BILAYER TABLET ; A PRAMOSING APPROACH FOR DELIVERY OF DUAL DRUGS

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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. Bi-layer tablets can be primary option to avoid chemical incompatibilities between APIs by physical separation and to enable the development of different drug release profiles. Bi-layer tablet is suitable for sequential release of two drugs in combination and also for sustained release of tablet in which one layer is for immediate release as loading dose and second layer is maintenance dose. In the present time in market new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. There is various application of the bi-layer tablet it consist of monolithic partially coated or multilayered matrixes .bi-layer tablet is a very different aspect for anti inflammatory ,anti diabetics , analgesic and antidepressant drugs.

Keyword - Bi-layer tablet, API (active pharmaceutical ingredient), layer separation.

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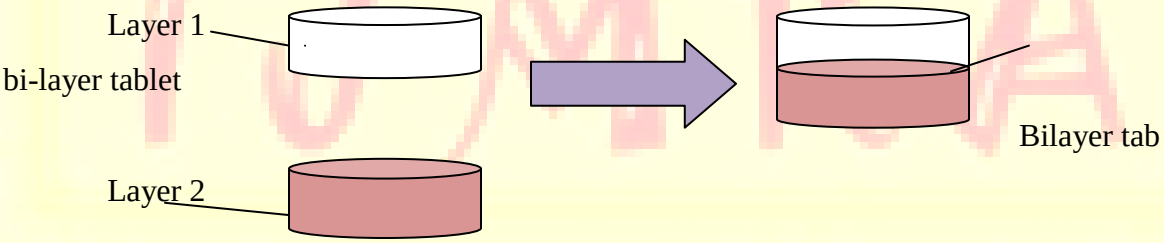
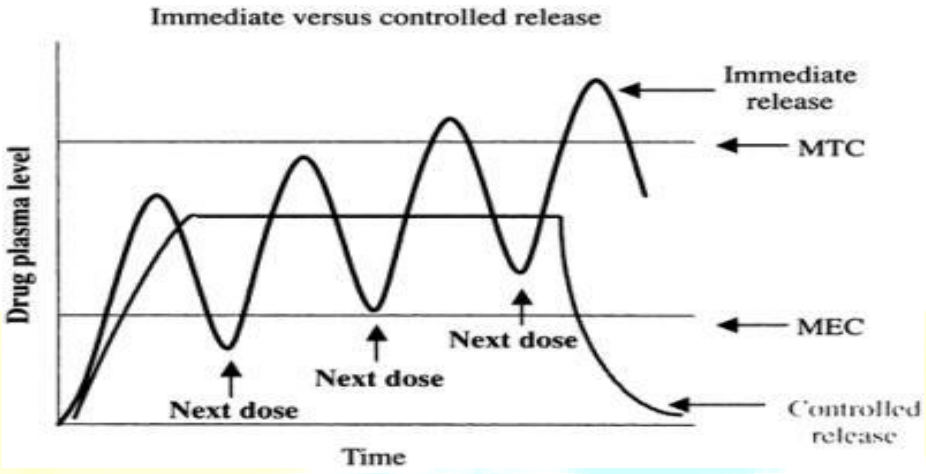
INTRODUCTION

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. 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. 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. A 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.



Time release technology (also known as sustained-release , sustained-action , extended-release timed-release controlled-release ,modified release or continuous-release is a mechanism used in tablets to dissolve a drug over time in order to be released slower and steadier into the bloodstream while having the advantage of being taken at less frequent intervals than immediate-release formulations of the same drug.



(Fig1)

RATIONAL FOR BI-LAYER TABLET

1) To control the delivery rate of either single 2 or two different active pharmaceutical ingredient.

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.

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.

ADVANTAGES

1) Release of both drugs start simultaneously.

2) Combination of incompatible drug.

3) Treat difference ailments in the same patient at the same time with one pill.

4) Combination of different release profile along with synergistic effect.

5) Reduced pills burden

6) Reduced side effect

7) Cost effective in packaging

BI-LAYER TABLETS GMP-REQUIREMENTSAND LIMITATIONS

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

1) To avoid the layer separation between two layer.
2) Layer weight ratio.
3) Elastic mismatch of the adjacent layer.
4) Preventing Cross contamination between layers.
5) Order of layer sequences
6) Producing a clear visual separation between the two layers.
7) High yield
8) Preventing capping and separation of the two individual layers

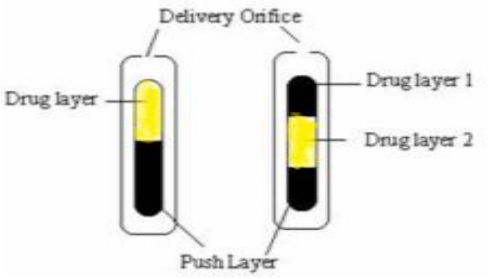
DISADVATAGES OF BI-LAYER TABLET

1. It is difficult to swallow in case of children.
2. Add complexity and bi-layer tablet presses are expensive.
3. Problem arises due to hardness, layer separation, and reduced yield.
4. Bitter testing drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation
5. Inaccurate individual layer weight control.

VARIOUS TECHNIQUES FOR BILAYER TABLETS

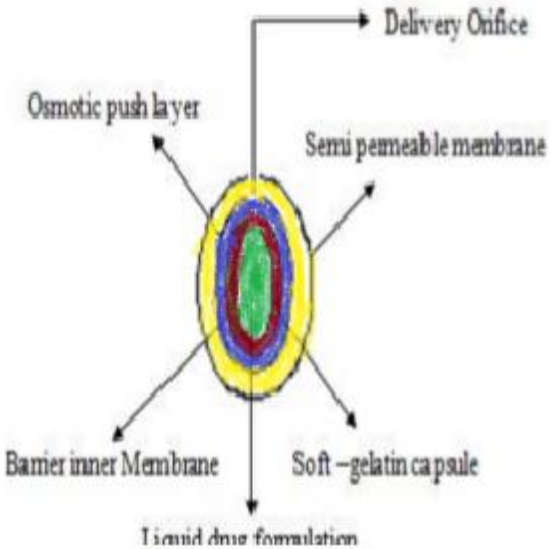
a) L-OROS tm technology

This method is used to enhance solubility. Here a lipid soft gel product containing drug in a dissolved state is initially prepared and then coated with a barrier membrane, than osmotic push layer and then a semi permeable membrane is drilled with an exit orifice.



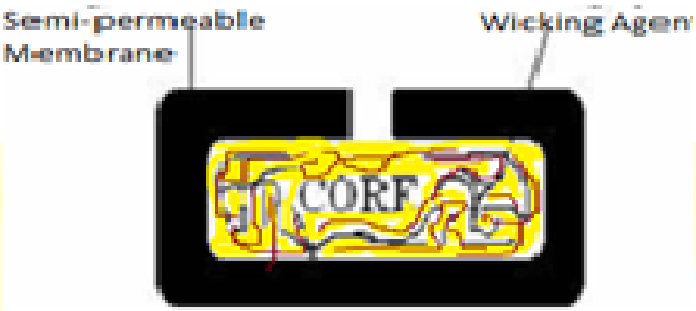
b) OROS® push pull technology

This method comprises of two or more layer and where one or more layer are of drug and the other one is of push layer. The drug layer mainly consists of drug along with one or more different agents and is in poorly soluble form. There is also addition of suspending agent and osmotic agent and finally the semi permeable membrane surrounds the tablet core.



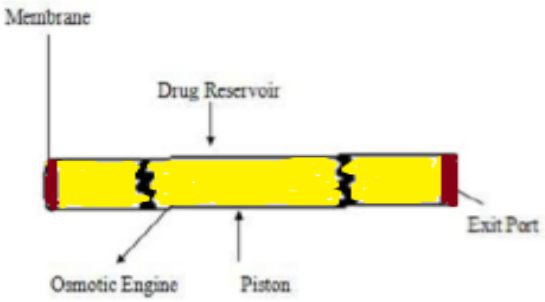
c) EN SO TROL technology

To create optimized dosage form and solubility enhancement of an order of magnitude 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

The system consists of an outer cylindrical titanium alloy reservoir which has high impact strength and protects the drug molecules from enzymes. This 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 bi-layer 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.

EVALUATION OF BI-LAYER TABLET

1. General Appearance:

The general appearance of a tablet, to visually identity the 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. Angle of repose:

The angle of repose of granules was determined by the funnel method Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. equation:

$$\text{Tan}\Theta = h/r$$

Where, h - height

r - Radius of the powder cone.

4. Bulk density:

Both loose bulk density & tapped bulk density were determined.

LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

5. Compressibility Index:

The compressibility index of the granules was determined by Carr's compressibility Index:

Carr's index (%) = [(TBD – LBD) * 100] / TBD

Where: LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

6. Thickness:

The thickness of the tablet was determined using a thickness gauge. Six tablets from each batch were used & average values were calculated.

7. Weight variation test:

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance & the test was performed according to the official method. The USP limit for weight variation in case of tablet weight between107.3 to 124.7 mg that is 7.5%.

8. Friability:

For each formulation the hardness of 6 tablets were determined using tablet hardness testers. The friability of 20 tablets was determined using Roche friabilator. The limit for friability is NMT 1%.

$$\% \text{ Friability} = 1 - \left(\frac{\text{loss in weight}}{\text{Initial w.t}}\right) \times 100$$

9. Hardness:

Hardness, which is appropriately called crushing strength. If the tablet is too hard, it may not disintegrate in the required period of time to, 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; hypodermic and chewable tablets are usually much softer (3 kg) and some sustained release tablets are much harder (10 -20 kg)

10. In Vitro Release Studies:

The in vitro dissolution studies 8 for all the formulations were carried out in two steeps, using USP apparatus type II at 100 rpm. The dissolution medium consisted of Hydrochloric acid buffer solution pH - 1.2 (900 ml), and Phosphate buffer pH – 6.8 (900ml), maintained at 37 0C ± 0.5 0C. The drug release at different time intervals was measured by UV-1700 UV-visible spectrophotometer at 280 nm (Hydrochloric acid buffer solution pH - 1.2) and at 265 nm (Phosphate buffer pH – 6.8). The release studies were conducted in triplicate (6 tablets in each set) .

11. Stability Study (Temperature dependent**)**

The bi-layer 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
Long term	25°c±2°c/60%RH±5%RH-30°C ± 2°C	12 Month
Intermediate	30°c ± 2°c/65%RH±5%	6 Month
Accelerated	40°c ± 2°C/75%RH ± 5%	6 Month

Combination therapy (SSRI) and benzodiazepine

There are several of drugs which are use in the combination therapy because they have toxic in the long term therapy. Such are like as antidepressant , anti anxiety and analgesic drugs. So overcome of this problem formulation of Selective Serotonin Reuptake Inhibitors, benzodiazepines in combination for useful in anxiety disorders.

SYNERGISTIC EFFECT

A application of combined selective serotonin reuptake inhibitors (SSRI) and benzodiazepine treatment for panic disorder, there has been relatively little systematic assessment of the safety and efficacy of this therapeutic strategy. Combined treatment with paroxetine and clonazepam resulted in more rapid response than with the Selective Serotonin Reuptake Inhibitor alone, but there was no differential benefit beyond the initial few weeks of therapy. Initiating combined treatment followed by benzodiazepine taper after a few weeks may provide early benefit while avoiding the potential adverse consequences of long-term combination therapy.

ADVANTAGE OF COMBINATION DRUGS

1. Lower the dose required for efficacy of both drugs
2. Enhancement of pharmacological activity
3. Protection from adverse effect and toxicity
4. Simultaneously two disorders can be overcome
5. No need of Repeat drug delivery
6. Improved Patient compliance

SNRIs and Benzodiazepines for Use in Anxiety Disorders

Selective Serotonin Reuptake Inhibitors, benzodiazepines are useful in anxiety disorders because of their rapid onset of effect. Benzodiazepines are highly effective anxiolytics In addition to their rapid onset of action, they are associated with high patient acceptance and a good tolerability profile. Adverse effects include sedation, psychomotor impairment, rebound anxiety with discontinuation of medication, the possibility of cognitive impairment, and the risk of fetal birth defects if taken during pregnancy.

A leading concern with prescribing benzodiazepines is their potential for abuse and dependence , Abuse is a psychoactive compound. Substance dependence implies an inability to control use, so that the substance is taken more frequently or in greater amounts than intended, and activities are given up to pursue use of the substance when SSRI or benzodiazepine therapy is halted and

require patient education and active clinical management, including drug tapering–Similarities between some SSRI and benzodiazepine discontinuation symptoms may derive from the changes in γ-amino butyric acid (GABA) signalling that result from both forms of therapy.

RECENT DEVELOPMENTS IN THE FIELD OF BILAYER TABLETS

The introduction of bi-layer 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.

S.NO.	DRUG	DOSAGE FORM	RATIONALES
1	Paroxetine , clonazepam	Bilayer tablet	Synergistic effect in anxiety and depression
2	Metformin , Glipizide	Bilayer tablet	Synergistic effect in diabetics
3	Solbutamol , Theophyline	Bilayer tablet	Synergistic effect in asthma
4	Diclofenac , Cyclobenzapine	Bilayer tablet	Synergistic effect in pain
5	DiclofenacSodium, Paracetamol	Bilayer tablet	Synergistic effect in pain
6	Metforminhcl , Glimipiride	Bilayer tablet	Synergistic effect in diabetics
7	Misorostol, Diclofenac	Bilayer tablet	To minimize contact between drugs
8	Amoldipine, , Atenolol	Bilayer tablet	To improve stability of drugs
9	Montelukast , Levocetrizine	Bilayer tablet	To improve stability of drugs
10	Metformin hcl , pioglitazone	Bilayer tablet	Synergistic effect in diabetics

CONCLUSION

Bi-layer tablet is improved technology to overcome the problems 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. Bi-layer tablet technology is a combination of drugs which have various synergistic effects. They have improved the adverse effect of the drug. These drugs are very harmful for the body , excess amount of these drugs cause toxicity (stomach upset, nausea, fatigue, headache, fatigue, tremor, nervousness and dry mouth. Some of the more persistent, or chronic, side effects are daytime fatigue, insomnia, sexual problems and weight gain) So the combination of bilayer tablet overcome of these problems.. They have overcome problem arising during administration of drugs like reduce dose burden, dose dumping. So use of bi-layer tablets is a very different aspect for anti-hypertensive, diabetic, anti-inflammatory and analgesic drugs where combination therapy is often used quality and GMP requirements for their production various techniques used for bi-layer tabletting and recent developments in the field of bi-layer technology.

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