical ingredient(s).[3,4]

2) 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).
3) 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. [5,6]
4) To administer fixed dose combinations of different APIs [7], prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device [8], buccal/ mucoadhesive delivery systems [9], and floating tablets for gastro-retentive drug delivery [10].

The advantages of the bi-layer tablet dosage form are

1) They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
2) Cost is lower compared to all other oral dosage form.
3) Lighter and compact.
4) Easiest and cheapest to package and strip.
5) Easy to swallowing with least tendency for hang-up.
6) Objectionable odour and bitter taste can be masked by coating technique.
7) Suitable for large scale production.
8) Greatest chemical and microbial stability over all oral dosage form.
9) Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.

Disadvantages of Bi-Layer Tablet Dosage Form are

1) Difficult to swallow in case of children and unconscious patients.
2) Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
3) 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.
4) Bitter testing drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating. [11]

General properties of Bi-Layer Tablet Dosage Forms

1) A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration, and contamination.
2) Should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
3) 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.
4) Must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.[12]

Bi-layer tablets
quality and GMP-requirements

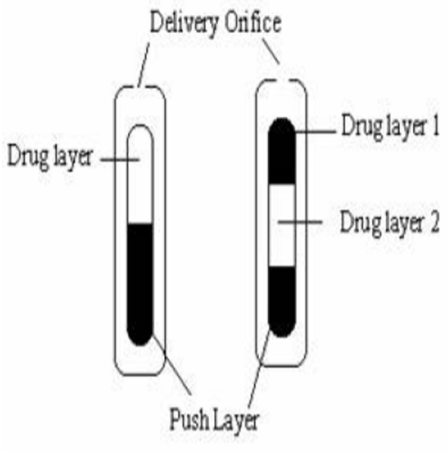
- To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the selected press is capable of:
- Preventing capping and separation of the two individual layers that constitute the bi-layer tablet.

- Providing sufficient tablet hardness
- Preventing cross-contamination between the two layers
- Producing a clear visual separation between the two layers.
- High yield.
- Accurate and individual weight control of the two layers. These requirements seem obvious but are not as easily accomplished as this article aims to demonstrate.

VARIOUS TECHNIQUES FOR BILAYER TABLETS

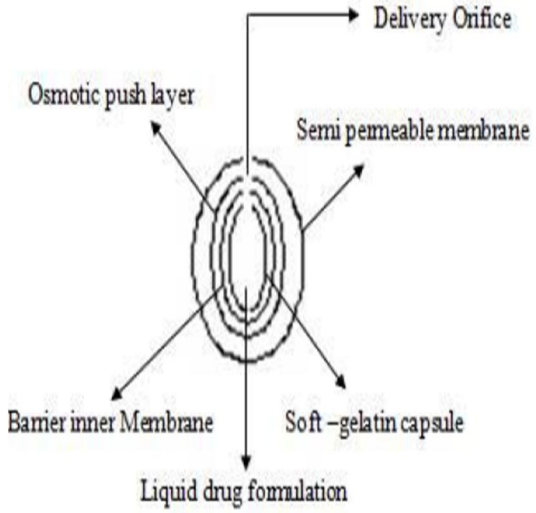
a) OROS® push pull technology[13]

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. 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 .



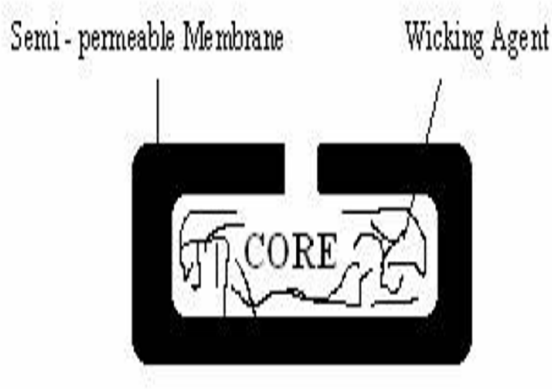
b) L-OROS tm technology

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 then a semi permeable membrane, drilled with an exit orifice.



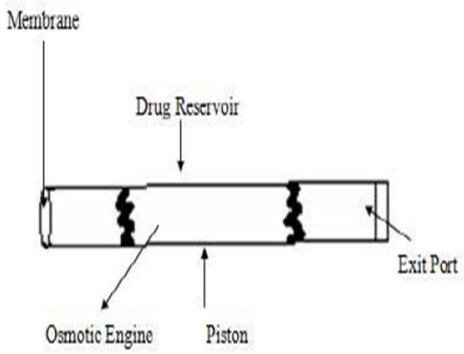
c) EN SO TROL technology[13]

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.



d) DUROS technology[14]

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.



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 tableting 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.

Benefits offered by the DUREDAS™ technology include

1) Bilayer Tableting technology.
2) Tailored release rate Of two drug components.
3) Capability Of two different CR Formulations combined.
4) Capability for immediate release and modified release components in one tablet
5) Unit dose tablet

The DUREDAS™ system can easily be manipulated to allow incorporation of two controlled release formulations in the bilayer. Two different release rates can be achieved from each side. In this way greater prolongation of sustained release can be achieved. Typically an immediate release granulate is first compressed followed by the addition of a controlled release element which is compressed onto the initial tablet. This gives the characteristic bilayer effect to the final dosage form. A further extension of the DUREDAS™ technology is the production of controlled release combination dosage forms whereby two different drugs are incorporated into the different layers and drug release of each is controlled to maximize the therapeutic effect of the combination. Again both immediate release and controlled release combinations of the two drugs are possible. A number of combination products utilizing this technology approach have been evaluated. The DUREDAS™ technology was initially employed in the development of a number of OTC controlled release analgesics. In this case a rapid release of analgesic is necessary for a fast onset of therapeutic effect. Hence one layer of the tablets is formulated as immediate releases granulate. By contrast, the second layer of the tablet, through use of hydrophilic polymers, releases drug in a controlled manner. The controlled release is due to a combination of diffusion and erosion through the hydrophilic polymer matrix.

Evaluation of Bilayer Tablets

1. General Appearance

The general appearance of a tablet, its visual identity and overall "elegance" is essential for consumer acceptance. Includes in are tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

2. Size and Shape

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

3. Tablet thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

4. Weight variation[15]

Standard procedures are followed as described in the official books.

5. Friability[15]

Friction and shock are the forces that most often cause tablets to chip, cap or break. 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. A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked up. Normally, when capping occurs, friability values are not calculated. A thick tablet may have less tendency to cap where as thin tablets of large diameter often show extensive capping, thus indicating that tablets with greater thickness have reduced internal stress the loss in the weight of tablet is the measure of friability and is expressed in percentage as:

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

6. Hardness (Crushing strength)[16]

The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The small and portable hardness tester was manufactured and introduced by Monsanto in the Mid 1930s. It is now designated as either the Monsanto or Stokes hardness tester. The instrument measures the force required to break the tablet when the force generated by a coil spring is applied diametrally to the tablet. The Strong-Cobb Pfizer and Schleuniger apparatus which were later introduced measures the diametrically applied force required to break the tablet. Hardness, which is now more appropriately called crushing strength determinations are made during tablet production and are used to determine the need for pressure adjustment on tablet machine. If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specifications; if it is too soft, it may not be able to withstand the handling during subsequent processing such as coating or packaging and shipping operations. The force required to break the tablet is measured in kilograms and a crushing strength of 4 Kg is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10 kg; however, hypodermic and chewable tablets are usually much softer (3 kg) and some sustained release tablets are much harder (10 -20 kg). Tablet hardness have been associated with other tablet properties such as density and porosity. Hardness generally increases with normal storage of tablets and depends on the shape, chemical properties, binding agent and pressure applied during compression.

7. Stability Study (Temperature dependent)

The bilayer tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

Study	Storage condition	Minimum time period covered by data at submission
Long term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

*It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH. **If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability and Dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25°C.

CONCLUSION

Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. There is various application of the bilayer tablet it consist of monolithic partially coated or multilayered matrices. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatable substance and also for sustain release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. The preparation of tablets in the form of multilayers is used to provide systems for the administration of drugs, which are incompatible and to provide control release tablet preparations by providing surrounding or multiple swelling layers. Bilayer tablet quality and GMP-requirements can vary widely. This explains why many different types of presses are being used to produce bilayer tablet, ranging from simple single-sided presses to highly sophisticated machines.

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