IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
August 2020 Vol.:19, Issue:1

An Overview on Novel Approach of Bi-Layer Tablet Technology

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

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Submission: 24 July 2020
Accepted: 30 July 2020
Published: 30 August 2020

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Bi-layer tablet, API (Active Pharmaceutical Ingredient), Incompatibility, Challenges

ABSTRACT

A bi-layer tablet is a new dosage form for the successful development of controlled release formulation along with various properties to provide successful drug delivery. Bi-layer tablet is often a key choice to avoid the chemical incompatibility between APIs by physical separation and used for the event of various drug release profiles. Bi-layer tablet is mainly used for sequential release of two drugs in combination and also for sustained release of tablet in which one layer is for immediate release as a loading dose and the second layer is the maintenance dose. So, a bi-layer tablet can be used for combination therapy in anti-hypertensive, diabetic, anti-inflammatory, and analgesic drugs. The present article provides an introduction to bi-layer tablet technology, challenges in bi-layer tablet manufacturing and remedies to overcome that challenges, various tablet presses used, quality, and GMP requirements for their production various techniques used for bi-layer tableting and recent developments in the field of bi-layer technology.

INTRODUCTION:

In the past few years, there is an increase in curiosity in developing a mixture of two or more Active Pharmaceutical Ingredients (API) meanwhile a single dosage form (bi-layer tablet) has been raised within the pharmaceutical industry, promoting patient convenience and compliance. [1-2]

Generally, the conventional dosage form generates wide-ranging variation into the drug concentration within the bloodstream and tissues with resultant unacceptable toxicity and poor efficiency. This factor-like frequency of dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery systems is to scale back the frequency of the dosing or to extend the effectiveness of the drug by localization at the positioning of action, reducing the dose required, or providing uniform drug delivery. The first objective of sustained-release drug delivery is to make sure safety and to boost the efficacy of medicine moreover as patient compliance.

Bi-layer tablet is appropriate for consecutive release of two drugs simultaneously, separate two incongruous substances and for sustained release tablet during which one layer is loading dose or immediate release and another layer is maintenance dose or sustained release.

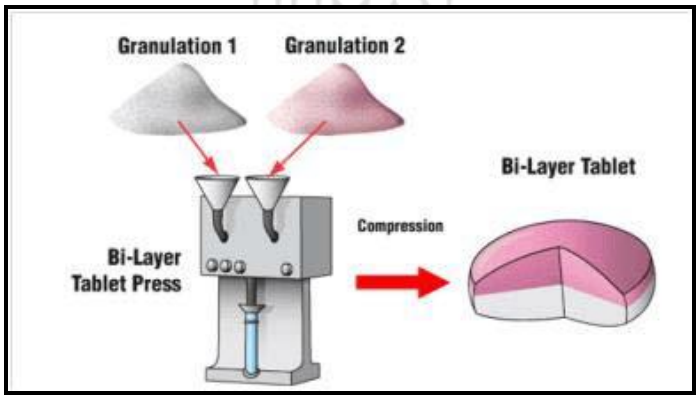

Figure No. 1: General concept of Bilayer tablet

A basic selection of bi-layer tablets to stop chemical incompatibilities between APIs by physical separation and to empower the event of assorted drug release profiles (immediate release along with sustained-release). Bi-layer tablets offer definite advantages over conventional release formulation of the identical drug. Several pharmaceutical companies are currently developing bi-layer tablets. The most objective of developing these systems is to extend the security of a product to increase its duration of action and reduce the side effects

of the medicine. These systems have more flexibility in dosage form design than conventional dosage form. [3-10]

Multi-layer tablet dosage forms are designed for a variety of reasons: [11-15]

- To control the delivery rate of either single or two different active pharmaceutical ingredients (APIs).
- To separate incompatible Active pharmaceutical ingredient (APIs) from one another, to regulate the discharge of API from one layer by utilizing the functional property of the opposite layer (such as osmotic property).
- To modify the entire area available for the API layer either by sandwiching with one or two inactive layers to realize swellable /erodible barriers for modified release.
- To administer fixed-dose combinations of various APIs, prolong the drug product life cycle, fabricate novel drug delivery systems.

Advantages of the bi-layer tablet dosage form-:

- They are unit dosage form and offer the best proficiency of all oral dosage form for the best dose precision and therefore the least content instability.
- The cost is lower compared to all or any other oral dosage form.
- Lighter and compact.
- Easiest and cheapest to package and strip.
- Easy to swallow with the least tendency for hang-up.
- Objectionable odor and bitter taste are often masked by the coating technique.
- Suitable for giant scale production.
- Greatest physical, microbial and chemical stability overall oral dosage form.
- Product identification is straightforward and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.

Disadvantages of Bi-Layer Tablet Dosage Form:

- Difficult to swallow just in case of youngsters and unconscious patients.
- Some drugs resist compression into dense compacts, due to amorphous nature, rarity character.
- Drugs with low wetting, slow dissolution properties, optimum absorption high in GIT could also be complicated to formulate or manufacture as a tablet which will still give adequate or full drug bioavailability.
- Bitter testing drugs, drugs with an objectionable odor, or drugs that are sensitive to oxygen may require encapsulation or coating.

Ideal characteristics of bilayer tablets-:

- It should be free from defects like chips, cracks, discoloration, and contamination.
- It should have sufficient strength during its production, packaging, shipping, and dispensing.
- It should have the chemical and physical stability overtime.
- It releases the agents in a predictable and reproducible manner.
- It must have chemical stability and shelf-life.

CHALLENGES IN BILAYER MANUFACTURING AND ITS REMEDIES-:[16]

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

1) Tablet Weight Variation:

Table No. 1: Tablet Weight Variation

Possible Cause	Remedies
1. Low flow trait of the fabric.	a) Wrong setting of the hopper. b) Material bridging in the hopper c) An excessive amount of recirculation
2. Dies not filling	a) Press running too fast. b) Wrong feeder paddle speed or shape
3. Sometimes material can be lost or gain during die fill.	a) Recirculation band leaking b) Too much amount of vacuum or nozzle inadequately located

2) Capping and Lamination:

Table No. 2: Capping and Lamination

Possible Cause	Remedies
1. Non-optimized formulation	a) Incorporate plastically deforming of the matrix.
2. High compression force	a) Reduced compression force. b) Reduced press speed.
3. The proportion of Pre-compression is to the main compression can be inadequate.	a) The pre-compression force high can be unsafe. b) Use the large compression roller diameter
4. Curled or damaged punches	a) Tools should be rewashed or replaced.

3) Low Hardness:

Table No. 3: Low Hardness

Possible Cause	Remedies
1. Factors which are related to machine	a) Tablet press having pre-compression and the main compression facilities. b) The velocity of the press is decreased to expand total compression time.
2. Lubricant level	a) Overmuch blend can decrease tablet hardness

4) Picking and Sticking:

Table No. 4: Picking and Sticking

Possible Cause	Remedies
1. Too much heat generation at the time of compression.	a) In compression, the section uses the cooling system.
2. Fouling the punch faces	a) Startup should be on the brink of excellent conditions.

5) Product Yield:

Table No. 5: Product Yield

Possible Cause	Remedies
1. Incorrect feeder fit die table.	a. Feeder bases inaccurately set (too high or not level)
2. Wrong activity on the recirculation band.	a. The gap between the bottom edge and the die table. b. Binding in mounting screw
3. Die table scraper activity is inadequate.	a. The scraper blade is worn or binding. b. Outboard edge permitting the material to flee.
4. The loss at the compression point.	a. Compressing too high within the die. b. Too much or misdirected suction on the exhaust nozzle.

6) Separation of Two Individual Layers:

Table No. 6: Separation of Two Individual Layers

Possible Cause	Remedies
1.The inadequate connection among the two layers meanwhile last compression of bilayer tablet	a. The first layer should be compressed at a small compression force so that this layer can still interact with the second layer meanwhile final compression of the tablet

7) Mottling:

Table No. 7: Mottling

Possible Cause	Remedies
1. The inaccurate setting of both feed frame	a. Both feed frames should set properly.
2. Because of weak suction.	a. Suction capacity should be such, all waste is sucked.

QUALITY AND GMP-REQUIREMENTS: [17]

To produce a high-quality bi-layer tablet, in a very validated and GMP-way, the chosen press must be capable of 5:

1. Preventing capping and separation of the two distinct layers that constitute the bi-layer tablet.
2. Providing sufficient tablet hardness.
3. Preventing cross-contamination between the two layers.
4. Producing a transparent visual separation between the two layers.
5. High yield Accurate and distinctive weight control of the two layers.

These requirements seem obvious but don't seem to be so easily accomplished.

TYPES OF BILAYER TABLET PRESS:

1) Single-sided tablet press:

The simplest design may be a single-sided press with both chambers of the doublet feeder separated from one another. Each chamber is gravity or forced fed with different power, producing the two distinct layers of tablets. When die passes under the feeder, it's first loaded with the primary layer powder followed by the second layer powder. Then the whole tablet is compressed in one or two steps [18].

Figure No. 2: Single-sided tablet press

Limitations of the single-sided press

1. No weight monitoring/control of the distinctive layers.
2. No apparent visual separation between the two layers.
3. Capping and hardness problems.

2. Double-sided tablet press-:

In most double-sided tablet presses with automated production, control use compression force to monitor and control tablet weight. The compression force exerted on each tablet or layer is measured by the control system at the main compression of the layer [19]. This compression force is the signal used by the control system to reject out of tolerance and correct the die fill depth when required.

Figure No. 3: Double-sided tablet press

3. Bilayer Tablet Press with Displacement Monitoring-:

The displacement tablet weight control principle is essentially distinct from the principle-based upon compression force. When measuring displacement, the system sensitivity doesn't depend upon the tablet weight but depends on the applied precompression force [20].

Advantages-:

1. Weight monitoring/control weight of the individual layers.

2. Avoid capping and separation of the two individual layers.

3. Independence from the machine stiffness.

4. Provide sufficient hardness at maximum turret speed.

5. Maximum avoidance of cross-contamination between the two layers.

6. The clear optical separation between the two layers and maximized yield.

Figure No. 4: Bilayer tablet press with displacement monitoring

MANUFACTURING PROCESS OF BILAYER TABLET:[21]

Bilayer tablets are prepared with one layer of the drug for immediate release and second layer designed to release drug either as a second dose or in an extended-release form. to supply adequate tablet formulation, certain requirements like sufficient mechanical strength and desired drug release profile must be met. At times, this might be a difficult task for a formulator to realize these conditions especially in bilayer tablet formulation, where double compression technique is involved, due to poor flow and compatibility characteristics of the drug which can end in capping and/or lamination.

Compaction:

The process by which the porosity of a given powder is decreased as a result of its grains being squeezed together by a load of mechanical means. The compaction of a cloth involves both the compressibility and consolidation.

Compression:

It's defined as a reduction in bulk volume by eliminating voids and bringing particles into closer contacts**.**

Consolidation:

It is the property of the fabric during which there are increased mechanical strength thanks to inter particulate interaction (bonding). The compression force on the first layer was found to be a major factor influencing tablet delamination.

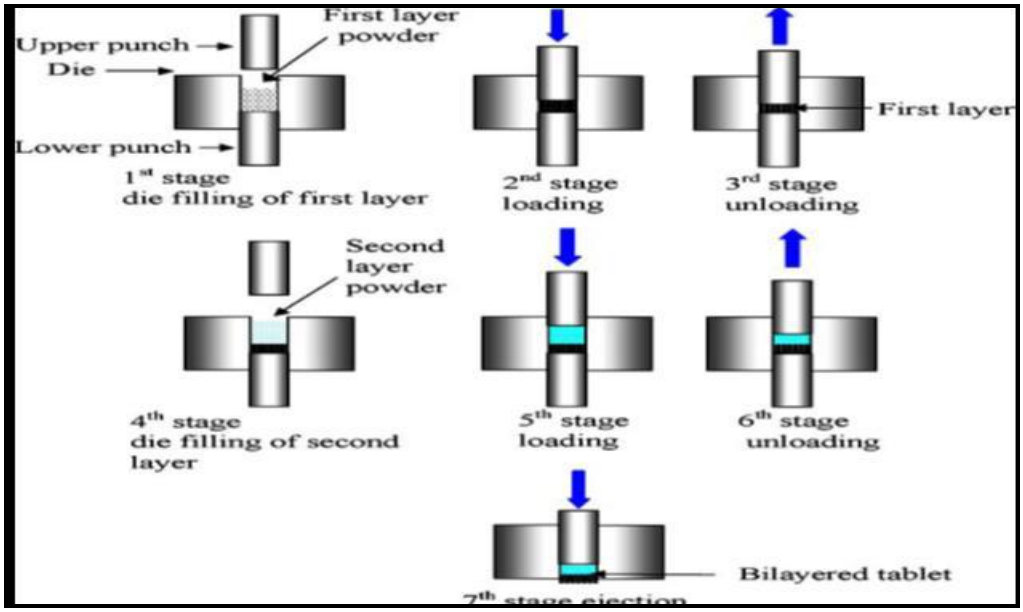

Figure No. 5: Production of bilayer tablets

VARIOUS TECHNIQUES FOR BILAYER TABLET: [22-23]

A) OROS® push-pulls Technology:

This system mainly has two or three layers from which the one or more layer is essential of the drug and other layers are consist of push layer. The drug layer mainly has drugs along

with two or more different agents. So, this drug layer consists of drug which is in poorly soluble form. There is more addition of suspending agent and osmotic agent. A semi-permeable membrane surrounds the tablet core.

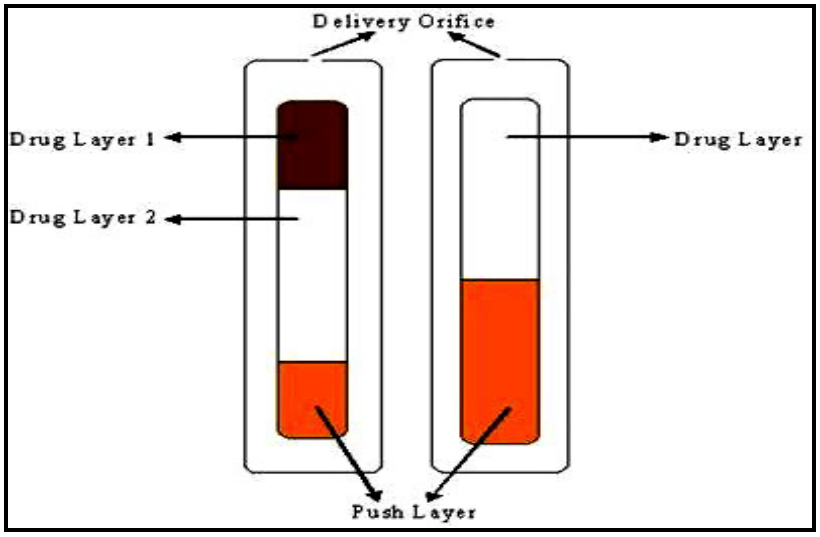

Figure No. 6: Bilayer and tri-layer OROS push-pull technology

B) L-OROSTM Technology:

This system incredibly used for the solubility problem Alza developed the L-OROS system where a lipid soft gel product containing the drug is in a dissolved state is initially manufactured and later on coated with a barrier membrane, then osmotic push layer and then a semi-permeable membrane, drilled with an exit orifice.

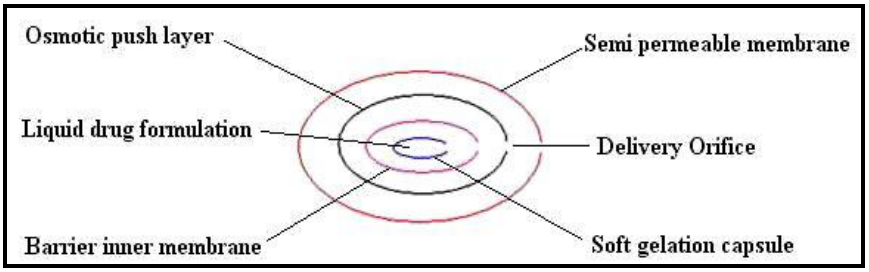

Figure No. 7: L-OROSTM Technology

C) EN SO TROL Technology:

Solubility enhancement function is mainly used to develop perfect dosage form Shire laboratory use a blended approach to develop drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies.

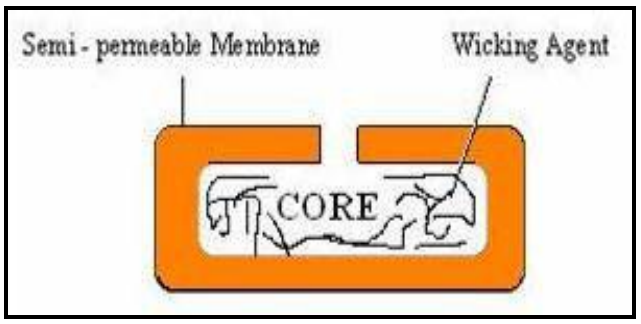

Figure No. 8: EN SO TROL Technology

D) DUREDAS™ Technology:

DUREDAS™ Technology is used for a bilayer tablet, which can show the immediate or sustained release of two drugs or different release rates of the one drug in a single dosage form. The tableting process can shows both properties like an immediate release granulate and second one 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.

Benefits offered by the DUREDAS™ technology include:

- Bilayer tableting technology.
- The tailored release rate of two drug components.
- The capability of two different CR formulations combined.
- Capability for immediate release and modified release combine in one tablet.
- Unit dose, tablet presentation.

E) DUROS Technology:

The system consists of an outer cylindrical titanium alloy reservoir. This reservoir has a 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 and releases minute quantity of concentrated form in continuous and consistent from over months or year.

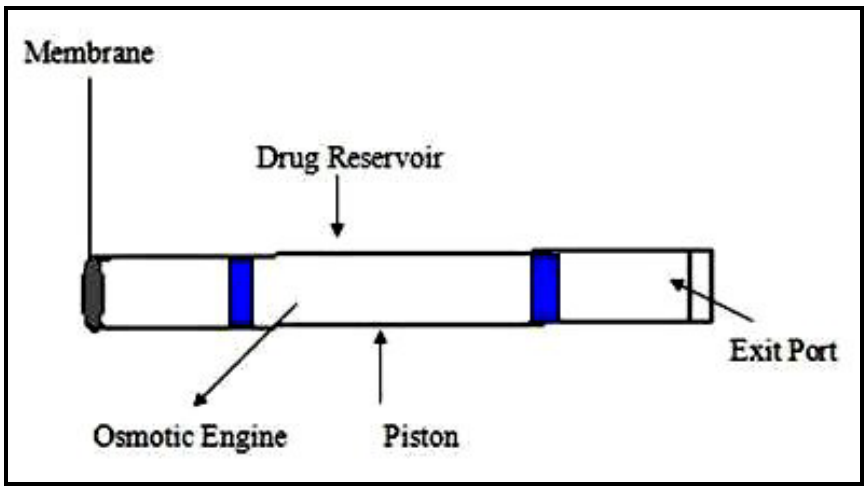

Figure No. 9: DUROS Technology

EVALUATION OF BILAYER TABLET:

1) Tablet Thickness and Size:[24]

Thickness and diameter of tablets were important properties for uniformity of tablet size. Thickness and diameter were measured using venire caliper.

2) Tablet Hardness:[26]

The resistance of tablets to shipping or breakage under various conditions like storage, transportation, and handling before usage depends on its hardness. The hardness of the tablet of each formulation was mainly measured by Monsanto hardness tester. The hardness was measured in kg/cm^2.

3) Friability:[25]

Friability is used to measure the strength of the tablet. Electrolab EF-2 friabilator (USP) was mainly used for testing the friability using the following procedure. Twenty tablets were randomly selected and 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 calculated.

4) Uniformity of Weight:[26]

Twenty tablets were randomly selected and the average weight was determined. Weight Variation was calculated.

5) Disintegration Study:[27]

A tablet disintegration study was performed for the immediate layer of the bilayer tablet as per instructions in IP1996. Disintegration time was determined using USP tablet disintegration tester (ED-2L, Electrolab Pvt. Ltd. Mumbai) in distilled water.

6) Stability Study:[28]

The bilayer tablets are packed in suitable packaging and stored under different temperature conditions for a period as prescribed by ICH guidelines for accelerated studies.

Table No. 8: Various Advancements in the Field of Bilayer Tablets

Author	Drug	Dosage Form	Rational	Method	Ref.No
Jamunadevi et al	Diclofenac Cyclobenzaprine HCl	Bilayer tablets	Synergistic effect in pain	Wet granulation	29
Swamy et al	Granisetron HCl	Bilayer buccal tablets	To overcome the bioavailability problem, reducing side effects	Direct compression	30
Pattanayak et al	Metformin HCl Glimepiride	Bilayer tablets	Synergistic effect in diabetes	Wet granulation	31
Jain et al	Indomethacin	Bilayer floating tablets	Biphasic drug release	Wet granulation	32
Mohindeen et al	Metformin HCl Atorvastatin Calcium	Bilayer tablets	To develop polytherapy for the treatment of NIDDS & hyperlipidemia	Wet granulation	33
Kumar et al	Cefixime Trihydrate Dicloxacillin Sodium	Bilayer tablets	Synergistic effect in Bacterial infections	Wet granulation	34
Jadhav et al	Piracetam Vinpocetine	Bilayer tablets	Synergistic effect in Alzheimer disease	Wet granulation	35
Rajendran et al	Metformin HCl Pioglitazone	Bilayer tablets	Synergistic effect in diabetes Mellitus	Wet granulation & direct	36

				compression	
Shirsand et al	Atenolol	Bilayer buccal tablets	To overcome bioavailability problem	Direct compression	37

CONCLUSION:

Bilayer tablet is a new and latest beneficial technology to beat the issues of the only layered tablet. Bi-layer tablet is often used for sequential release of two drugs together, physical separation of two incompatible substances, and also for sustained release tablet during which one Layer is instant release as initial dose and the second layer is the maintenance dose. The preparation of tablets within the sort of multilayers is employed to supply systems for the administration of medicine, which is incompatible and to supply controlled release tablet preparations by delivering surrounding or multiple swelling layers. Bi-layer tablet quality and GMP-requirements can vary widely. This explains why many various sorts of presses are getting used to supply bi-layer tablets, starting from simple single-sided presses to highly sophisticated machines like the Courtoy-R292F. Whenever top quality bi-layer tablets got to be produced at high speed, the utilization of an 'air compensator' together with displacement control appears to be the simplest solution.

REFERENCES:

1. Martindale, the Extra Pharmacopoeia, 31st ed. The Pharmaceutical Press, London; 1996.p.936–937.
2. Shiyani B et al. Formulation and evaluation of bilayer tablet of Metoclopramide hydrochloride and Ibuprofen. AAPS Pharm Sci Tech 2008;9(3):818-27. Pranjal Kumar Singh et al, Sanjoo Kumar et al Bilayer, and Floating Bioadhesive Tablets: Innovative approach to Gastroretention, Journal of Drug Delivery & Therapeutics; 2011, 1(1): 32-35.
3. Chien YW, Fundamentals of controlled-release of drug administration in J. Swarbrick (Ed.), Novel Drug Delivery System Marcel Dekker, New York, 1982, pp. 465–574.
4. Buri P, Puisicux F., Doelker E., Benoit JP, Formes Pharma centiques Nouvelles, Ed. Technique et Documentation, Lavoisier, Paris, 1985.
5. Wilding IR, Coupe AJ, Davis SS, The role of gamma scintigraphy in oral drug delivery, Adv. Drug Deliv. Rev. 1991; 7: 87– 117.
6. Lee L. Diffusion-controlled matrix systems, in A. Kydonieus (Ed.), Treatise on Controlled Drug Delivery, Marcel Dekker, New York, 1992, pp. 155– 198.
7. Peppas NA. Hydrogels in Medicine and Pharmacy, vols. I, II, and III, CRC Press, Boca Raton, FL, 1988.
8. Martindale. The Extra Pharmacopoeia, 31st Ed. The Pharmaceutical Press, London1996, pp. 936–937.
9. Martin A, Bustamante P and Chun A, Micromeritics, in Physical Pharmacy-Physical Chemical Principles in the Pharmaceutical Sciences, 4th ed., Lippincott Williams and Wilkins, Baltimore 2002, pp. 446–448.
10. Bogan, R.K. Treatment options for insomnia—pharmacodynamics of zolpidem extended-release to benefit next-day performance. Postgrad. Med. 2008; 120: 161–171.
11. Aulton ME. Pharmaceutics – the science of dosage form design, second edition, Churchill Livingstone 2002, 200-206,412,423-439, 575.
12. Bogda MJ. Tablet compression: Machine theory, design, and process troubleshooting.

13. Encyclopedia of Pharmaceutical Technology. J. Swarbrick, J. Boylan (eds.). Marcel and Dekker Inc 2 nd edition (2002), 2669-2688.
14. Remington's- The science & practice of pharmacy, 21st edition 2005, vol. 1, 894-896.
15. www.durect.com.
16. Shila V. Devtalu, Ashwini E. Patil, Manoj M. Bari, Dr. Shashikant D. Barhate. A Review on Novel Approach – Bilayer Tablet Technology. Int. J. Pharm. Sci. Rev. Res., 21(1), Jul – Aug 2013; n° 09, 46-52.
17. Rudnic EM et al, Kottke et al MK Tablet dosage form. In Banker GS, Rhodes CT, editors. Modern Pharmaceutics. 3rd ed., vol 72. New York: Marcel Dekker Inc. p 369.
18. Patel M, Sockan GN, and Kavitha MT (2010). Challenges in the formulation of bilayered tablets: A review. International Journal of Pharma Research and Development, 0974 – 9446.
19. Singh PK and Kumar S. (2011). Bilayer and floating bioadhesive tablets: Innovative approach to gastro retention. Journal of Drug Delivery & Therapeutics, 1(1), 32-35.
20. Hamachek TR. (2002). Innovative oral drug delivery technologies, Penwest pharmaceuticals. The Pharmaceutical Press, London. 936–937.
21. Li SP, Karth MG, Feld KM, Pendharkar CM, and Willams RO. (1995). Evaluation of bilayer tablet machines: A Case study. Drug Development and Industrial Pharmacy, 21(5), 571-590.
22. URL:http://www.durect.com.
23. Naisarg d. Pujara Ronak k. Gokani, Jalpa s. paun. Bilayer tablet –An emerging trend IJPRD, 2011; vol 4(04): june-2012 (102 - 111).
24. Singh, B. N., & Kim, K. H. (2000). Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. Journal of Controlled Release, 63(3), 235-259.
25. A Tadavi, S., & Patel, M. R. (2011). Brief Overview on Compaction & Compression of Bilayer Technology. Journal of Pharmacy Research, 4(9), 2987-2990.
26. Hutt V et al, Bonn R et al, Fritschi E et al, Jaeger H et al, Evaluation of the pharmacokinetics and absolute bioavailability of three isosorbide- 5- mononitrate preparation in healthy volunteers, Arzneim.- Forsch./Drug Res.;1995:142–145.
27. Raparla D V and Murthy TE. Formulation and evaluation of oral controlled release Glimepiride matrix tablets. Adv. Phamacol. Toxical. 8, 2007, p.59-62.
28. Jamunadhevi V, Sahoo PK and Kailasam P. Formulation and in vitro evaluation of bi-layer tablet of cyclobenzaprine hydrochloride ER and diclofenac potassium IR- A novel fixed dose combination. Int J Res Pharm Sci 2011; 2(2):170-8.
29. Swamy P V, Kinagi M B, Biradar S S, Gada S N, and Shilpa H. Formulation design and evaluation of bilayer buccal tablets of granisetron hydrochloride. Ind J Pharm Edu Res 2011 45(3):242-7.
30. Pattanayak D P and Dinda S C. Bilayer tablet formulation of Metformin HCl and Glimepiride: A novel approach to improve therapeutic efficacy. Int J Drug Discovery Herb Res 2011; 1(1):1-4.
31. Jain J, Marya B H, Mittal RP, and Patel M. Formulation and evaluation of indomethacin bilayer sustained release tablets. Int J Pharm Tech Res 2011; 3(2):11328.
32. Mohindeen S, Jyothi B, Pavani S, Satyanarayana T, Kumar SP, and Krishna NS. Formulation and evaluation of bilayered tablets of metformin hydrochloride and atorvastatin calcium. Int J Pharm Sci Rev Res 2011; 10(2):130-4.
33. Kumar G V, Babu K A, and Ramasanay C. Formulation and evaluation of bilayered tablets of cefixime trihydrate and dicloxacillin sodium. Int J Pharm Tech Res 2011; 3(2):613-8.
34. Jadhav R T, Patil P H, and Patil P R. Formulation and evaluation of bilayered tablets of piracetam and vinpocetine. J Chem Pharm Res 2011; 3(3):423-31.
35. Rajendran N N, Natarajan R, Subhashini R and Patel H. Formulation and evaluation of sustained release bilayer tablets of metformin HCl and pioglitazone HCl. Int J Curr Pharm Res 2011;3(3):118-22.
36. Shirsand S B, Swamy P V, and Keshavshetti G G. Design and evaluation of atenolol bilayer buccal tablets. RGUHS J Pharm Sci 2011; 1(1):4-10.