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REVIEW ARTICLE: ELEGANT BILAYER TABLETS

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ABSTRACT

In the pharmaceutical industry Bilayer tablet is the novel technology for the development of controlled release formulation and developing a combination of two or more active pharmaceutical (API) ingredients in a single dosage form. Now a day the use of bilayer tablets has been increased. Bilayer tablet plays an important role for development of controlled release in order to give a successful drug delivery and can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles. To reduce capital investment, quite often existing but modified tablet presses are used to develop and produce such tablets. The objective of this review article is to ensure that to reduce the frequency of dosing and drugs are available to its citizen are not only safe and effective, but are also properly manufactured and packaged to meet the established quality target product profile over it shelf life.

KEYWORDS: Bilayer tablets, API, Formulation, Controlled release, frequency of dosing.

INTRODUCTION

Pharmaceutical tablet is the dominant dosage form for drug delivery, occupying two-thirds of the global market. Generally, they are produced by compressing dry powder blends consisting of a number of components with different functionalities in a die. It is technically difficult to ensure that a tablet possesses both a certain mechanical strength and a low packing density, so that it is sufficiently strong to maintain its integrity during handling and transport and also weak enough to satisfy the dispersion and dissolution requirements.[1][2][3]

An ideal drug delivery system is such that provides the required drug amount within a short duration and also maintains the steady level of drug concentration throughout the dosing period.[4] However, any conventional dosage form behaves as per its type which can be either immediate release or sustained release. Furthermore, the drugs with shorter half life should be administered multiple times to maintain required drug level. Controlled drug delivery system has been introduced to overcome the drawback of fluctuating drug levels associated with conventional dosage forms.[5][2]

Type of Tablets & Class of Tablets.[6]

Table No. 1: Type of tablets and class of tablets.

1. Oral Tablets for Ingestion I. Standard compressed tablets II. Multiple compressed tablets : a) Layered tablets b) Compression coated tablets c) Inlay tablets III. Modified release tablets IV. Delayed action tablets V. Targeted tablets: a) Floating tablets b) Colon targeted tablets VI. Chewable tablets	**2. Tablets Used In the Oral Cavity** I. Buccal tablets II. Sublingual tablets III. Troches and lozenges IV. Dental cones **3. Tablets Administered By Other Routes** I. Implantation tablets II. Vaginal tablets	**4. Tablets Used To Prepare Solution** I. Effervescent tablets II. Dispersible tablets III. Hypodermic tablets IV. Tablet triturates

Need of Developing Bilayer Tablets

- To separate incompatible API's with each other, to control the release of one layer by utilizing the functional property of the other layer (such as osmotic property).[7-9]
- For the purpose of developing novel drug delivery system such as buccal/Mucoadhesive delivery system and floating tablets for gastro retentive drug delivery system. It helps in controlling drug delivery rate of single or two APIs.[10]

- The preparation of bilayer tablets is used to provide systems for the administration of drugs which are incompatible and to provide controlled release tablet preparations with surrounding multiple swelling layers.[11][12]
- In case of drugs having a low half-life, each of the two layers of the tablet respectively content a loading dose and maintenance dose of the same and thus increase the bioavailability of the drug.
- Analytical work may be simplified by separating of the layer prior to assay.
- Frequency of the dose administration is reduced which ultimately improve the patient compliance.[13-15]

General properties of Bilayer Tablet[16]

1. A bi-layer tablet should posses an elegant product identity and should be free of defects like cracks, chips, contamination and discoloration.
2. Must have sufficient strength which will handle mechanical shock during its production.
3. It must have the chemical and physical stability to maintain its physical attributes over time.
4. Must have a chemical stability shelf-life.

GMP Requirements for Bilayer Tablet

To produce a quality bi-layer tablet, in a validated and GMP-way, it is very important to follow the following criteria for the selection of bilayer press. These requirements seem obvious but are not so easily accomplish. The press should be capable of:

1. Preventing capping and separation of the two individual layers that constitute the bi-layer tablet.
2. Preventing cross-contamination between the two layers.
3. Providing sufficient tablet hardness.
4. Accurate and individual weight control of the two layers.
5. Producing a clear visual separation between the two layers.
6. Manufacturing products of high yield.

ICH Guidelines For Bilayer Tablets

As per ICH guidelines, protocols have been issued for clinical study of medicinal products for hypertension, testing and licensing criteria for fixed combination products, bioavailability and bioequivalence studies, ratio and/or predetermined content of one component in a combination drug product. Bilayer technology has the potential to provide better patient compliance at an affordable cost however the constantly increasing cost of healthcare reduced by the way of research. The field of bilayer tablet is use to develop more efficient products with a novel mode for drug release and to cover most of the drug combinations products.

Applications[17-19]

1. Bi-layer tablets are suitable for sequential release of two drugs in combination.
2. It is improved technology to overcome the shortcoming of the single layered tablet.
3. Bilayer tablets are used to deliver the loading dose and sustained dose of the same or different drugs.
4. Bilayer tablets are used to deliver the two different drugs having different release profiles.

Advantages of Bilayer Tablet Over The Other Conventional Tablet[13][14][15]

- This formulation can be used to separate two incompatible substances.
- When the two different layers of the tablet contain two different drugs, then the tablet can be easily used in combination therapy.
- It makes possible Extended-release preparations with the immediate-release quantity in one and the slow-release portion in the second layer.
- Two-layer tablet require less material than compression coated tablets, weight less, and may be thinner.
- The weight of each layer can be accurately controlled, in the contrast to putting one drug of a combination product in a sugar coating.
- For chronic condition requiring repeated dosing.
- Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.

Disadvantages of Bilayer Tablet[13][14][15]

- One of the major challenges in bilayer formulation is lack of sufficient bonding and adhesion at the interface between the adjacent compacted layers which is often the result of an interfacial crack and layer separation.
- If the compacted layers are too soft or too hard, they will not bind securely with each other which can lead to compromised mechanical integrity and also the separation of the layers.
- Other challenges during development include establishing the order of layer sequence, layer weight ratio, elastic mismatch of the adjacent layers, first layer tamping force, and cross contamination between layers.
- Administration of sustained release bilayer tablet does not permit the prompt termination of therapy.
- The physician has a less flexibility on adjusting the dose regimens.

Bilayer Tablet[20-22]

Bilayer tablets are efficient for sequential and simultaneous release of two different API's. In this two layers are immediate release and second one is sustained release.

Bilayer tablet is suitable form to deliver two drugs at one time without any dynamic and pharmacological interaction with each other. The bilayer tablet containing subunits that may be either the same drug (homogeneous) or different drugs (heterogeneous),

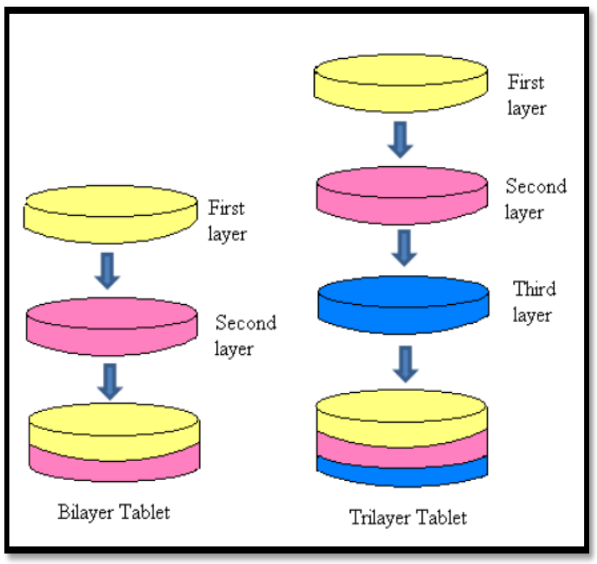


Figure 1: Types of Multi-layered tablet.

A. Homogenous type

Bilayer tablets are mainly referred when the release profiles of the drugs are different from one another. Bilayer tablets allows for designing and modulating the dissolution profile and release rate characteristics. Bilayer tablets are formulating with one layer of drug for immediate release while second layer designed to release drug in the extended release manner.

B. Heterogeneous type

Bilayer tablet is suitable for sequential release of two components in combination, separate two incompatible substances.

Various Techniques For Bilayer Tablets

1. OROS push pull Technology[23]

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.

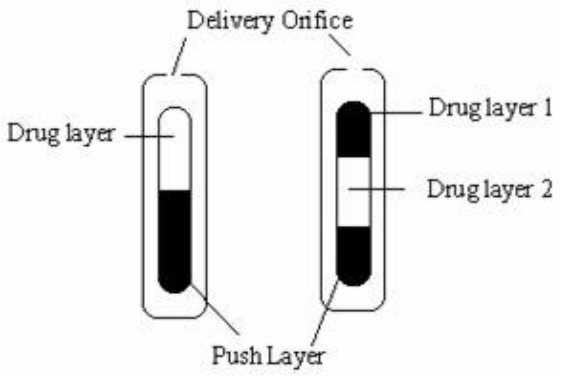


Figure 2: Bilayer and trilayer OROS Push pull technology.

2. L-OROS tm Technology[23]

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

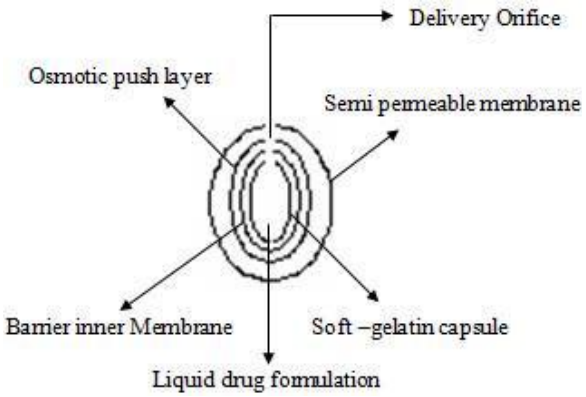


Figure 3: L – OROS tm technology.

3. EN SO TROL Technology[23]

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.

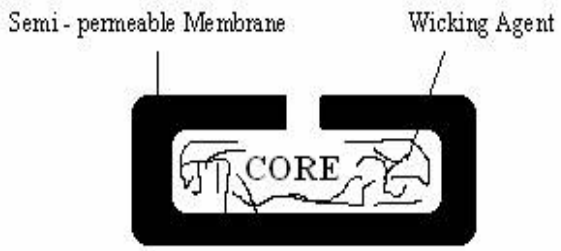


Figure 4: EN SO TROL Technology.

4. DUROS Technology[24]

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.

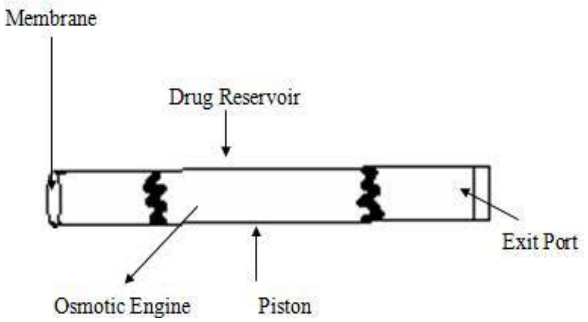


Figure 5: DUROS technology.

5. 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.

Manufacturing Process of Bilayer Tablet[25]

Manufacturing processes such as wet granulation/roller compaction and addition of binders increases the level of complexity in understanding the critical factors governing compression and tablet breaking force. Thus, the tablet breaking force and the tablet's susceptibility for delamination /capping either during manufacturing or during storage need to be carefully observed. Apart from the critical material attributes of individual components and final blend, the tablet press has large influence on the manufacture of multilayer tablets. The level of pre-compression force, punch velocity, consolidation time (time when punches are changing their vertical position in reference to the rolls as the distance between the punch tips are decreased), dwell time (time when punches are not changing their vertical position in reference to the rolls), relaxation time (time when both punches are changing their vertical position in reference to the rolls as the distance between the punch tips increases before losing contact with the rolls), and the applied force can have significant effect on the critical quality of the tablet. The extent of compact densification and resistance to compressibility within the die cavity was impacted by compaction pressure and the punch velocity.

EVALUATION OF BILAYER TABLETS

A. Pre-Compression Evaluation

1. Particle size distribution

The particle size distribution was measured using sieving method.[26][27]

2. Photo-microscope study

Photo-microscope image of TGG and GG was taken (X450 magnifications) by Photomicroscope.[26][27]

3. Angle of repose

In order to determine the flow property, the Angle of repose was determined. It is the maximum angle that can be obtained between the free standing surface of the powder heap and the horizontal plan.[28][29]

Tan -1 (h/r) Where, h= height, r = radius

4. Determination of bulk density and tapped density

A quantity of 5g of the powder (W) from each formula was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using the following formulas.[30][31][32]

Bulk density = W / VO Tapped density = W / Vf

Where, W = weight of the powder, VO = initial volume, Vf = final volume

5. Compressibility index (carr's indices)

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. A material having values of less than 20 to 30% is defined as the free flowing material.[30][31][32]

CI = 100 (VO – Vf)/V Where, CI = Compressibility index, VO = initial volume, Vf = final volume.

6. Hausner's ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.[30][31][32]

7. Moisture sorption capacity

All disintegrates have capacity to absorb moisture from atmosphere which affects moisture Sensitive drugs. Moisture sorption capacity was performed by taking 1 g of disintegrate Uniformly distributed in petri-dish and kept in stability chamber at 37±1°c and 100% relative Humidity for 2 days and investigated for the amount of moisture uptake by difference Between weights.[26][27]

B. Post-Compression Evaluation

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.[33,34]

2. Size and Shape

The size and shape of the compressed tablets were examined under the magnifying lens.[33,34]

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.[35]

4. Friability Test

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed (w0 initial) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (w).[36]

The % friability was then calculated by: **Percentage of Friability = 100 (1-w/w0)** Percentage friability of tablets less than 1% is considered acceptable.

5. Weight Variation Test

Twenty tablets were selected at random and the average weight was determined. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation shown in table and none deviates by more than twice the percentage. USP official limits of percentage deviation of tablet are presented in the table.[26]

6. Swelling Studies

Swelling property of tablet was determined by placing it in the dissolution test apparatus, in 900 ml of 0.1 N HCl at 37 ± 2 0C. The weight and volume reached by the matrix tablets over time was determined by withdrawing the tablets periodically from dissolution medium. The tablets were weighed on an analytical balance after slight blotting with tissue paper to remove the excess test liquid. The volume of the tablets was obtained by measuring the thickness and diameter, considering a right circular cylinder form. The determined weight and volume were used to calculate the tablet density over the dissolution study. Swelling characteristics were expressed in terms of percentage water uptake (WU %) according to the equation:[37]

WU % = Wt. of swollen tablet – Initial wt. of tablet / Initial wt. of tablet × 100.

7. Hardness (Crushing Strength)

The resistance of tablets to capping**,** abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness**.** Monsanto hardness tester measures the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet. The Strong-Cobb Pfizer and Schleuniger apparatus 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). Hardness generally increases with normal storage of tablets and depends on the shape, chemical properties, binding agent and pressure applied during compression.[38]

8. Disintegration Test

Disintegration test apparatus is generally used to measure disintegration time of tablet. For Disintegration time, one tablet is placed in each tube and the basket arch is positioned in 1 L beaker containing water at 37°C ± 2°C. A standard motor driven device is used to move the basket assembly up and down. To comply with USP standard, all tablets must disintegrate and all particles must pass through the 10 mesh in the time specified.[39]

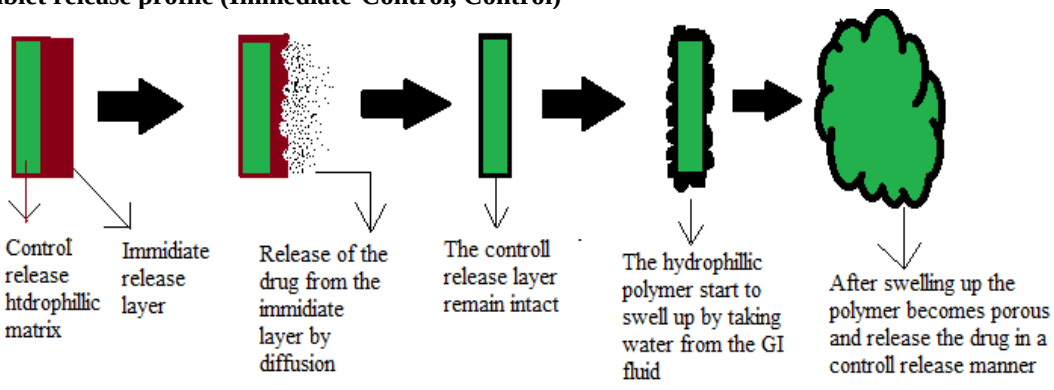
9. Dissolution Studies

Drug release studies are carry 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 about 2 hours. The dissolution medium was replaced with pH 6.8 phosphate buffer (900ml) and experiment continued for another 10 hours. The samples withdrawn during dissolution test are analyzed by UV spectrophotometer using multi component mode of analysis.[36]

10. Stability Study

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. 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.[40]

Bilayer tablet release profile (Immediate-Control, Control)[41]



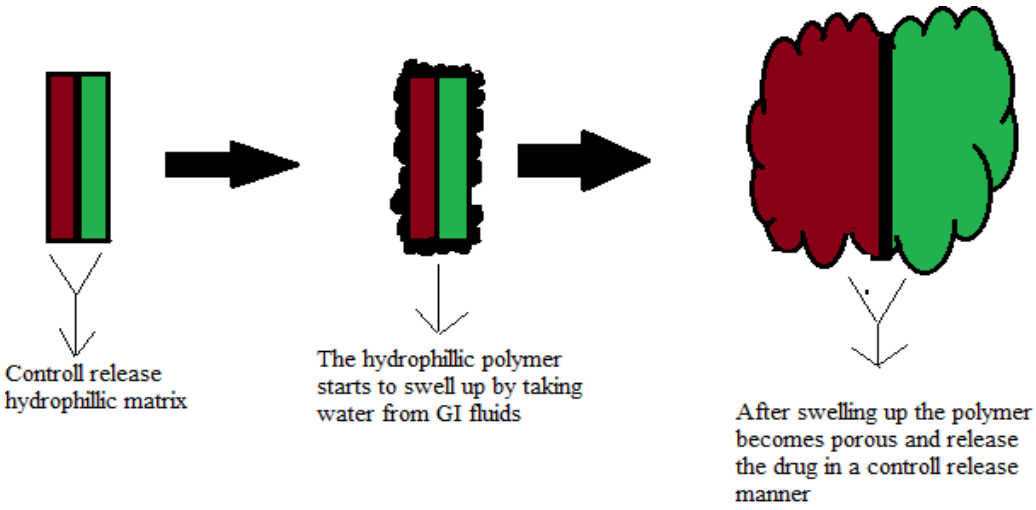


Figure 6: Immediate-Control, Control Profile.

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.

DUREDAS or Dual Release Drug Absorption System (Elan Corporation) utilizes bilayer-tabletting technology, which has been specifically developed to provide two different release rates or dual release of a drug from a single dosage form. The tablets are prepared by two separate compression steps that combine an immediate-release granulate (for rapid onset of action) and a controlled-release hydrophilic matrix complex within one tablet. The immediate release layer, release the drug immediately after going into the GIT (stomach or intestine) in a diffusion and dissolution manner and the controlled-release matrix remains intact and slowly absorbs fluid from the GI tract, which causes the matrix to expand and transforms the hydrophilic polymers into a porous, viscous gel that serves as a barrier between the drug and the surrounding fluid. As the gel continues to expand, fluid penetrates further into the dosage form, dissolving the drug and allowing the resulting solution to diffuse out in a controlled manner.[42]

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 the drug release of each is controlled to maximize therapeutic effect of the combination.[43]

Table No. 2: Commercially marketed bilayer tablets[44]

S.No	Product Name	Chemical Name	Developer
1	ALPRAX PLUS	Sertraline, Alprazolam	Torrent Pharmaceutcals Ltd.
2	Glycomet®-GP2Forte	Metformin, Glimepiride	USV Limited
3	Newcold Plus	Levocetrizine hydrochloride, Phenylpropanolamine, Paracetamol	Piramol Healthcare Ltd.
4	DIAMICRON®XRMEX500	Gliclazide,Metformin hydrochloride	Sedia® Pharmaceuticals (India) Pvt. Ltd.
5	DIUCONTIN-K®20/250	Furosemide, Potassium chloride	T.C. Health Care Pvt. Ltd.
6	TRIOMUNE 30	Nevirapine, Lamivudine, Stavudine	Cipla Ltd.
7	PIOKIND®-M15	Pioglitazone, metformine Hydrochloride	Psychotropics India Ltd.
8	Revelol®-Am 25/5	Metoprolol succinate, Amlodipine Besilate	Ipca Laboratories Ltd.

CONCLUSION

Present review article mainly focused on, why bilayer tablet is considered as better option than conventional tablet. Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles using DUREDAS technology. Present review mainly focuses on fundamentals of bilayer tablets and it's applications in Pharmaceutical industries. Several pharmaceutical companies are developing bilayer tablet for co-administration of drugs to improve the therapeutic efficacy as well as to reduce the chances of drug-drug interaction.

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