IJPSR (2012), Vol. 3, Issue 12 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 31 August, 2012; received in revised form 16 October, 2012; accepted 24 November, 2012

RECENT APPORACHES IN BILAYERED TECHNOLOGY: REVIEW

Parnapalli Malathi* and Arshad Bashir Khan

Department of Pharmaceutics, Krupanidhi College of Pharmacy, Sarjapura main road, Carmelaram post, Bangalore-560 035, Karnataka, India

Keywords:
Bilayered tablets Push Pull Technology,
OROS technology,
DUROS technology,
GMP requirements for Bilayered Tablets,
Evaluation of Bilayered Tablets

Correspondence to Author:

Arshad Bashir Khan,

Assistant Professor, Department of Pharmaceutics, Krupanidhi College of Pharmacy, Sarjapura main road, Carmelaram post, Bangalore-560 035, Karnataka, India

E-mail: arbakh@gmail.com

ABSTRACT

Bilayered tablet is an important pharmaceutical technology for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. Bi-layer tablet is suitable for sequential release of two drugs in combination, to separate incompatible substances and also formulating sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. Now days the pharmaceutical companies are currently developing bi-layer tablets due to variety of reasons such as patent extension, therapeutic benefit and a marketing strategy. To reduce capital investment, quite often existing but modified tablet presses are used to develop and produce such tablets. This article explains about different techniques of bilayered tablet preparation the development and production of bilayered tablets needs to be carried out on purpose built tablet presses to overcome common bilayered problems such as layer separation, insufficient hardness, and inaccurate individual layer weight control, cross-contamination between the layers, reduced yield and evaluation of bilayered tablets.

INTRODUCTION: Bilayer tablets have some key advantages compared to conventional monolayer tablets. For instance, such tablets are commonly used to avoid chemical incompatibilities of formulation components by physical separation. In addition, bilayer tablets have enabled the development of controlled delivery of active pharmaceutical ingredients with pre-determined release profiles by combining layers with various release patterns, or by combining slow-release with immediate-release layers.

Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release layer delivers initial dose and second layer delivers maintenance dose [1, 2].

The bilayer tablet is a concept utilized by Skye Pharma PLC in their Geomatrix tablet, which is composed of different layers. The system allows the incorporation of more than one drug into the dosage form. Formulation of layers from different polymers allows manipulation over more than one rate-controlling polymer, thus enabling different types of drug delivery of one or more drugs, i.e. where the drug may be released with a bolus and then at a controlled rate or by targeted drug delivery in the GI tract using pH dependant polymers.

QUICK RESPONSE CODE

IJPSR: ICV (2011)- 5.07

Website: www.ijpsr.com

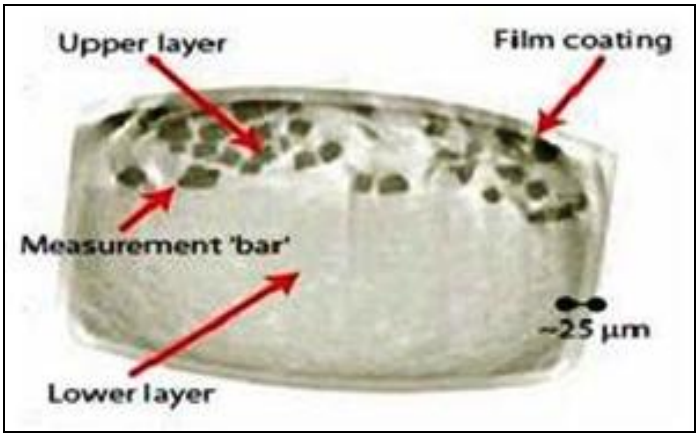

FIGURE 1: CONVENTIONAL BILAYER TABLET STRUCTURE

There are clearly a number of issues of concern to the production of bilayered tablets. While the mechanical strength of layered tablets has been observed not to be a controlling factor in drug release, the determination of this property could be beneficial in understanding the adhesion between various layers and provide an improved characterization of the systems. Bi-layer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug later, either as a second dose or in an extended release manner.

Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two substances and also for sustained release tablet in which one layer is immediate release layer delivers initial dose and second layer delivers maintenance dosev[3].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 tablet preparations by providing surrounding or multiple swelling layers. Control release systems have also been proposed for showing how the different designs can be used to control the drug release profile such as constant, delayed, pulsatile and multi modal release profiles.[4]

Need of Bilayer Tablets [5,6,7]:

1. For the administration of fixed dose combinations of different APIs,to prolong the drug product life cycle, buccal/ mucoadhesive delivery systems, fabrication of novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery.
2. 2. Controlling the delivery rate of either single or two different active pharmaceutical ingredients.
3. 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.
4. To separate incompatible (APIs) Active pharmaceutical ingredient from each other, to control the release of API from one layer by utilizing the functional property of the other layer (such as, osmotic property).

Advantages of the Tablet Dosage Form:

1. Cost is lower compared to all other oral dosage form.
2. Greatest chemical and microbial stability over all oral dosage form.
3. Objectionable odour and bitter taste can be masked by coating technique.
4. Flexible concept.
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. Suitable for large scale production.

Disadvantages of Bi-Layer Tablet Dosage Form:

1. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
2. Bitter testing drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.
3. Difficult to swallow in case of children and unconscious patients.
4. Drugs with poor wetting, slow dissolution properties, lower absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.

Various Techniques for Bilayer Tablet Duredas [8, 9]: Duredas or Dual Release Drug Absorption System (Elan Corporation) utilizes bilayer-tableting 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 direct-compression steps that combine an immediate-release granulate (for rapid onset of action) and a controlled-release hydrophilic matrix complex within one tablet. 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 Benefits offered by the DUREDAS technology include: Bilayer tabletting technology. Tailored release rate of two drug components. Capability of two different CR formulations combined. Capability for immediate release and modified release components in one tablet. Unit dose, tablet presentation. 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. Again both immediate- release and controlled-release combinations of the two drugs are feasible.

Geomatrix Technologies [9]**:** Geomatrix system is a multilayer tablet with a matrix core containing the active ingredient and one or more modulating layers (barriers) applied to the core during the tableting process. The function of these barriers is to delay the interaction of the core with the dissolution medium.

Eight Geomatrix technologies are designed to meet a wide range of therapeutic objectives: Zero-order release provides a constant rate of drug release over a defined period of time; binary release is used to provide the controlled release of two different drugs in a single tablet; quick-slow release provides a quick burst of drug release followed by a constant rate of release over a defined period of time; slow-quick release provides an initial constant rate of release followed by a quick burst of drug release at a predetermined time; positioned release delivers the drug to a predetermined position in the digestive system before it begins to release the active drug compounds; accelerated release provides a constantly accelerating rate of drug release; delayed release provides a predetermined time lag before it begins releasing drug molecules; multiple pulse provides an initial quick burst of drug release followed by a predetermined period of no release. Some of the drugs that are marketed based on this technology are diltiazem hydrochloride, nifedipine, and diclofenac sodium.

L-OROS tm TECHNOLOGY [10]: This system used for the solubility issue Alza developed the L-OROS system where a lipid soft gel product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, than osmotic push layer and then a semi permeable membrane, drilled with an exit orifice.

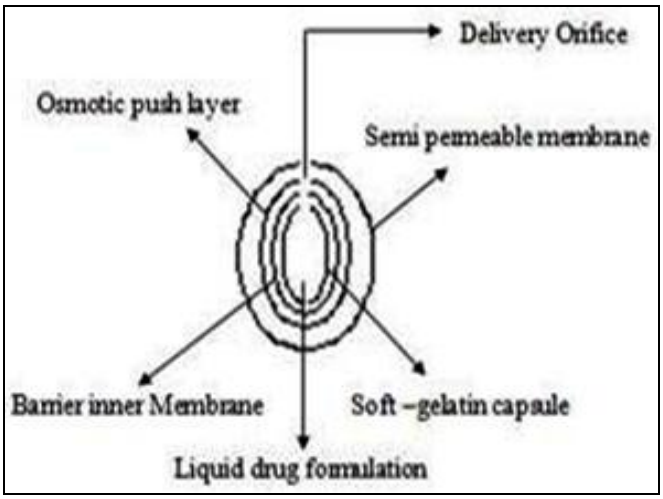

FIGURE 2: L-OROS TM TECHNOLOGY

OROS® push pull technology [10]**:** This system consists of mainly two or three layers among which the one or more layer consists of the drug and other layer are consist of push layer (**Fig. 1**). 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.

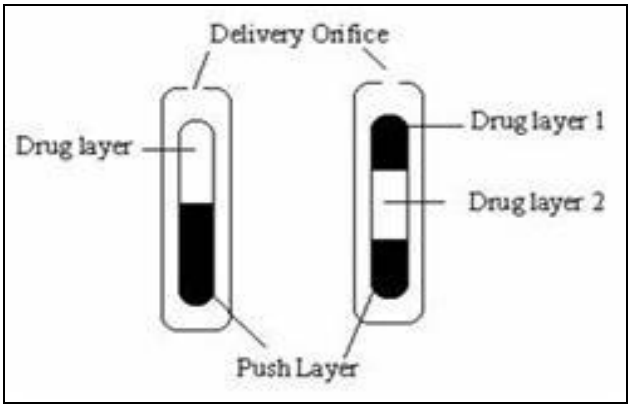

FIGURE 3: OROS PUSH PULL TECHNOLOGY

EN SO TROL technology [10, 11]: Solubility enhancement of an order of magnitude to create optimized dosage form. Shire laboratory use an integrated approach o drug delivery or focusing on identification and incorporation of the identified enhancer intto controlled release technologies.

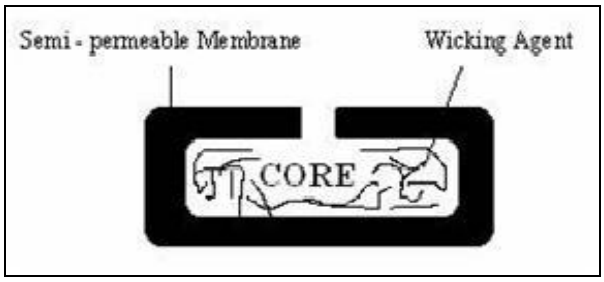

FIGURE 4: EN SO TROL TECHNOLOGY

DUROS technology [9, 10]: DUROS (Alza Corporation) is based on implant technology, which provides an alternative for the delivery of a wide range of therapeutic compounds, including peptides, proteins, and other bioactive macromolecules. These implants are miniature titanium cylinders designed to provide continuous osmotically driven delivery of drugs within the body for up to one year. Following implantation, DUROS implants enable continuous, precise delivery of the therapeutic compound at rates as low as 1% of a drop of water per day.

The cylinder is manufactured from titanium because of the material's tolerability to human tissue and its long use in medical devices such as implantable defibrillators and joint replacements. The cylinder protects therapeutic agents from degradation in the body and enables a drug to remain stable for extended periods of time. Recently, Viadur (leuprolide acetate implant), which is based upon this technology, has been approved for once-yearly palliative treatment of advanced prostate cancer.

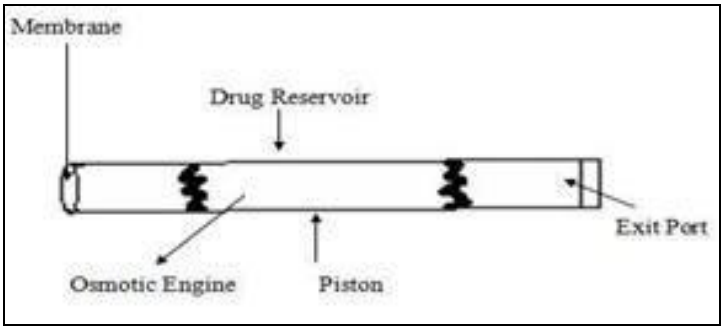

FIGURE 5: DUROS TECHNOLOGY

Geminex [12]: Geminex is a dual drug delivery technology that can deliver one or more drugs at different times. The Geminex technology controls the release rate of the two drugs to maximize their individual therapeutic effect and minimize side effects. The benefit of Geminex to the pharmaceutical industry, and ultimately to patients, is that two different active ingradients or the same active ingredient can be delivered at differing rates in a single tablet. Penwest is actively applying its Geminex technology to the following therapeutic areas: cardiovascular disorders, diabetes, cancer, and disorders of the central nervous system.

PRODAS or Programmable Oral Drug Absorption System [13]: (Elan Corporation) is a multiparticulate drug delivery technology that is based on the encapsulation of controlled-release minitablets in the size range of 1.5 to 4 mm in diameter. This technology represents a combination of multiparticulate and hydrophilic matrix tablet technologies and thus provides the benefits of both these drug delivery systems in one dosage form.Minitablets with different release rates can be combined and incorporated into a single dosage form to provide the desired release rates. These combinations may include immediate-release, delayed-release, and/or controlled-release minitablets. In addition to controlled absorption over a specified period, PRODAS technology also enables targeted delivery of drug to specified sites of absorption throughout the GI tract. Combination products also are possible by using minitablets formulated with different active ingredients.

Erodible Molded Multilayer Tablet [14]: Egalet erodible molded tablets are an erosion-based platform. It has the advantage of delivering zero-order or delayed release with minimal impact from the gastrointestinal conditions.

Egalet erodible molded multilayered tablets are prepared by injection molding.Egalet technology contains a coat and a matrix. Drug release is controlled through the gradual erosion of the matrix part. The mode and rate of release are designed and engineered by altering the matrix, the coat, and the geometry to achieve either a zero-order release or a delayed release. For a zero-order release, a drug is dispersed through the matrix. The coat is biodegradable but has poor water permeability to prevent its penetration.

The matrix tends to erode when in contact with available water. The erosion of the matrix is caused by GI fluids and promoted by gut movements in the GI tract. The drug release is mediated almost wholly by erosion because the dosage form is designed to slow down the water diffusion into the matrix. It is definitely more desirable for drugs with chemical and physical stability issues after contacting with water. Egalet delivery technology is developed based on standard plastic injection molding to ensure accuracy, reproducibility, and low production cost.

Bi-Layer Tablets:

Quality and GMP Requirements [15]: To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the selected press is capable of:

- Preventing capping and separation of the two individual layers that constitute the bi-layer tablet
- Providing sufficient tablet hardness
- Preventing cross-contamination between the two layers
- Producing a clear visual separation between the two layers
- Producing high yield
- Accurate and individual weight control of the two layers.

Single Sided Press: Various types of bi-layer presses have been designed over the years. The simplest design is a single sided press with both chambers of the double feeder separated from each other. Each chamber is gravity- or forced-fed with a different powder, thus producing the two individual layers of the tablet. When the die passes under the feeder, it is at first loaded with the first-layer powder followed by the second-layer powder. Then the entire tablet is compressed in one or two steps (two = pre- and main compression). The two layers in the die mix slightly at their interface and in most cases bound sufficiently so that no layer-separation occurs when the tablet is produced. This is the simplest way of producing a bilayer tablet.

Limitations of Single-Sided Press [15, 16, 17]: Various types of bi-layer presses have been designed over the years. The simplest design is a single-sided press with both chambers of the double feeder separated from each other. Each chamber is gravity- or forced-fed with a different powder, thus producing the two individual layers of the tablet. When the die passes under the feeder, it is at first loaded with the first-layer powder followed by the second-layer powder. Then the entire tablet is compressed in one or two steps (two = pre- and main compression). The two layers in the die mix slightly at their interface and in most cases bond sufficiently. So that no layer-separation occurs when the tablet is produced.This is the simplest way of producing a bilayer tablet. It undergoes certain limitation as follow.

- No weight monitoring/control of the individual Layers.
- No distinct visual separation between the two Layers.
- Very short first layer-dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping and hardness problems. This may be corrected by reducing the turret-rotation speed (to extend the dwell time) but with the consequence of lower tablet output.
- Very difficult first-layer tablet sampling and sample transport to a test unit for in-line quality control and weight recalibration to eliminate these limitations, a double-sided tablet press is preferred over a single-sided press. A double-sided press offers an individual fill station, pre – compression and main compression for each layer. In fact, the bi-layer tablet will go through the compression stages before being ejected from the press.

Double Sided Tablet Presses [18]: Double-sided tablet presses have been specifically designed and developed for the production of quality bi-layer tablets and provide:

- 'displacement' weight monitoring/control for accurate and independent weight control of the individual layers
- Low compression force exerted on the first layer to avoid capping and separation of the two individual layers
- Increased dwell time at pre-compression of both first and second layer to provide sufficient hardness at maximum turret speed
- Maximum prevention of cross-contamination between the two layers
- A clear visual separation between the two layers
- Maximised yield

Preparation of Bilayered Tablet [19, 20, 21, 22]: Bilayer tablets are prepared with one layer of drug for immediate release with the second layer designed to release drug later, either as a second dose or in an extended release form. The bilayer tablets with two incompatible drugs can also be prepared by compressing separate layers of each drug so as to minimize area of contact between two layers. An additional intermediate layer of inert material may also be included.

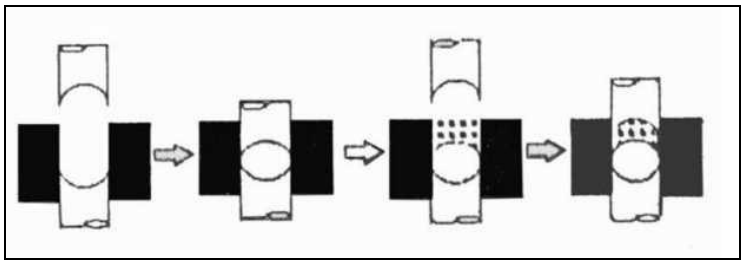

FIGURE 6: PREPARATION OF BILAYER TABLET

Compaction: To produce adequate tablet formulation, certain requirements such as sufficient mechanical strength and desired drug release profile must be met. At times, this may be difficult task for formulator to achieve these conditions especially in bilayer tablet formulation where double compression technique is involved, because of poor flow and compatibility characteristic of the drug which will result in capping and/or lamination. The compaction of a material involves both the compressibility and consolidation.

Compression: it is defined as reduction in bulk volume by eliminating voids and bringing particles into closer contacts.

Consolidation: it is the property of the material in which there is increased mechanical strength due to interparticulate interaction (bonding). The compression force on layer 1 was found to be major factor influencing tablet delamination.

BI-Layer Tablet Press [23]: The XM 12 Bi-Layer Tablet Press features a retractable second layer feeder that permits automated first layer sampling at production speeds. The first layer sampling capability also offers a hardening feature, in which the main compression station will automatically compress the first layer tablet for in-process measurement. The two feeders are zero clearance and are configured with an integrated dust extraction manifold which cleans the die table and completely eliminates any potential for cross contamination. WipCon® solution available is potent for Small-Scale Bi-layer Applications. The KORSCH XM 12 Bi- Layer Tablet Press is a small-scale press which is ideal for product development scale-up, clinical trials and midrange production.

The bi-layer execution, single-layer conversion kit and exchangeable turret offer unprecedented flexibility. The XM 12 Bi-Layer Tablet Press offers a new standard in GMP with extreme accessibility to the compression zone and a combination of quick disconnects and smooths surfaces that permit fast cleaning and changeover. The machine features a 5 KN tamping station, 40 KN precompression station, 80 KN main compression station, and a unique structural design that eliminates vibration to the head piece and base frame. The result is an extreme reduction in the operating noise level.

Small-Scale Bi-Layer Tablet:

1. 5 KN First Layer Tamping Force.
2. 40 KN Precompression Force.
3. 80 KN Main Compression Force.
4. Single-Layer Conversion Capability

Bi-Layer Application [24]: The XM 12 features an exchangeable turret capability to permit a single machine to run all press tool sizes to provide maximum flexibility and versatility. An internal lift arm eliminates the cost and space requirement of a large external turret removal device.

1. Single layer conversion kit adds yet another dimension of flexibility.
2. Single Layer Conversion.
3. 30 Minute Conversion Time.
4. High Speed Single-Layer Capability (120 RPM)

Advantages: [25,26]

a. Flexible Concept.
b. Bi-Layer execution with optional single-layer conversion kit.
c. Exchangeable turret.
d. Turret sizes for product development, scale-up, and mid-range production.
e. Full production capability in a scale-up machine.
f. Self-contained, fully portable design.
g. Fast and Easy Changeover.
h. Internal turret lift device for extreme simplicity in turret removal and installation.
i. Clean compression zone with quick-disconnect design.

CHARACTERIZATION OF BILAYER TABLET[26, 27]

1. **Particle size distribution:** The particle size distribution was measured using sieving method.
2. **Photo-microscope study**: Photo-microscope image of TGG and GG was taken (X450 magnifications) by photomicroscope.
3. **Angle of Repose:** The diameter of the powder cone was measured and the angle of repose was calculated using the following equation

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

Where h and r are the height and radius of the powder cone.

4. **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.
5. **Density**: The loose bulk density (LBD) and tapped bulk density (TBD) were determined and Calculated using the following formulas.

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

TBD ¼ weight of the powder=tapped volume of the packing ð3Þ

6. **Compressibility**: The compressibility index of the disintegrate was determined by Carr's compressibility index.

$$C = 100 \times (1 - \rho B/\rho T)$$

Evaluation of Sustain Release Bilayer Tablet:

1. **Tablet Thickness and Size** [28, 29]: Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter was measured using venire calliper.
2. **Tablet Hardness** [28,29]: The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in $kg/cm^{2.}$
3. **Friability** [28, 29]**:** Friability is the measure of tablet strength. Electrolab EF-2 friabilator (USP) was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each

revolution. After 4 min, the tablets were weighed and the percentage loss in tablet weight was determined.

% loss = [(Initial wt. of tablets - Final wt. of tablets)/ Initial wt. of tablets] ×100

4. **Uniformity of Weight:** Twenty tablets were selected at random and the average weight was calculated. Weight Variation was calculated.

CONCLUSION: Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. There is various application of the bilayer tablet it consist of monolithic partially coated or multilayered matrices. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose. 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 tablet preparations by providing surrounding or multiple swelling layers.

Bi-layer tablet quality and GMP-requirements can vary widely. This explains why many different types of presses are being used to produce bi-layer tablets, ranging from simple single-sided presses to highly sophisticated machines such as the Courtoy-R292F. Whenever high quality bi-layer 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.

REFERENCES:

1. Shiyani B, Gattani S, Surana S: Formulation and evaluation of bi-layer tablet of Metoclopramide hydrochloride and Ibuprofen. AAPS Pharm Sci Tech 2008; 9(3):818-27.
2. Pranjal Kumar Singh, Sanjoo Kumar: Bilayer and Floating Bioadhesive Tablets: Innovative approach to Gastroretention. Journal of Drug Delivery & Therapeutics 2011; 1(1): 32-35.
3. Micheal AE, Modified release per oral dosage forms. Pharmaceutics-The Science of Dosage form Design, Churchill LivingSton New York: 575.
4. Banker S, Gilbert J, Rhodes T: Christopher, Modern Pharmaceutics, Marcel Dekker, Inc., New York: 575.
5. 5)Pranjal Kumar Singh , Sanjoo Kumar : Bilayer and Floating Bioadhesive Tablets: Innovative approach to Gastroretention, Journal of Drug Delivery & Therapeutics 2011; 1(1): 32-35.
6. Kulkarni A, Bhatia: Development and evaluation of bilayer floating tablets of atenolol and lovastatin for biphasic release profile. Iran J. Pharm. Res. 2009; 8: 15-25.
7. Nirmal J, Saisivam S, Peddanna C, Muralidharan S, Nagarajan M: Bilayer tablets of atorvastatin calcium and nicotinicacid: formulation and evaluation. Chem. Pharm. Bull. 2008; 56: 1455-1458, 26-102-105.
8. Sachin S, Viraj S., Saste: Bilayer Tablet, International Journal of Pharmaceutical Sciences Review and Research; 2011: vol 9, article 005.
9. Rajan K, Sanjay Garg: "Current Status of Drug Delivery Technologies and Future Directions," Pharmaceutical Technology; 2001; 25 (2): 1-14.
10. Divya A, Kavitha, Rupesh Kumar M: Journal of Applied Pharmaceutical Science; 2011: 01 (08):43-47.
11. Kale S, Saste VS, Prajkta L, Ughade, Dheeraj T, Bhaviskar: Bilayer tablet: Review. Int J Pharm Sci Rev and Res 2011; 9(1):25-30.
12. Tod R. Hamachek *et al*, Innovative oral drug delivery technologies, Penwest Pharmaceuticals Co., 2002
13. Rajan K. Verma et al, Sanjay Garg *et al*, "Current Status of Drug Delivery Technologies and Future Directions," Pharmaceutical Technology; 2001; 25 (2): 1-14.
14. Pederson AV *et al*. Erosion-based drug delivery. Manuf. Chem. 2006; 11:1-6.
15. Patel Mehul,Ganesh, Nanjan Sockan: Challenges in the Formulation of Bilayered Tablets: A Review, International Journal of Pharma Research and Development, 2010, ISSN 0974 - 9446.
16. 16) Abshagen U, Spo ¨rl-Radun S: First data on the effects and pharmacokinetics of isosorbide-5-mononitrate in normal man, Eur. J.Clin.Pharmacol 1981; 19: 423-429.
17. Hutt V, Bonn R, Fritschi E, Jaeger H: Evaluation of the pharmacokinetics and absolute bioavailability of three isosorbide- 5-mononitrate preparation in healthy volunteers, Arzneim.-Forsch./Drug Res 1995:142-145.
18. Jan Vogeleer: Bi-layer tablets - why special technology is required The Courtoy-R292F tablet press designed for quality bi-layer tablets Niro Pharma Systems.
19. Rudnic EM, Kottke : MK Tablet dosage form. In Banker GS, Rhodes CT, editors. Modern Pharmaceutics. 3rd ed, vol 72. New York:Marcel Dekker Inc. 369.
20. Breech AJ, Lucisano L J, and Franz RM: Investigation into substrate cracking of a film coated bilayered tablet. J. Pharm.Pharmacol. 1998;40:282-283.
21. Kalam M.A, Humayun M, Parvez N ,Yadav S,Garg A, Amin S, Sultana Y: J. Pharmaceutical Science 2007;1:30 – 35.
22. Li S.P., Karth M.G., Feld K.M., Pendharkar C.M., Willams R.O.: Evaluation of Bilayer tablet machines. A Case study.Drug Dev. Ind. Pharm. 1995; 21(5): 571 590.
23. http://www.elan.com/
24. Lachman L, Lieberman HA , Joseph KL: The Theory and practices of Industrial Pharmacy , Varghese publishing House , Bombay;3rd ed: 430-431.
25. Bhatt, Padmanabh, Osmotic delivery system for poorly soluble drug, The Drug delivery companies Report Autumn/Winter 2004 ©PharmaVentures Ltd 2004.
26. Notari, R: Biopharmaceutics and Clinical Pharmacokinetics, An Introduction, 3rd Ed., Marcel Dekker Inc. New York 1980: 152-154.
27. The United States Pharmacopoeia, United states Pharmacopoeial convention, Inc., Rockville, MD, 2000: 1944.
28. Singh B. N, Kim, K.H:Floating drug delivery systems an approach to oral controlled drug delivery via gastric retention, J Control Rel 2000: 235-59.

How to cite this article:
Malathi P and Khan AB: Recent Approaches in Bilayered Technology: A Review. *Int J Pharm Sci Res*. 3(12); 4681-4688.