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BILAYER TABLET - AN EMERGING TREND

Shaikh Aamer Khaleel, P. R. Patil*, P. R. Mahaparale and Monika Bhagat

Department of Pharmaceutics, Government College of Pharmacy, Aurangabad (MH), India. 431005.

***Corresponding Author: P. R. Patil**

Department of Pharmaceutics, Government College of Pharmacy, Aurangabad (MH), India.431005.

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ABSTRACT

Bilayer tablet technology is a new emerging era, in the pharmaceutical industry. Over a past few decades, around 90% drugs have been formulated for the purpose of oral delivery. Oral ingestion is the most convenient and commonly employed route of drug delivery, due to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design of dosage form. Due to these properties oral dosage form has gained much attention and became the popular class of formulation worldwide. Bilayer tablets do offer a definite advantage over conventional release formulations of the same drug. So as to overcome the problems associated with the conventional dosage form, there arose an interest in developing the controlled drug delivery system. Bilayer tablet technology can be a crucial way to avoid tablet chemical incompatibilities between API's by physical separation, and to facilitate the development of different drug release profiles, also involves the combine effect of slow release with the immediate release formulations. By adding an inert intermediate layer, the two incompatible drugs can be formulated. Drugs which are formulated in the form of biphasic system have different biological applications such as analgesic, antipyretic, antiallergenic, coronary vasodilators, antihypertensive and anti-histaminic.

This review deals with the various modern technologies, marketed formulations and patented formulations in the form of bilayer tablet which facilitates the need of researchers in the development of new bilayer tablet formulations.

KEYWORDS: Bilayer tablet, physical/layer separation, chemical incompatibilities**.**

INTRODUCTION

Now days, there is increased interest in developing those drug deliveries which Provide therapeutic amount of drug at proper site in body to achieve promptly and then maintain, desired drug concentration. Ideal drug delivery should deliver drug at a rate dictated by body need over period of treatment. There are two types of drug deliveries mainly,

1. Spatial delivery
2. Temporal delivery

Spatial delivery, targeting drug to specific organ or tissue, while temporal delivery refers the rate of drug delivery to target tissue.[1]

In recent times, various developed and developing countries looking for combination therapy for treatment of various diseases and disorders, which requires chronic treatment. Monotherapy, side effects are overcome by Combination therapy. Combination therapy has various advantages over such as problem of dose dependent side effects is minimized, a low dose combination of two different agents reduces the dose related risk and the addition of one agent may potentiate effects of other occur with maximal dosage of individual component of the combined tablet and thus dose of the single components can be reduced.[2]

Bilayer tablets are novel drug delivery systems where combination of two or more drugs in a single unit having different release profiles improves patient compliance, prolongs the drugs action, avoid saw true kinetics resulting in effective therapy along with better control of plasma drug level.[2]

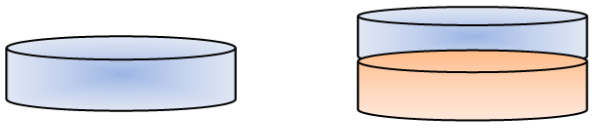

Fig. 1: Conventional Tablet and Bilayer Tablet.[3]

Bilayer tablet is a solid oral dosage form, usually round, spherical, oval or biconcave in shape and consist of one or more than one medicament designed in two layer system which can be suitable for combination therapy and biphasic release therapy. Bilayer tablet is the new era for the successful development of controlled release

formulation. Bilayer tablet is better than the traditionally used dosage forms.[4]

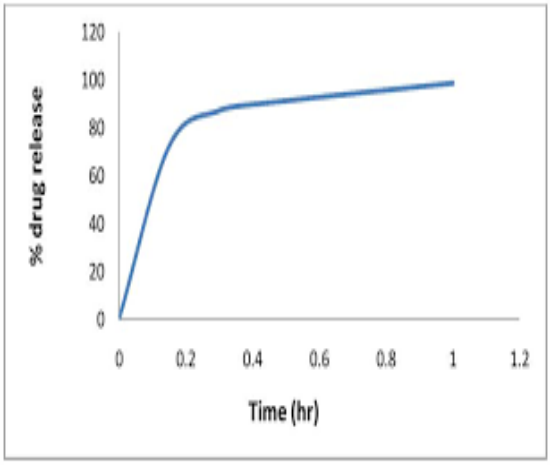

Fig. 2: Release Pattern (IR) of Bilayer Tablet[5]

Types of Bilayer Tablet[6]

a) Homogeneous Type

These are preferred when drug showing release profile different from each other. These are developed in such a manner that one-layer acts as loading dose for immediate release and other layer for giving maintenance dose or extended release.[6]

b) Heterogeneous Type

These are formulated with two incompatible substances in single dosage form separated from each other. Two drugs providing sequential release in combination are the example of this type.[6]

- **Need of Bilayer Tablet[4,7]**

1. Administration of dual release fixed dose combinations of different APIs.
2. For development of novel drug delivery system.
3. Control of drug delivery rate of single or two APIs.
4. Combination of incompatible API in one dosage.

- **Advantages[4,7]**

1. Combination of incompatible drugs.
2. Release of drug in controlled manner.
3. Combination of different release profile.
4. Reduced pill burden.
5. Elegance to product.
6. Reduced side effects.
7. Used in co morbid condition.
8. Low cost than other oral dosage form.
9. It is suitable for large scale manufacturing.
10. Increased patient compliance.
11. Chemical incompatibility prevented by physical separation.

- **Disadvantages[4,7]**

1. Difficult swallow for children
2. Difficulty in compression due to amorphous nature of drugs into compact mass.
3. Bitter drug, bad odour drug sensitive drugs required coating.
4. drugs with poor wetting properties, slow dissolution rate, optimum absorption high in GIT showing problem formulating into bilayer
5. cross contamination
6. required different tablet presses

- **Different Techniques of Bilayer Tablet**

1) Erodible molded multilayer tablet
2) Rotab Bilayer
3) DUROS Technology
4) L-Oros Tm Technology
5) PRODAS or programmable oral drug absorption system
6) EN SO TROL Technology
7) Oros ® Push Pull Technology
8) Elan Drug Technologies' Dual Release Drug Delivery System (DUREDAS™ Technology)
9) Geminex Technology

1) Erodible Molded Multilayer Tablet

This technology contains coat and matrix, based on standard plastic injection moulding. Erodible molded multilayered tablet technique is Egalet delivery technology.

In Egalet erodible molded tablets, Drug release is controlled by gradual erosion of matrix part. This technique useful in delivering zero order or delayed release pattern of drug without affecting GI conditions.

The coat used is of poor water permeability and biodegradable. Erosion of matrix takes place when come in contact with available water or by GI fluids and promote by gut movements in the GI tract. This technology assures accuracy, reproducibility and low production cost.[7,8]

2) Rotab Bilayer

1. Software

It's software of modular design, to which additional functions can be added. Fast graphical evaluations with accurate results can be achieved by one of the advanced system known, PC- system with 15" touch- screens''.

2. Working

Rotab bilayer is an automatically regulating system, when using for production mode switched towards it. With the help of it dose and compression force is automatically regulated by adjusting filling speed and die table. Hardness is also regulated when required.

3. R and D Modified Technique

R and D modified Rotab Bilayer are useful for graphical visualization and evaluation with measuring points on which there are. These playing important functions of controlling punch tightness. These have R and D plus with possibility of anytime upgration.

4. R and D Plus

R and D Plus showing great importance in tableting technology, provides improved standards. It is useful in controlling important functions such as control of punch tightness, force displacement display and scraper force of tablet.[9]

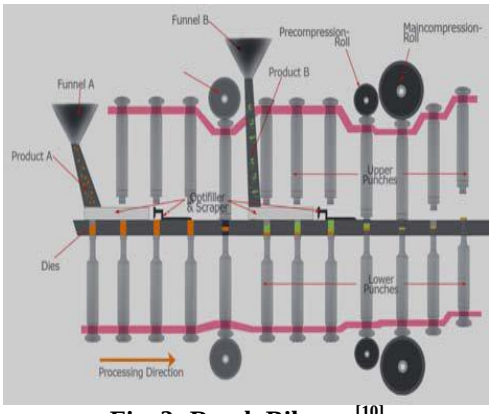

Fig. 3: Rotab Bilayer.[10]

3) Duros Technology

DUROS Technology is popularly known as "Miniature drug dispensing technology", in which miniature syringe releases drug in, continues and consistent manner in small concentrated form over long time period. Cylindrical titanium alloy reservoir having impact strength protected drug molecules from enzyme.[3,4]

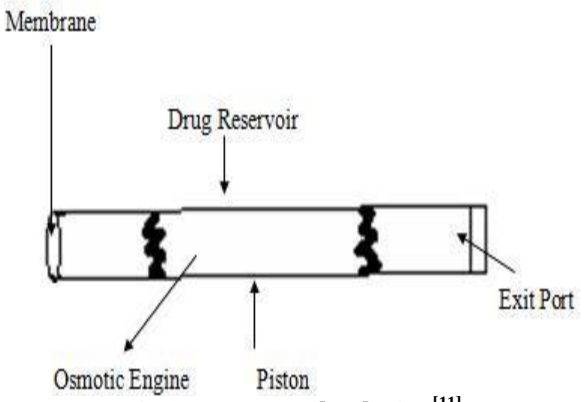

Fig. 4: Duros Technologies.[11]

4) L-Oros Tm Technology

Firstly Alza developed L-OROS system for solving solubility issue. Lipid soft gel product containing drug in a dissolved state is initially manufactured. Then it coated with a barrier membrane. Then there is application of osmotic push layer. Then a semipermeable membrane which drilled with an exit orifice.[11,12]

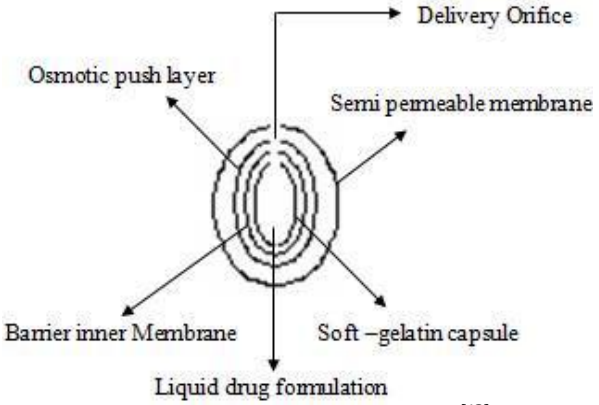

Fig.5: L–Oros TM Technology.[12]

5) Prodas 0r Programmable Oral Drug Absorption System

PRODAS is also known as multi particulate drug technology (Elan Corporation). In this technology, controlled release mini tablets (size range 1.5 to 4 mm) are encapsulated. This technology having combination of multi particulate and hydrophilic matrix tablet technologies, used to provide usefulness of above technologies in single dosage form.

PRODAS technology useful in targeted delivery of drug, for targeting to GIT. Different release rate Minitab, (immediate-release, delayed-release and/or controlled release) lets combined together in single dosage form to provide desired release rate. Sometime Minitab let are combined with different API to form products of desired release pattern.[9,11,7,8]

6) En So Trol Technology

This technology useful in increasing solubility. Integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies, used by Shire laboratory.[4,11]

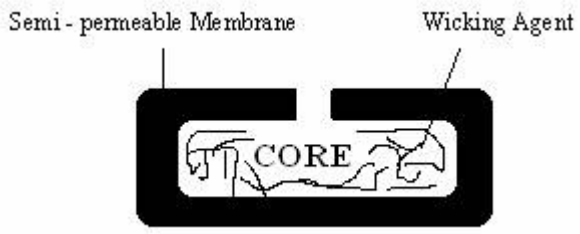

Fig. 6: En So Trol Technology.[11]

7) Oros ® Push Pull Technology

This technology consist of one or more layer of the drug and other layer consist of push layer. In this semipermeable membrane surrounds the tablet core. In this technology composed of suspending agent and osmotic agent.[11]

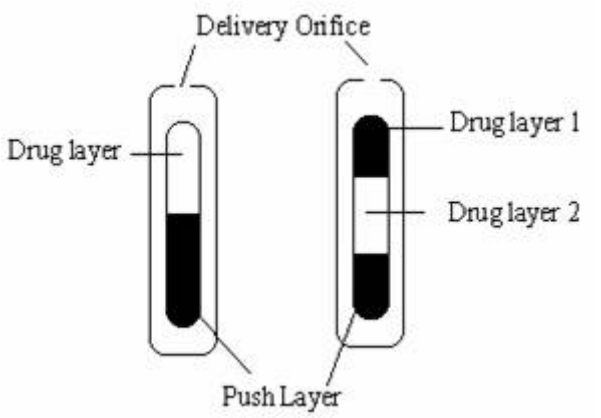

Fig. 7: Bilayer and Trilayer Oros Push Pull Technology[7,11]

8) Elan Drug Technologies' Dual Release Drug Delivery System (DUREDAS™ Technology)

DUREDAS™ Technology 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 and modified–release hydrophilic matrix complex as separate layers within one tablet. The modified release properties of the dosage form are provided by combination of hydrophilic polymers.[11]

9) Geminex Technology

Geminex Technology actively applied by penwest in following areas diabetes, cardiovascular diseases, cancer and CNS disorders. In this technique one or more drug with different release rate in single dosage form which increases therapeutic efficacy of drugs.[9,7,11]

- **Different Types of Bilayer Tablet Press**

1. Single sided tablet press.
2. Double sided tablet press
3. Bilayer tablet press with displacement monitoring.
4. Multilayer compression basics

1. Single Sided Tablet Press[4,11]

There are number of presses available for bilayer tablet manufacturing, but single sided tablet press is simplest design available for bilayer tablet development. In these tablet presses double feeder chambers separated from each other. Each chamber run as per gravitational force, or force fed with different powders thus producing bilayer tablet. As the die comes under the feeder firstly get loaded with first layer of powder followed by pre compression and then second layer powder with following second precompression and then final main compression, hence entire tablet manufactured in one or two steps (two pre and main compression). While developing bilayer tablet there should be sufficient bond between two layers so that no layer separation occurs when the tablet is produced.

Following Limitations of Single Sided Press

- There is no proper weight monitoring or control of the individual layers.
- No distinct visual separation between the 2 layers.
- Dwell time
- Compression force.
- Poor deration capping and hardness problems

Dwell Time

It is defined as the time during which compression force is above 90% of its peak value. Major factor in the production of quality tablets is longer dwell time.

Compression Force

Compression force of 100 daN require for many bilayer tablets for first layer compression for the retaining ability to form bond with the second layer. 100 daN compression force. Sufficient for proper bonding between two layers but above this force, ability of bonding may be lost. This results in separation of the 2 layers due to low hardness of bilayer tablet.

Fig. 8: Single Sided Tablet Press.[13]

2. Double Sided Tablet Press[11]

Automated production control used by most of double sided tablet presses, which with compression force is useful in monitor and control of tablet weight. Control system is used for measuring peak compression force exerted on each individual tablet or layer at the stage of final main compression of bilayer tablet.it proved useful for rejection out of tolerance and correction of the die fill depth with help of the signal produced by control system.

Advantages

- To avoid capping and separation of the individual layer by applying low compression force on first layer.
- Sufficient hardness is built in tablet by increasing dwell time at precompression of both first and second layer.
- There is maximum avoidance of cross contamination in bilayer tablet.
- In bilayer tablet clear visual separation between the layers.
- High production yield.

- Control system is very useful in accurate and independent weight control of the individual layer.

Limitations

As for proper bonding between two layers in bilayer precompression force required for first layer should be less than second one. Bonding is not possible if precompression done at high compression force. Accuracy of the weight monitoring/control of the first layer in the case of tablet presses with "compression force measurement" reduces unfortunately by low compression force used for the first layer precompression. Most of automatically controlled tablet presses have principle of compression force.

Fig. 9: Double Sided Tablet Press.[13]

3. Bilayer Tablet Press With Displacement Monitoring[11]

This tablet press worked on principle displacement tablet weight control, which is different from the principle of compression force. As based on principle sensitivity of control system does not depend on the tablet weight but depends on applied precompression force. In this case the risk of capping and separation increases at higher production speed increases but can be reduced by sufficient dwell time at all four compressions.

Advantages

- Principle useful for accurate independent weight control of the individual layers.
- Proper bonding possible as there is use of low compression force applied on the first layer avoids capping and separation of the two individual layers.
- Maximum production yield and clear visual separation between layers in tablet.
- Avoid cross contamination between the layers.
- Ability to build sufficient hardness to tablet at maximum turret speed by increased dwell time at pre-compression of both first and second layer.
- There is no any effect of stiffness on bilayer tablet.

Fig. 10: Bilayer Tablet Press With Displacement.[13]

4. Multilayer Compression Basics[11]

Multilayer tablet means two or more layers in tablets and are able to provide multiple release pattern of drugs. Multilayer tablets are developed on presses designed specifically for multilayer compression or standard double press can be converted for multilayers. Multilayer tablet technology used for sustained release purpose. Release pattern of drug depends on granules, fast releasing granules leads to sudden rise in blood concentration work as loading dose whereas plasma drug level maintained at a steady state by sustained releasing granules.

- **Preparation Of Bilayer Tablets**[4]

Bilayer tablets are prepared with double compression technique,

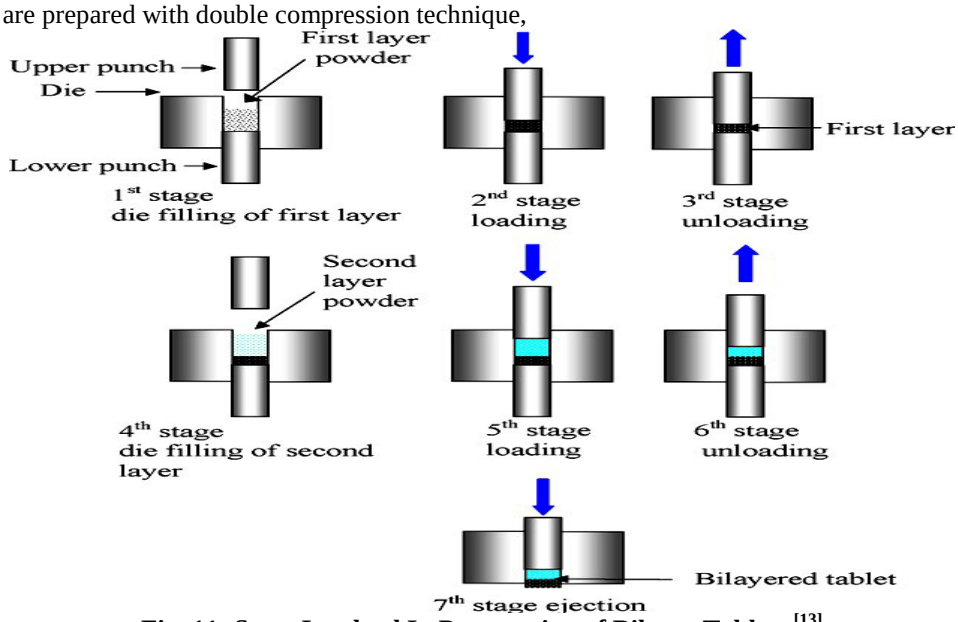

Fig. 11: Steps Involved In Preparation of Bilayer Tablets.[13]

- **Challenges In Development Of Bilayer Tablet**[4]
- Cross contamination
- Production yield
- Cost
- Delamination

- **Characterization of Bilayer Tablet**

1. Particle Size Distribution

There are number of methods for measuring particle size. Mostly sieving method used for measuring particle size distribution.[11]

2. Photon Microscope Study

Photomicroscope (X450 magnifications) used for taking Photo-microscope image of TGG and GG.[11]

3. Angle of Repose

Angle made by the pile of the powder from horizontal surface. The diameter of the powder cone measured and the angle of repose was calculated. By using following equation,

Tan Ø=h/r

OR

Ø= Tan¯ h/r

Where,

Ø =Angle of repose,

h = height of the pile,

r = radius of the powder cone.[11]

4. Moisture Sorption Capacity

There are different patterns of moisture absorption, by all disintegrate from atmosphere which affects moisture sensitive drugs. This property checked with help of taking 1 g disintegrant in Petri-dish. Which at 37± 1°C kept in stability chamber and at 100% RH for 2 days. Amount of moisture uptake was calculated by weight difference.[11]

5. Density

LBD ¼ weight of the powder=volume of the packing ð2Þ

TBD ¼ weight of the powder=tapped volume of the packing ð3Þ.[11]

6. Compressibility

Compressibility measured with help of Carrs Index.

CI = (TD-BD) /TD × 100

Where,

TD = Tapped density,

BD = Bulk density.[11]

7. Hausners Ratio

It is important to indicate flow properties of powder or granules

Hausner's Ratio = Tapped density/Bulk density.[14]

Table 1: Current Patents Status Of Bilayer Tablet Technology –a Glimpse.[15]

Patent No.	Field of Invention	Drug Candidate	Year of Publication	Inventors
US 2015/0037410 A1	Pharmaceutical composition of ranolazine and dronedarone	Ranolazine and dronedarone	2015	Gerber et al.
US 8,637,078 B2	Bilayer tablet comprising telmisartan and diuretic	Telmisartan and hydrochlorothiazide	2014	Nakatani et al.
US 8,741,345 B2	Modified release pharmaceutical compositions of dexlansoprazole	Dexlansoprazole	2014	Cifter et al.
US 8,535,715 B2	Bilayer tablet formulations	Metformin	2013	Abebe et al.
US 8,524,278 B2	Controlled release pharmaceutical formulations of nitazoxanide	Nitazoxanide	2013	Rossignol et al.
US 7,332,183 B2	Multilayer dosage form containing nsaids and triptans	Naproxen	2008	Plachetka et al.
US 2006/0141037 A1	Bilayer tablets of oxcarbazepine	Oxcarbazepine	2006	Mehta et al.
US2006/0110450A1	Bilayer tablet of telmisartan and amlodipine	Telmisartan and amlodipine	2006	Eisenreich et al.
US 2005/0220877 A1	Bilayer tablet compprising an antihistamine and a decongestant	Ibuprofen	2005	Patel et al.

Table 2: Various Advancements In The Field Of Bilayer Tablets.[15]

Drug(s)	Dosage form	Clinical significance	Method of preparation	Year
Amoxycillin and potassium clavulanate	Bilayer tablets	Produce effect against microbial infections	Dry Granulation	2014
Atorvastatin and atenolol	Bilayer tablets	Treatment of hypertension and hypercholestrolemia	Direct compression	2014
Losartan Potassium	Bilayer tablets	Biphasic release profile	Direct compression	2014
Diclofenac Sodium, Paracetamol	Bilayer tablets	Effective in reducing pain	Wet Granulation	2013
Telmisartan and hydrochlorthiazide	Bilayer tablets	To minimize contact b/w hydrochlorothiazide and basic component of telmisartan	Direct compression	2013
Rifampicin and Isoniazid	Bilayer tablets	Treatment of Tuberculosis	Wet Granulation	2012
Metformin Hydrochloride and Glipizide	Bilayer tablets	Treatment of Diabetes	Direct compression	2011
Ibuprofen, Methocarbamol	Bilayer tablets	Produce synergistic effect in back pain	Wet Granulation	2010
Metoprolol succinate and Amlodipine Besilate	Bilayer tablets	Treatment of hypertension	Wet Granulation	2010
Propranolol Hydrochloride	Bilayer tablets	Bimodal drug release	Direct compression	2009

Table 3. Marketed Formulation Of Bilayer Tablets.[15,16]

Sr.no	Product Name	Chemical Name	Developer	Therapeutic
1	Glycomet®-GP2Forte	Metformin hydrochloride, Glimepiride	USV Limited	Anti-diabetic
2	Amlopin M	Metoprolol tartrate & amlodipine	USV	Antidiabetic
3	Mypride-M	Glimepiride, metformin HCL	Rech Elist pharma	Antidiabetic
4	Tribet-1	Glimepiride, Pioglitazone hydrochloride, Metformin hydrochloride	Abbott Healthcare Pvt. Ltd.	Antidiabetic
5	DIAMICRON®XRMEX 500	Gliclazide, Metformin hydrochloride	Sedia® Pharmaceuticals (India) Pvt. Ltd.	Antidiabetic
6	PIOKIND®-M15	Pioglitazone, metformin hydrochloride	Psychotropics India Ltd.	Antidiabetic
7	3D-OHA	Glimepiride, metformin	Stvides	Antidiabetic
8	Glispo 2M	Glimepiride & metformin	Visham lifecare	Antidiabetic
9	Betaloc-H	Hydrochlorothiazide, metoprolol	Astrazeneca	Antihypertensive
10	Revelol®-Am 25/5	Metoprolol, succinate, Amlodipine besilate	Ipca Laboratories Ltd.	Antihypertensive
11	Acard	Amlodipine, atenolol	Edward	Antihypertensive
12	Actiblok AM	Amlodipine, metoprolol	Biocon	Antihypertensive
13	Cortel-A	Telmisartan, amlodipine	Corona laboratorial	Antihypertensive

14	ANAMONT-L	Montelukast	Savamedica	Antiasthmatic & COPD
15	DOXOVENT-M	Doxofylline	Glenmark	Antiasthmatic & COPD
16	BICLOMOL	Diclofenac & paracetamol	Olcare	NSAID
17	A-Niclo P	Aceclofenac, paracetamol	Aknil biotech	NSAID
18	Newcold Plus	Levocetrizine hydrochloride, Phenylpropanolamine, Paracetamol	Piramol Healthcare Ltd.	NSAID
19	HEADSET	Saumatriptan	LUPIN	Antimigraine
20	JUDO-P	Tramadolt, Paracetamol	AAMORB	Analgesic
21	STARPESS-H	Metoprolol Hydrothiazine	LUPIN	Beta blocker
22	ATOREM-F	Atorvastatin & fenofibrate	MNS-lab	Disylipidamic agent
23	DEPLATT-A	Aspirin & Dopidogrel	Torrent	Antipletlet anticoagulant
24	DIUCONTIN-K®20/250	Furosemide, Potassium chloride	T.C. Health Care Pvt. Ltd.	Diuretic
25	TRIOMUNE 30	Nevirapine, Lamivudine, Stavudine	Cipla Ltd.	Anti-Viral
26	AMLONG-MT	Amlodipine	Micro carsyon	Antianginal
27	Artesun-plus	Artesunate, Amodiaquine	Guilin pharmaceuticals	Antimalarial
28	Mucinex	Guaifenesin	Mucinex	Expectorant
29	D montus	Doxofylline, montelucast sodium	Jarrow pharmaceutical	Antiasthmatic
30	Alpha lipoic	Alpha lipoic, Biotin	Jarrow pharmaceutical	Antioxidant
31	PIO-M	Pioglitazine, metformin hydrochloride	Cipla	Antidiabetic
32	Volise-m	Voglibose,Metformin hydrochloride	Ranbaxy laboratories Ltd.	Antidiabetic
33	Unistar	Rosuvastatin, Aspirin	Unichem laboratories Ltd	Dyslipidemic agent
34	Pioglu	Pioglitazone, Metformin hydrochloride	Emcure pharmaceutical Ltd.	Antidiabetic
35	Glimeto-MP	Glimepride,Pioglitazone	RPG life Sciences Ltd.	Antidiabetic

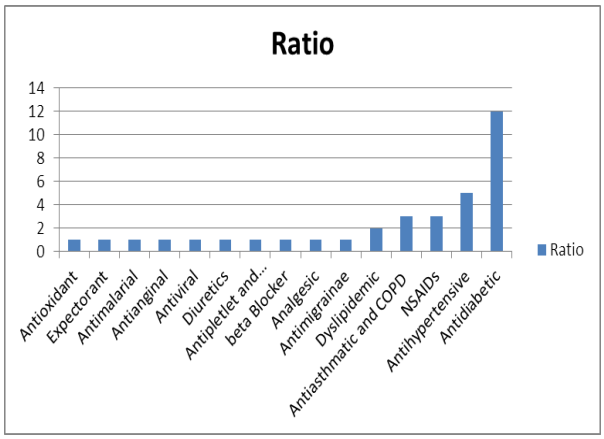

Fig.12 Marketed Distribution of Bilayer Tablet.

CONCLUSION

Bilayer technique is new advancement in field of tableting over the conventional tablet.It is an excellent improved technique for providing combine release pattern of immediate release and sustained release drugs. This technology is very efficient for incorporating incompatible drugs together in single dosage form. Controlled release can be obtained by swellable surrounding.

The literature reveals that antidiabetic and antihypertensive drugs are mostly formulated as a bilayer tablet. This review specifically deals with the various technologies ,marketed formulations as well as patented bilayer tablet formulations which facilitates the need of researchers to select the specific drugs and formulation technologies for development of new bilayer tablet dosage forms..

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