

**AN OVERVIEW ON BILAYERED TABLET TECHNOLOGY**

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**ABSTRACT**

Bi-layer tablet is a new era for successful development of controlled release formulation along with various features to provide successful drug delivery. Bi-layer tablets can be primary option to avoid chemical incompatibilities between APIs by physical separation and to enable the development of different drug release profiles. Bi-layer tablet is suitable for sequential release of two drugs in combination and also for sustained release of tablet in which one layer is for immediate release as loading dose and second layer is maintenance dose. So use of bi-layer tablets is a very different aspect for anti-hypertensive, diabetic, anti-inflammatory and analgesic drugs where combination therapy is often used. Several pharmaceutical companies are currently developing bi-layer tablets, for a variety of reasons: patent extension, therapeutic, marketing to name a few. General tablet manufacturing principles remain the same, there is much more to consider because making multi-layer tablets involves multiple often incompatible products, additional equipment and many formulation and operation challenges. The present article provides an introduction to bi-layer tablet technology, challenges in bi-layer tablet manufacturing, 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.

**Keywords:** Bi-layer tablet. API (active pharmaceutical ingredient). incompatibilities. such as chewing device and floating tablets for gastro-retentive drug delivery.

**INTRODUCTION<sup>1, 2</sup>**

In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bi-layer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance.

Bi-layer tablets can be a primary option to avoid chemical incompatibilities between APIs by physical separation, and to enable the development of different drug release profiles (immediate release with extended release).

**NEED OF BILAYER TABLETS<sup>3, 4, 5</sup>**

1. For the administration of fixed dose combinations of different APIs, prolong the drug product life cycle, buccal/mucoadhesive delivery systems; fabricate novel drug delivery systems

2. Controlling the delivery rate of either single or two different active pharmaceutical ingredient(s)
3. To modify the total surface area available for API layer either by sandwiching with one or two in active layers in order to achieve swellable/erodible barriers for modified release.
4. To separate incompatible Active pharmaceutical ingredient (APIs) 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 BILAYER TABLET****DOSAGE FORM**

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

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

#### **DISADVANTAGES OF BILAYER TABLET DOSAGE FORM**

1. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
2. Bitter tasting 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, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.

#### **IDEAL CHARACTERISTICS OF BILAYER TABLETS**

1. A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration and contamination.
2. It should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
3. It should have the chemical and physical stability to maintain its physical attributes over time. The bi-layer tablet must be able to release the medicinal agents in a predictable and reproducible manner.

4. It must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

#### **CHALLENGES IN BILAYER MANUFACTURING <sup>6</sup>**

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

**Delamination:** Tablet falls apart when the two halves of the tablet do not bond completely. The two granulations should adhere when compressed.

**Cross-contamination:** When the granulation of the first layer intermingles with the granulation of the second layer or vice versa, cross-contamination occurs. It may conquer the very purpose of the bilayer tablet. Proper dust collection goes a long way toward preventing cross contamination.

**Production yields:** To prevent cross contamination, dust collection is required which leads to losses. Thus, bilayer tablets have lower yields than single-layer tablets.

**Cost:** Bilayer tableting is more expensive than single-layer tableting for several reasons. First, the tablet press costs more. Second, the press generally runs more slowly in bilayer mode. Third, development of two compatible granulations is must, which means more time spent on formulation development, analysis and validation. These factors, if not well controlled/optimized, in one way or another will impact the bilayer compression per se and the quality attributes of the bilayer tablets (sufficient mechanical strength to maintain its integrity and individual layer weight control). Therefore, it is critical to obtain an insight into the root causes to enable design of a robust product and process.

#### **Types of bilayer tablet press:**

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

### 1. Single sided press: <sup>7</sup>

The simplest design is a single sided press with both chambers of the doublet feeder separated from each other. Each chamber is gravity or forced fed with different power, producing the two individual layers of tablets. When die passes under the feeder, it is first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps.

#### Limitations of the single sided press: <sup>8, 9, 10</sup>

1. No weight monitoring / control of the individual layers.
2. No distinct visual separation between the two layers.
3. Very short first layer dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping and hardness problems.
4. This may be corrected by reducing the turret-rotation speed (to extend the dwell time) but with the consequence of lower tablet output.

### 2. Double sided tablet press: <sup>7</sup>

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

### 3. Bilayer tablet press with displacement monitoring:

The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied precompression force.

### Advantages:

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

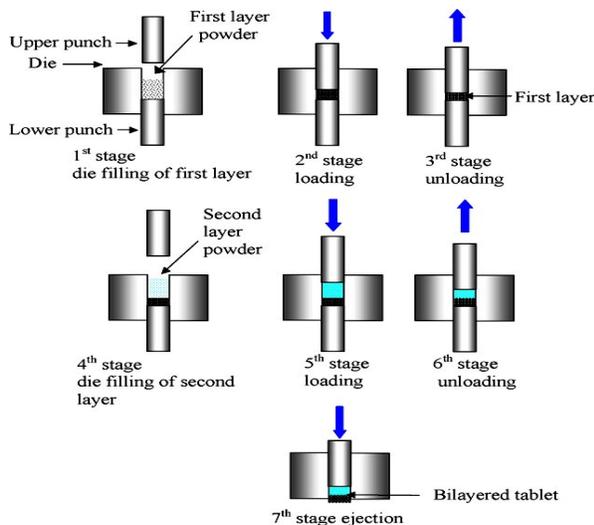
### PREPARATION OF BILAYER TABLETS <sup>11, 12, 13, 14</sup>

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<sup>8</sup>. 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.

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.



**Fig 1:** Preparation of bilayer tablet Compaction

**QUALITY AND GMP-REQUIREMENTS<sup>11</sup>**

To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the Selected press is capable of 5:

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

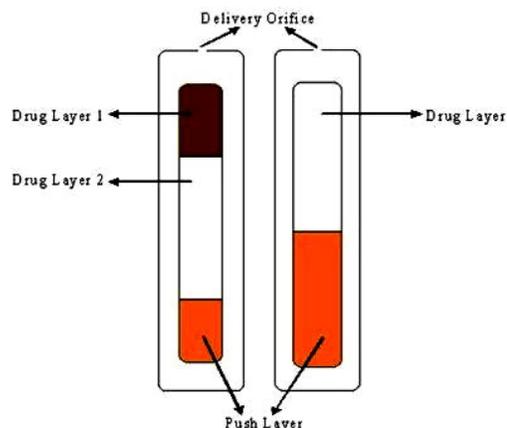
These requirements seem obvious but are not so easily accomplished.

**VARIOUS TECHNIQUES FOR BILAYER TABLET<sup>15,16</sup>**

**A) OROS® push pulls Technology**

This system consist of mainly two or three layer among which the one or more layer are essential

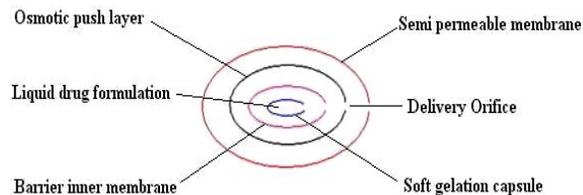
of the drug and other layer are consist of push layer. The drug layer mainly consists of drug along with two or more different agents. So this drug layer comprises of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core (Figure 2).



**Fig. 2:** Bilayer and trilayer OROS push pull technology

**B) L-OROS™ Technology**

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 3).



**Fig.3:** L-OROS™ Technology

**C) EN SO TROL Technology**

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 (Figure4).

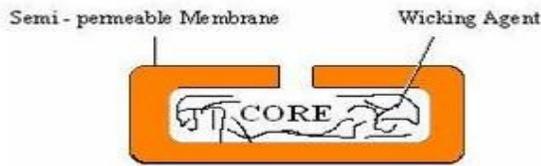


Fig. 4: EN SO TROL Technology

#### D) DUREDAS™ Technology

This system is also known as 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 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.

#### E) DUROS Technology

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 and release minute quantity of concentrated form in continues and consistent from over months or year(Figure 5).

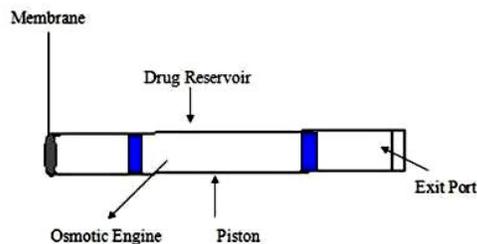


Fig. 5: DUROS Technology

### VARIOUS APPROACHES USED IN THE BILAYER TABLET<sup>16, 17</sup>

#### a) Floating Drug Delivery System

From the formulation and technological point of view, the floating drug delivery systems are considerably easy and logical approach in the

development of Gastro retentive dosage forms (GRDFs).

#### Approaches to design Floating Drug Delivery System

The following approaches have been used for the design of floating dosage forms of single- and multiple-unit systems.

##### Intra gastric bilayered floating tablets

These are also compressed tablet as shown in figure and contain two layers i.e. Immediate and sustained release

##### Multiple unit type floating pills

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. (Figure 6)

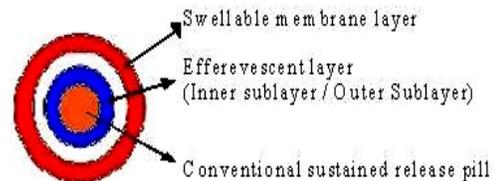


Fig. 6: Multiple units of oral FDDS

#### b) Polymeric Bio adhesive System

These are designed to imbibe fluid following administration such that the outer layer becomes a viscous, tacky material that adheres to the gastric mucosa/mucus layer. This should encourage gastric retention until the adhesive forces are weakened. These are prepared as one layer with immediate dosing and other layer with bio adhesive property.

**Disadvantages:** The success is seen in animal models with such system has not been translated to human subjects due to differences in mucous amounts, consistency between animals and humans.

The system adheres to mucous not mucosa. The mucous layer in humans would appear to slough off readily, carrying any dosage form with it. Therefore, bio adhesive dosage form would not appear to offer a

solution for extended delivery of drug over a period of more than a few hours.

### c) Swelling System

These are designed to be sufficiently small on administration so as not to make ingestion of the dosage form difficult (e.g., less than approximately 23 mm long and less than 11 mm wide for an oval or capsule -shaped tablet whereas 10- 12mm in diameter for round tablets). On ingestion they rapidly swell or disintegrate or unfold to a size that precludes passage through the pylorus until after drug release has progressed to a required degree. Gradual erosion of the system or its breakdown into smaller particles

enables it to leave stomach. The simple bilayer tablet may contain an immediate release layer with the other layer as extended release or conventional release.

### RECENT DEVELOPMENTS IN THE FIELD OF BILAYER TABLETS

The introduction of bilayer tablets into the pharmaceutical industry has enabled the development of pre-determined release profiles of active ingredients and incorporation of incompatible active ingredients into the single unit dosage form. Large number of work has been done in this field. Some of the recent findings are explained in the preceding table-1.

**Table-1: Various Advancements in the Field of Bilayer Tablets**

DRUG(S)	DOSAGE FORM	RATIONALE	REF.NO.
Diclofenac, Cyclobenza-prine	Bilayer tablets	Synergistic effect in pain	18
Granisetron HCl	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects	19
Metformin HCl, Glimipiride	Bilayer tablets	Synergistic effect in diabetes	20
Indomethacin	Bilayer floating tablets	Biphasic drug release	21
Metformin HCl Atorvastatin Calcium	Bilayer tablets	To develop polytherapy for the treatment of NIDDS & hyperlipidemia	22
Cefixime Trihydrate Dicloxacilline Sodium	Bilayer tablets	Synergistic effect in bacterial infections	23
Piracetam, Vinpocetin	Bilayer tablets	Synergistic effect in Alzheimer disease	24
Metformin HCl, Pioglitazone	Bilayer tablets	Synergistic effect in diabetes mellitus	25
Atenolol	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects and frequency of administration	26
Cefuroxime Axetil Potassium Clavulanate	Bilayer tablets	Synergistic effect against microbial infections and to minimize dose dependent side effects	27
Amlodipine Besilate Metoprolol Succinate	Bilayer tablets	Synergistic effect in hypertension	28,41
Diclofenac Sodium, Paracetamol	Bilayer tablets	Synergistic effect in pain	29
Ibuprofen, Methocarpa-mol	Bilayer tablets	Synergistic effect of drugs in back pain	30
Atorvastatin, Calcium	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects and frequency of administration	31
Paracetamol diclofenac	Bilayer tablets	Synergistic effect of drugs in pain	32
Losartan	Bilayer tablets	Biphasic release profile	33
Metformin HCl, Pioglitazone	Bilayer tablets	Synergistic effect in diabetes mellitus	34
Guaifenesin	Bilayer tablets	Biphasic release profile	35
Tramadol, Acetaminophen	Bilayer tablets	Synergistic effect of drugs in pain	36
Atenolol, Lovastatin	Bilayer floating tablets	Synergistic effect in hypertension and biphasic release profile	37
Montelukast, Levocetizine	Bilayer tablets	To improve the stability of drugs in combination	38
Salbutamol, Theophylline	Bilayer tablets	Synergistic effect of drugs in asthma	39
Glipizide, Metformin HCl	Bilayer tablets	To avoid interaction b/w incompatible drugs	40
Telmisartan Hydrochlor- thiazide	Bilayer tablets	To minimize contact b/w hydrochlorothiazide & basic component of telmisartan	42
Amlodipine, Atenolol	Bilayer tablets	To improve the stability of drugs in combination	43
Ascorbic acid, Cyano-cobalamine	Double layer suppositories	To avoid interaction b/w incompatible vitamins	44
Rifampicin, Isoniazid	Capsule & tablet in Capsule	To avoid interaction b/w incompatible drugs	45
Misorostol, Diclofenac	Bilayer tablets	To minimize contact b/w drugs	46

Propranolol HCl	Bilayer tablets	Bimodal drug release	47
Artesunate, Amlodipine	Tablet-in-tablet	To minimize contact b/w drugs	48
Telmisartan, Simvastatin	Bilayer tablets	To minimize contact b/n Simvastatin & telmisartan	49
Cefuroxime axetil	Bilayer floating tablets	Bimodal drug release	50
Metformin, Glipizide	Bilayer tablets	Synergistic effect of drugs in diabetes	51
Ranitidine Aspirin	Single layer coated tablets	To minimize the contact of two incompatible drugs	52
Aspirin Ranitidine	Single layer tablets	To minimize the contact of two incompatible drugs	53
Statin Aspirin	Bilayer tablets	To minimize interaction b/w two drugs and side effects due to aspirin	54
Furosemide	Bilayer floating tablets	To enhance bioavailability	55

### CONCLUSION:

Bi-layer tablets offer an excellent opportunity for manufacturers to separate themselves from their competitors, improve their products' efficacy, and protect against impersonator products. 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. When a quality bi-layer tablet needs to be produced in conjunction with accurate weight control of both layers, compression force-controlled presses are clearly limited because of their insufficient sensitivity and hence lack of accuracy at low compression forces required to secure interlayer bonding. Such problems become even more apparent when the tableting speed is high or increased. Accurate individual layer weight monitoring/control at high speed and in combination with reduced layer separation risk can be achieved with the displacement weight control system based presses.

### REFERENCES

1. Martindale, the Extra Pharmacopoeia, 31<sup>st</sup>ed. The Pharmaceutical Press, London; 1996.p.936-937.
2. Shiyani B *et al*. Formulation and evaluation of bi-layer tablet of Metoclopramide hydrochloride and Ibuprofen. AAPS Pharm Sci Tech 2008;9(3):818-27.
3. Kulkarni A *et al*, Development and evaluation of bilayer floating tablets of atenolol and lovastatin for biphasic release profile.
4. Panchel hiten ashok, Tiwari ajay kumar, A Novel approach of bilayer tablet technology-A review, IRJP, 3(5), 2012.
5. Nirmal J *et al*, Saisivam S *et al*, Peddanna C *et al*, Muralidharan S *et al*, Nagarajan M *et al*, Bilayer tablets of atorvastatin calcium and nicotinic acid: formulation and evaluation. Chem. Pharm.Bull.2008;56: 1455-1458,26-102-1PB.
6. Varaiya C. Bi-layer neutraceutical tablets: Rewards and challenges. In: Keefer R, Calvin J, Kirsch D, Bubb G, Bowman L, Matthews S. Multi-layer tableting Q & A. CSC Publishing.
7. Jan Voegelé *et al* Bi-layer tablets - why special technology is required The Courtoy-R292F tablet press, designed for quality bi-layer tablets Niro Pharma Systems.
8. Abshagen U *et al*, Spo "rl-Radun S *et al*, First data on the effects and pharmacokinetics of isosorbide-5-mononitrate in normal man, Eur. J. Clin.Pharmacol.;1981; 19p.423-429.
9. 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, p.142-145.
10. Patel Mehul,Ganesh *et al*, Nanjan Sockan *et al*, Challenges in the Formulation of Bilayered Tablets: A Review, International Journal of Pharma Research and Development,2010, ISSN 0974 - 9446.
11. 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.

12. Breech AJ *et al*, Lucisano L J *et al*, Franz RM *et al* Investigation into substrate cracking of a film coated bilayered tablet. *J. Pharm.Pharmacol.* 1998; 40:282-283.
13. M.A. Kalam *et al*, M. Humayun *et al*, N. Parvez *et al*, S.Yadav *et al*, A.Garg *et al*, S.Amin *et al*, Y. Sultana *et al* and A. Ali., *Continental et al J. Pharmaceutical Sciences*;2007,1: 30 – 35
14. Li S.P. *et al*, Karth M.G. *et al*, Feld K.M. *et al*, Pendharkar C.M. *et al*, Willams R.O. *et al*, Evaluation of Bilayer tablet machines. A Case study. *Drug Dev. Ind. Pharm.* 1995; 21(5): 571-590.
15. Science and Technologies [online]. [cited 2012 Available from URL: <http://www.durect.com>
16. Naisarg d. Pujara ronak k. Gokani, Jalpa s. paun. Bilayer tablet –An emerging trend *ijprd*, 2011; vol 4(04): june-2012 (102 - 111).
17. Shirwalkar A A, Kumar SM, Jacob S. Recent developments in floating drug delivery systems for gastric retention of drugs, an overview. *Indian drugs.* 2006; 43(9): 697-704.
18. Jamunadhevi V, Sahoo P K 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.
19. 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.
20. Pattanayak D P and Dinda S C. Bilayer tablet formulation of Metformin HCl and Glimperide: A novel approach to improve therapeutic efficacy. *Int J Drug Discovery Herb Res* 2011; 1(1):1-4.
21. Jain J, Marya B H, Mittal RP and Patel M. Formulation and evaluation of indomethacin bilayer sustained release tablets. *Int J PharmTech Res* 2011; 3(2):1132-8.
22. 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.
23. Kumar G V, Babu K A and Ramasanay C. Formulation and evaluation of bilayered tablets of cefixime trihydrate and dicloxacillin sodium. *Int J PharmTech Res* 2011; 3(2):613-8.
24. 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.
25. 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.
26. Shirsand S B, Swamy P V, and Keshavshetti G. Design and evaluation of atenolol bilayer buccal tablets. *RGUHS J Pharm Sci* 2011; 1(1):4-10.
27. Parmar C K and Pednekar P P. Development and evaluation of bilayer tablets of cefuroxime axetil and potassium clavulanate. *Int J Pharm Res Dev* 2011; 3(7):16-23.
28. Jayaprakash S, Halith S M, Pillai K K, Balasubramaniam P, Firthouse P U M and Boopathi M. Formulation and evaluation of bilayer tablets of amlodipine besilate and metoprolol succinate. *Derr pharmacia Lettre* 2011; 3(4):143-54.
29. Musle K, Payghan S A and Disuza J I. Formulation, evaluation and development of bilayer tablet. *Int J Pharm Res Dev* 2011; 3(10):80-7.
30. Remya P N, Damodharan N and Kumar CVS. Formulation and evaluation of bilayered tablets of ibuprofen and methocarbamol. *Int J PharmTech Res* 2010; 2(2):1250-55.
31. John AS, Sathesh B P R, Divakar G, Jangid M K and Purohit K K. Development and evaluation of buccoadhesive drug delivery system for Atorvastatin calcium. *J Curr Pharm Res* 2010; 1:31-8.
32. Gohel M C, Parikh R K, Nagori S A and Jethwa B A. Fabrication and evaluation of bi-layer tablet containing conventional paracetamol and modified diclofenac sodium. *Indian J Pharm Sci* 2010; 72(2):191-6.
33. Hiremath D, Goudanavar P, Azharuddin M, Udipi R H and Sarfaraz M. Design and characterization of bilayer controlled release matrix tablets of losartan potassium. *Int J Pharm Res* 2010; 2(4):34-9.
34. Ramesh A. Formulation and evaluation of bilayer sustained release matrix tablets of Metformin HCl and Pioglitazone. *Amer-Euras J Sci Res* 2010; 5(3):176-82.

35. Kumar V B, Prasad G, Ganesh B, Swathi C, Rashmi A and Reddy AG. Development and evaluation of guaifenesin bilayer tablet. *Int J Pharm Sci Nanotech* 2010; 3(3):1122-8.
36. Naeem M A, Mahmood A, Khan S A and Shahiq Z. Development and evaluation of controlled release bilayer tablets containing microencapsulated tramadol and acetaminophen. *Trop J Pharm Res* 2010; 9(4):347-54.
37. Kulkarni A and Bhatia M. Development and evaluation of regioselective bilayer floating tablets of atenolol and lovastatin for biphasic release profile. *Iranian J Pharm Res* 2009; 8:15-25.
38. Rathod R T and Misra D. FDC of montelukast with levocetirizine: Focus on bilayer technology. *J Indian Med Assoc* 2009; 107(8):562-4.
39. Nagaraju R and Kaza R. Formulation and evaluation of bilayer sustained release tablets of salbutamol and theophylline. *Int J Pharm Sci Nanotech* 2009; 2(3):638-46.
40. Kadam V V, Waghmare M U, Venkatpurwar V P and Pokharkar V B. Preparation and evaluation of glipizide-metformin HCl sustained release bilayer tablet [online]. 2009 [cited 15 Sept 2009]. Available From: [www.scientificipca.org/paper/2009/09/15/200909151256230A.doc](http://www.scientificipca.org/paper/2009/09/15/200909151256230A.doc) [accessed on 1 July 2011]. URL:
41. Atram S C, Udavant Y K, Salunke R J, Neb G B, Shahi S R, Gulecha B S and Padalkar A N. Formulation and evaluation of bilayer tablet containing Metoprolol succinate and Amlodipine besylate as a model drug for anti hypertensive therapy. *J Pharm Res* 2009; 2(8):1335-47.
42. Friedl T and Schepky G, inventors; Boehringer Ingelheim USA Corporation, assignee. Bilayer pharmaceutical tablet comprising telmisartan and a diuretic and preparation thereof. US patent 0227802 A1. 2009 Sept 10.
43. Aryal S and Skalko-Basnet N. Stability of amlodipine besylate and atenolol in multicomponent tablets of mono-layer and bi-layer types. *Acta Pharm* 2008; 58:299-308.
44. Bakuridze A D, Maglakelidze G M, Kurdiani N G, Tsagarejshvili NT and Berashvili DT. Technology of vitamins containing double layer suppositories. *Georgian Med News* 2008; 158:49-51.
45. Gohel M C and Sarvaiya K G. A novel solid dosage form of rifampicin and isoniazid with improved functionality. *AAPS PharmSci Tech* 2007; 8(3): article 68. doi: 10.1208/pt0803068.
46. Ouali A and Azad A K, inventors; Pharmascience Inc, assignee. Stabilized pharmaceutical composition of nonsteroidal anti-inflammatory agent and a prostaglandin. WO 2000/056339. 2007 Jan 03.
47. Patra C N, Kumar A B, Pandit H K, Singh S P and Devi MN. Design and evaluation of sustained release bilayer tablets of propranolol hydrochloride. *Acta Pharma* 2007; 57:479-89.
48. Godha P, Bansal Y K, Sengupta S and Singh N, inventors; IPCA Laboratories Limited, assignee. Antimalarial combination and methods of formulation. WO 2007/043061 A1. 2007 Apr 19.
49. Kohlrausch A, inventor; Boehringer Ingelheim International GmbH, assignee. Bilayer tablet of telmisartan and simvastatin. US patent 0078615 A1. 2006 Apr 13.
50. Dhupal R S, Rajmane S T, Dhupal S T and Pawar A P. Design and evaluation of bilayer floating tablets of cefuroxime axetil for bimodal release. *J Sci Ind Res* 2006; 65:812-6.
51. De-fang O, Shu-fang N, Compound metformin/glipizide bilayer extended release tablets: Development and *in vitro* release. 2005; 14(3):169-72.
52. Fernandez I M, inventor. Glaxo Wellcome S A, assignee. Pharmaceutical formulation. EP 1363604A2. 2003 Nov 26.
53. Wang X, Cui F, Yonezawa Y and Hisakazu S. Preparation and evaluation of combination tablet containing incompatible active ingredients. *Chem Pharm Bull* 2003; 51(7):772-8.
54. Ullah I and Jain N B, inventors; Bristol-Mayer Squibb Company, assignee. Pharmaceutical composition containing a combination of a statin and aspirin and method, US patent 6235311 B1. 2001 May 22.
55. Ozdemir N, Ordu S and Ozkan Y. Studies of floating dosage forms of furosemide: *In vitro* and *in vivo* evaluations of bilayer tablet formulations. *Drug Dev Ind Pharm* 2000; 26(8):857-66.

