ISSN 0976 – 3333

Available Online at www.ijpba.info

International Journal of Pharmaceutical & Biological Archives 2014; 5(4): 9- 18

REVIEW ARTICLE

Bilayered Tablet Technology: A Review

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Received 04Apr 2014; Revised 24Jul 2014; Accepted 06Aug 2014

ABSTRACT

Bi-layer tablets have been developed to achieve controlled delivery of different drugs with pre-defined release profiles. The introduction of bilayer tablet in the last decade had developed an interest in developing a combination of two or more active ingredients in a single dosage form in the pharmaceutical industry, promoting patient compliance and acceptance. Bi-layer tablet is suitable for release of two drugs in combination or inseparate layer for the delivery of two incompatible substances and also for sustained release tablet in which one Layer is immediate release as initial dose and second layer is loading dose. Bi-layer tablets are an effective drug delivery system for the treatment of hypertension, diabetes, inflammation and analgesic because in these diseases combination therapies are often used. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. This review explains the therapeutic advantages of bilayer tablet by releasing the medicaments for the immediate relief and then maintaining the level of medicament for the certain time in order to get the sustain release of drug.

Key words: Bilayer tablet, RoTotab push technology, OROS® push pull technology, DUROS technology.

INTRODUCTION

The concept of bilayer has been introduced to attain sustain release of drug which refers to tablet containing subunits that either may be same (Homogeneous) or different (Heterogeneous). Bilayer tablet allows for designing and modulating the dissolution and release characteristics. Bilayer tablet are prepared for one layer for immediate release while second layer is designed to release drug, later as second dose or in an extended release pattern. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances. Bilayer tablet are preferred when the release profiles of the drugs are different from each other. [1]

Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity andpoor efficiency. The problems of repetitive dosing and unpredictable absorption of the dosage form led to the concept of controlled drug delivery systems. The goal behind this delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization of the drug at the site of action which in turn reduces the dose requirement and thus providing uniform drug delivery. The rational of sustained release drug delivery is to ensure safety and to improve effectiveness of drugs as well as patient compliance. [2]

Fig 1: Bilayer Tablet

ADVANTAGES OF THE BILAYER TABLET DOSAGE FORM

1. Bi-Layer execution with optional single-layer conversion kit.
2. Cost is lower compared to all other oral dosage form.

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3. Greatest chemical and microbial stability over all oral dosage form.
4. Objectionable odor and bitter taste can be masked by coating technique.
5. 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.
6. Easy to swallowing with least tendency for hang-up.
7. Suitable for large scale production.[3]

DISADVANTAGES OF BILAYER TABLET DOSAGE FORM

1. Some drugs resist compression into dense compacts due to their amorphous nature and low density character.
2. Bitter tasting drugs, drugs with an objectionable odors or drugs that are sensitive to oxygen may require encapsulation or coating.
3. Difficult to swallow in case of children and unconscious patients because the size of bilayer tablet is large as compared with normal conventional tablet.
4. Drugs with poor wetting, slow dissolution rate, highly absorptive in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.

IDEAL CHARACTERSTICS OF BILAYER TABLETS

1. A bi-layer tablet should have elegant product identity while free of defects like chipping, cracking, mottling and contamination.
2. It should have sufficient strength to withstand mechanical shock during its manufacturing, packaging, shipping and dispensing.
3. It should have the chemical and physical stability to maintain its physical appearance over time. The bi-layer tablet must be able to release the pharmaceutical agents in a predictable and reproducible manner.
4. It must have a chemical stability shelf-life, so that it may not alter the medicinal agents because of chemical instability.

QUALITY AND GMP-REQUIREMENTS [4]

To manufacture a quality bi-layer tablet, it should specify following GMP requirements

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 to accomplish it is not an easy job.

CHALLENGES IN BILAYER MANUFACTURING [5]

Conceptually, bilayer tablets can be seen as two single-layer tablets compressed into one. In Practice, there are some manufacturing challenges.

- **Delamination:** Delamination is one major problem in the production of bilayer tablet. Considerations have shown that thermal stresses due to the development of heat during powder compression results in delamination. Use of proper binding agents prevents delamination. It can also be prevented by Correct bonding which can only be obtained when the first layer is compressed at a low compression force so that this layer can still interact with the second layer during final compression of the tablet.
- **Cross-contamination:** When the granulation of the first layer intermingles with the granulation of the second layer or vice versa, cross-contamination occurs. Cross-contamination can be prevented by maintain proper sterile conditions in the environment and also the medicaments used must be checked for chemical incompatibility.
- **Production yields:** To prevent cross contamination, dust collection of the formulation is required. Thus, bilayer tablets have lower yields than single-layer tablets.
- **Cost:** Bilayer tableting is more expensive than single layer tableting for several reasons. Firstly, the cost of tablet press is more and Secondly, the press generally runs more slowly in bilayer mode. Thirdly, development of two compatible granulations is must, which means more time spent on its production and evaluation. These factors have to be well

controlled/optimized for the better quality attributes of the bilayer tablets. Therefore, it is critical to maintain these factors to enable design of a robust product and process.

VARIOUS TECHNIQUES FOR BILAYERTABLET [6, 7]

A) L-OROSTM Technology:

This system is used for the solubility issue. Alza developed the L-OROS system in which a lipid soft gel product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, over then osmotic push layer followed by a semi permeable membrane, an exit orifice delivers the drug to the body fluid.

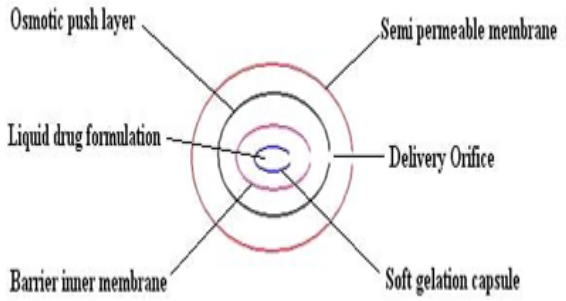

Fig 3: L–OROSTM Technology

B) OROS® push pulls Technology:

This system consists of mainly two or three layer among which the one or more layer is essentially of the drug and other layer is of push layer. The drug layer consists of drug as well as twoor more different agents. So the drug is mainly available in poorly soluble form. Suspending agent and osmotic agent are the important part of the system. The tablet core is surrounded by a semi permeable membrane.

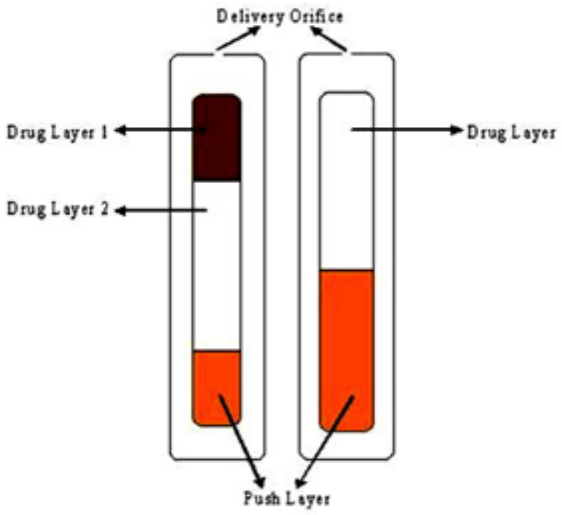

Fig 2: Bilayer and Trilayer OROS push pull technology

C) EN SO TROL Technology: [8]

This technology was introduced by Shrine laboratory .This formulation has been patented and effectively delivers the poorly soluble drug in the controlled release manner. Wicking agent is the most important component of this system which provides enhanced flow channels for the pharmaceutical agent which has been made predominantly into its solubilized form by the solubilizing agent within the tablet. In this approach the interior of the tablet had a hydrophobic core surrounded by a hydrophilic layer within the tablet. As such, water entering the tablet moved towards the hydrophilic layer and so very little drug was released. In this approach the interior of the tablet is made up of two separate layers, one layer containing the pharmaceutical agent and the other being a layer of material that swells when coming into contact with water. The pharmaceutical agent is delivered through the openings due to the mechanism of volume expansion. The pharmaceutical agents are primarily released as insoluble particles, and hence have limited bioavailability.

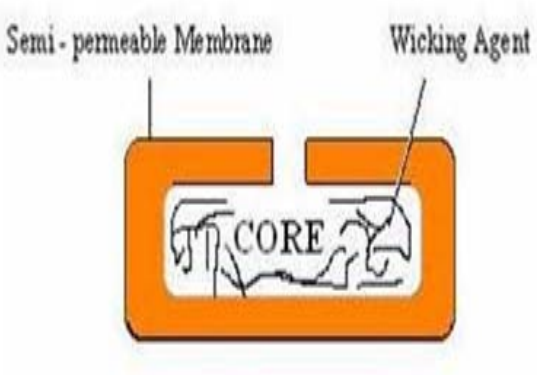

Fig 4: EN SO TROL Technology

D) DUREDAS™ Technology:

This system is also known as “Elan drug technologies’ Dual release drug delivery system”. This technology is based upon the bilayer tablet which can provide immediate or sustained release of two drugs or different release rates of the same drug in a single dosage form. The tableting process can provide an immediate release system and a controlled release hydrophilic complex as separate layers within one tablet. The controlled release properties of the dosage form are provided by combination ofhydrophilic polymers.

A number of combination products utilizing this technology have been evaluated. The DUREDAS™ technology was firstly 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 action. Hence one layer of the tablets is formulated as immediate releases granulate and the second layer of the tablet of hydrophilic polymers which is the component for releasing drug in a controlled manner. The controlled release is due to a combination of diffusion and erosion through the hydrophilic polymer matrix.

DUREDAS™ technology offers the following benefits:

- Bilayer tableting technology.
- Tailored release rate of two drug components.
- Capability for immediate release and controlled release components in one tablet.
- Unit dose, tablet presentation.

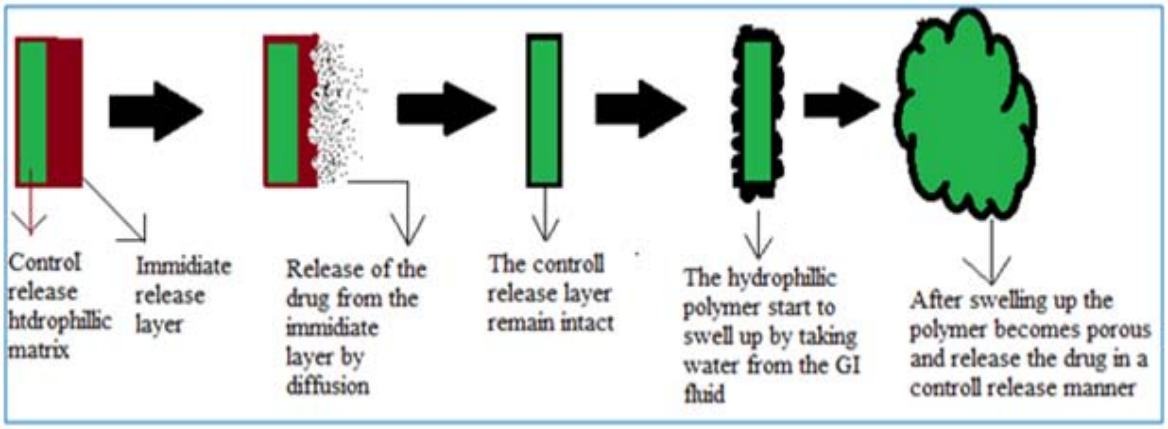

Fig 5: DUREDAS Technology [32]

E) DUROS Technology: [9]

DUROS® delivery technology consists of sterile, nonbiodegradable, single-use devices which consist of an outer cylindrical titanium alloy reservoir. This reservoir has high impact strength and protects the drug molecules from enzymes.

The DUROS® pump conceptually resembles a miniature syringe in which drug is pushed out in highly controlled, minute dosages. Through osmosis, water from the body is slowly drawn through the semi-permeable membrane into the pump by salt(osmotic agent) residing in the engine compartment. The water drawn into the engine compartment expands the osmotic agent and slowly and continuously displaces a piston to dispense small amounts of drug formulation from the drug reservoir through the orifice. The osmotic engine does not require batteries, switches or other electromechanical parts to operate. The system delivers the drug for about several months.

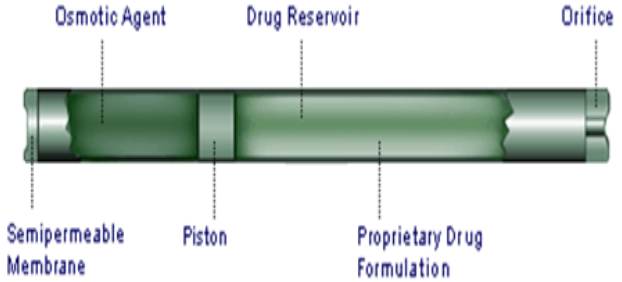

Fig 5: DUROS Technology

PRESS DESIGNED FOR QUALITY BILAYER TABLET

Bilayer tablet can be punched by following methods:

1. Single sided tablet press.
2. Double sided tablet press.
3. Bilayer tablet press with displacement monitoring.

1. Single sided press: [10]

The simplest design is a single-sided press with both chambers of the double feeder separated from each other. The chambers' having different powders are gravity- or forced-fed and thus produces the two individual layers of the tablet. The die passes under the feeder, which firstly compressed the first-layer powder and then the second-layer powder is being compressed. Lastly the entire tablet is compressed in one or two steps (two = pre- and main-compression). Both the layers in the die mix slightly at their interface and bond sufficiently so that no layer-separation occurs when the tablet is produced. This is one of the easiest way of producing a bi-layer tablet.

Limitations of the single sided press: [11, 12]

1. No weight monitoring / control of the individual layers.
2. No distinct visual separation between the two layers.

3. Very short first layer dwell time due to the small compression roller, possibly resulting in poor deaeration, tablet defects like capping and hardness problems. These defects can be overcome by reducing the turret rotation speed (to extend the dwell time) but with the consequence of lower tablet output.

Dwell time:

Dwell time is defined as the time during which compression force is above 90% of its peak value. While producing a quality a tablet longer dwell time is the major factor, especially when compressing a difficult formulation.

Fig 6: Single sided tablet press

2. Double sided tablet press: [13]

In most double sided tablet presses with automated production control use compression force to monitor and control tablet weight. In this press, there is a control system attached which measures the effective peak compression force exerted on each individual tablet or layer. The measured peak compression force is the signal used by the control system to reject out of tolerance and correct the die fill depth when required.

Compression force:

A compression force-controlled system requires a minimal compression force of several hundreds of daN. However, many bi-layer formulations require a first layer compression force of less than 100 daNbecause above 100daN, the ability to bond with the second layer may be lost and bonding between both layers may not be sufficient, which results in low hardness of the bilayer tablet and separation of the two layers.

Fig 7: Double sided tablet press

3. Bilayer tablet press with displacement monitoring:

"Displacement measurement" as the alternative to "compression force measurement" has the advantage that accuracy increases with reduced compression force. The displacement tablet weight control principle is fundamentally different from the principle based upon compression force in the double sided tablet press. While measuring displacement, the sensitivity of control system does not depend on the tablet weight but depends on the applied precompression force.

Fig 8: Bilayer tablet press with displacement

Tablet weight control using 'displacement' is based on the measurement of thickness variations under constant force and is measured at pre-compression. This measurement is possible when using the so-called 'pneumatic compensator'.

- In the Pneumatic compensator, the upper pre-compression roller is attached to an air-piston, which can move up/down in an air-cylinder.
- The air pressure [p] in the cylinder is set as a product Parameter at initial product set-

up and is kept at a constant value by the machine's control system.

- This pressure [p] multiplied by the piston surface [Spiston] is the constant force at which the piston and consequently the roller is pushed downwards against a fixed stop.
- During every pre-compression, the upper punch hits the upper roller and is initially pushed downwards into the die cavity and the lower punch is pushed upwards by the lower roller, the powder is being compressed to produce bilayer tablet.

Advantages:

1. Weight monitoring / control for accurate and independent weight control of the individual layers.
2. Low compression force exerted on the first layer to avoid capping and separation of the two individual layers.
3. Independence from the machine stiffness.
4. Increased dwell time at precompression of both first and second layer to provide sufficient hardness at maximum turret speed.
5. Maximum prevention of cross-contamination between the two layers.
6. Clear visual separation between the two layers and maximized yield.

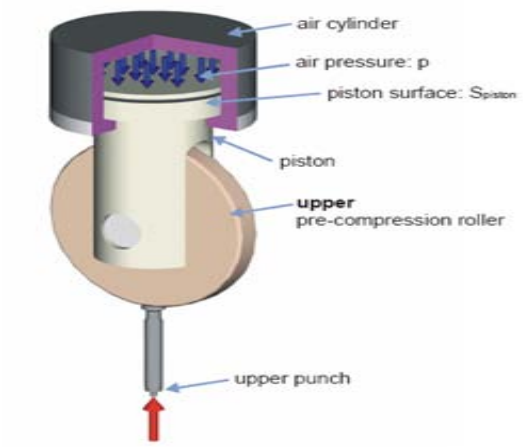

Fig 9: Pneumatic compensator

CHARACTERIZATION AND EVALUATION OF BILAYER TABLET: [14, 15, 16]

1. Particle size distribution:

Sieving method is most commonly used for the measurement of particle size distribution.

2. Angle of repose:

The diameter of the powder cone was measured and the angle of repose was calculated using the following equation,

$$\text{Tan}\emptyset = \frac{h}{r}$$

Where, h = height of the powder cone.r = radius of the powder cone.

3. Hausnser's ratio:

It is calculated by the formula,

$$H = \frac{\text{Bulk Density}}{\text{Tapped Density}}$$

4. General Appearance:

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

5. Size and Shape:

The size and shape of the tablet is an important parameter which had to be monitored and controlled.

6. Tablet thickness:

Thickness of tablets was important for uniformity of tablet size and shape. Vernier caliper is used for the measurement of thickness and diameter.

7. Tablet hardness:

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on the hardness of tablet. The hardness of tablet of each tablet is measured by Monsanto hardness tester. Its unit is kg/cm^2.

8. 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.

9. Friability:

Friction and shock are the forces that most often cause tablets defects like chipping, capping or breaking. This 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. These factors are evaluated by the use of the Roche friabilator.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 for four minutes at the rate of 25revolutions/min. After that the tablets are weighed and the weight compared with the initial weight. The final weight determines the loss due to abrasion which measures the tablet friability. A weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable. The loss in the weight of tablet is the measure of friability and is expressed in percentage as:

$$\% \textbf{ Friability} = 1 - \frac{\textbf{Loss in Weight}}{\textbf{Iniiial Weight}} \times 100$$

10. 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 drug delivery. Dissolution studieswere 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 2 hours. The medium was then replaced with pH 6.8 Phosphate buffer (900ml) and experiment continued for a specified time. 5ml of the samples were pipette out, at different time intervals and replaced with 5ml of drug-free medium. The withdrawn samples were analyzed by UV spectrophotometer.

11. Disintegration time: [17]

The disintegration time of the tablet was carried out using tablet disintegration test apparatus. 6 tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The medium, water was maintained at a temperature of 37° ± 2°C and time taken for the entire tablet to disintegrate completely was noted. Average of three determinations was taken.

12. Swelling studies: [18]

The extent of swelling was measured in terms of % of weight gained by the tablet. One tablet from eachformulation was weighed and kept in petri dish containing 50 ml of 0.1N HCl buffer solution. After a specified time intervals tablets were withdrawn from petri dish and excess buffer blotted with tissue paper and weighed. The % of weight gained by the tablet was calculated by using following formula:

$$\textbf{Swelling index } (\%) = \frac{\textbf{Mt} - \textbf{Mo}}{\textbf{Mo}} \times 100$$

Where, M_t = weight of tablets at time‘t’;
M_o = weight of tablets at time ‘0’.

13. 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 stability studies. The tablets were taken off after a period of 15 days and analyzed for physical characterization (General appearance, Tablet defects, Hardness, and Drug release studies etc..) and drug content. The experimental values obtained are fitted into first order equations to determine the kinetics of drug degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25°C.

Table 1: Conditions of Stability Studies

S. No	STUDY	STORAGE CONDITION	MINIMUM TIME PERIOD
1	Long term	25°C ± 2°C/60% RH ± 5% RH Or 30°C ± 2°C/65% RH ± 5% RH	12 Months
2	Intermediate	30°C ± 2°C/65% RH ± 5% RH	6 Months
3	Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 Months

RECENT DEVELOPMENTS IN THE FIELD OFBILAYER TABLETS [19]

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. Many researches has been done in this field. Some of the recent findings are explained in the preceding (Table 2).

Table 2: Tablet having Biphasic Drug Delivery System

DRUG 1	DRUG 2	RATIONALE	REF.NO.
Diclofenac	Cyclobenzaprine	Synergistic effect in pain	20
Glimipiride	Metformin HCl	Synergistic effect in diabetes	21
Amlodipine Besilate	Metoprolol Succinate	Synergistic effect in hypertension	22
Tramadol	Acetaminophen	Synergistic effect of drugs in pain	23
Montelukast	Levocetrizine	To improve the stability of drugs in combination	24
Telmisartan	Hydrochlorthiazide	To minimize contact b/w hydrochlorothiazide & basic component of telmisartan	25
Piracetam	Vinpocetin	Synergistic effect in Alzheimer disease	26
Telmisartan	Simvastatin	To minimize contact b/n Simvastatin &telmisartan	27
Ranitidine	Aspirin	To minimize the contact of two incompatible drugs	28
Metformin	Glipizide	Synergistic effect of drugs in diabetes	29
Metoclopramide Hydrochloride	Ibuprofen	Synergistic effect in migraine	1
Salbutamol	Theophylline	Synergistic effect of drugs in asthma	30
CefiximeTrihydrate	Dicloxacilline Sodium	Synergistic effect in bacterial infections	31

Table 3: Commercially Marketed Bilayer Tablets [32]

Product Name	Chemical Name	Developer
Revelol®-Am 25/5	Metoprolol succinate, Amlodipine besilate	Ipca Laboratories Ltd
PIOKIND®-M15	Pioglitazone, metformin hydrochloride	Psychotropics India Ltd.
Glycomet® GP2Forte	Metformin hydrochloride, Glimepiride	USV Limited
ALPRAX PLUS	Sertraline, Alprazolam	Torrent Pharmaceuticals Ltd.
DIAMICRON®XRMEX500	Gliclazide, Metformin hydrochloride	Sedia® Pharmaceuticals (India) Pvt. Ltd.
Newcold Plus	Levocetrizine hydrochloride, Phenylpropanolamine, Paracetamol	Piramal Healthcare Ltd.
DIUCONTIN-K®20/250	Furosemide, Potassium chloride	Abbott Healthcare Pvt. Ltd.

CONCLUSION

Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layer conventional tablet. Bi-layer tablets offer an excellent opportunity for manufacturers to separate themselves from their competitors in low cost and improved efficiency. There are various applications of the bi-layer tablet and is a very effective drug delivery system, it consist of monolithic partially coated or multilayered Matrices. Bilayer tablet is suitable for sequential release of two drugs in combination, two incompatible substances and also for sustained release tablet in which one Layer is immediate release as initial dose and second layer is loading 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. Bilayer tablet provides quality and GMP-requirements which can vary easily. That's why many different types of presses are being used to produce bi-layer tablets, ranging from simple single sided presses to highly sophisticated machines in which high quality bilayer tablets need to be produced at high speed, the use of an 'air compensator' in combination with displacement control appears to be the best solution.

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