REVIEW ARTICLE

Polytherapeutic approach using bilayer matrix technology

Sanjay Kumar Sharma, Shailender Mohan, Manish Jaimini, Rohit Tiwari

Department of Pharmaceutics, Jaipur College of Pharmacy, Sitapura, Jaipur, Rajasthan, India

Oral administration of the drug is the most popular route for systemic effects owing to its ease of ingestion, pain, versatility, and most importantly, patient compliance. Combinational therapy have been found to have various advantages over monotherapy such as problem of dose-dependent side effects is minimized, a low-dose combination of two different agents reduces the dose-related risk, the addition of one agent may counteract some deleterious effects of the other, using low dosage of two different agents minimize the clinical and metabolic effects that occur with maximal dosage of individual component of the combined tablet. Multilayer tableting is getting increasing attention from a variety of industries for a variety of reasons viz. patent extension, therapeutic, and marketing attendance. To reduce capital investment, quite often existing, but modified tablet presses are used to develop and produce such tablets. Although the general tablet manufacturing principles remain the same, there is much more to consider, since making multilayer tablets involves multiple often incompatible products, additional equipment, and many formulation and operation challenges.

Key words: *Bilayer matrix, combination therapy, multilayer tabletting, polytherapy*

INTRODUCTION

Oral administration is considered to be the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility, and most importantly, patient compliance. Also solid oral delivery systems do not require sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Excipients and equipments choices will be significantly affected should solid dosage form technologies change in response to the unprecedented shifts in the drug discovery such as genomics.[1] Pharmaceutical tablets are the dominant dosage form for drug delivery, occupying two-thirds of the global market. In general, 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. In addition, layered tablets, such as bilayered tablets,[2-5] and even triple-layered tablets,[6,7] have been developed to achieve controlled drug delivery with predefined release profiles for different active ingredients.

Bilayer tablets are composed of two layers of granulation compressed together. Two-layer tablets require fewer materials than compression-coated tablets weigh less and may be thinner. Monograms and other distinctive markings may be impressed in the surfaces of the multilayer tablets. Coloring the separate layers provides many possibilities for unique tablet identity. Separation of the layers prior to assay may simplify the analytical work as well. Since there is no transfer to a second set of punches and dies, as with the dry-coating machine, odd shapes (such as triangles, squares, and ovals) present no operating problems except for those common to keyed tooling [Figure 1].[8]

Various problems are also associated with the formulation of bilayer tablets, such as layer-separation, insufficient hardness, inaccurate individual layer weight control, cross-contamination between the layers,

Address for correspondence:
Mr. Sanjay Kumar Sharma,
Department of Pharmaceutics, Jaipur College of Pharmacy,
ISI-15, RIICO, Sitapura Institutional Area,
Sitapura, Jaipur - 302 022, Rajasthan, India.
E-mail: sanjaysharma.pharma@gmail.com

Access this article online

Quick Response Code:

Website: www.asiapharmaceutics.info

DOI: 10.4103/0973-8398.134961

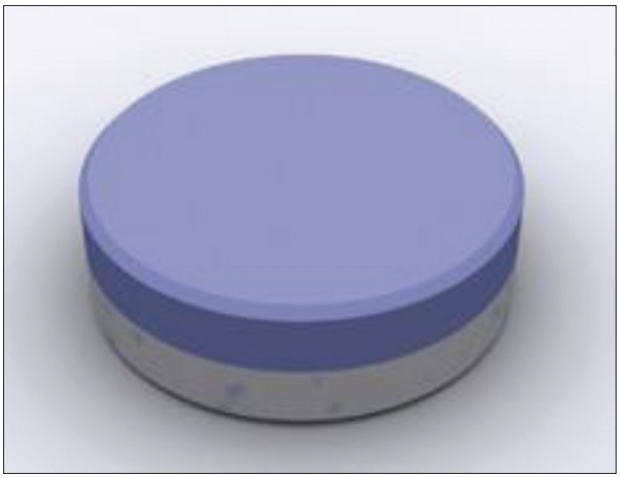

Figure 1: Bilayer tablets

reduced yield, etc. To overcome these problems, development and production of quality bilayer tablets need to be carried out on purpose-built tablet presses.[9]

Objectives for designing bilayer matrix tablets

1. To control the delivery rate of either single[10] or two different active pharmaceutical ingredient(s)[11,12]
2. To separate the incompatible drugs from each other, or to control the release of one drug from one layer by utilizing the functional property of other layers (such as osmotic properties)
3. To modify the total surface area available for drug layer by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release[13,14]
4. To administer fixed dose combinations of different drugs[15]
5. Prolong the drug-product lifecycle; fabricate novel drug delivery system such as chewing devices,[16] buccal/mucoadhesive delivery systems,[17] and floating tablets for gastro retentive drug delivery (GRDD).[18]

Advantages of bilayer technology

1. It offers great capabilities of all oral dosage forms for the greatest dose precision and the least content variability
2. Light and compact
3. Objectionable and bitter taste can be masked by coating technique
4. Great microbial and chemical stability.

Disadvantages of bilayer technology

1. Some drug resists compression into dense compacts, owing to amorphous nature, low density profile
2. Drugs with poor wetting, slow dissolution properties, and optimum absorption in gastrointestinal tract (GIT) may be difficult to formulate as a tablet that will still provide adequate or full drug availability
3. Tableting problems such as capping and lamination may occur during the compaction process.

Good manufacturing process (GMP) requirements for bilayer matrix technology

To produce a quality bilayer tablet, in accordance with International Conference on Harmonisation (ICH), it is important that the selected press should be capable of:

1. Preventing capping and separation of the two individual layers that constitute the bilayer tablets
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.

Various techniques for bilayer tablet

OROS® push-pull technology

This system generally consists of two or three layer among which one or more layer are essentially of the drugs and other layer consists of push layer (or osmotic layer). A semipermeable membrane generally surrounds the tablet core [Figure 2].

L-OROS™ technology

This system is used to eliminate the solubility consequence. Alza developed the L-OROS system where a lipid soft gel product containing drug in a dissolved state is initially fabricated and then coated with a barrier membrane and the osmotic push layer and a semipermeable membrane, are drilled with an exit orifice [Figure 3].

EN SO TROL technology

Solubility enhancement of an order of magnitude or to create optimized dosage form, Shire Laboratory used an integrated approach to drug delivery focusing on the identification and incorporation of the identified enhancer into controlled-release (CR) technologies.[19]

DUROS technology

This system consists from an outer cylindrical titanium alloy reservoir. This reservoir has high impact strength and offers to protect the drug molecules from enzymes. The DUROS technology is the small drug dispensing system that looks like a miniature syringe and releases minute quantity of concentrated form in continuous and consistent form over months or year [Figure 4].

Elan drug technologies' dual release drug delivery system (DUREDAS™ technology)

It 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 a tablet. The modified-release properties of the dosage form are provided by a combination of hydrophilic polymers.

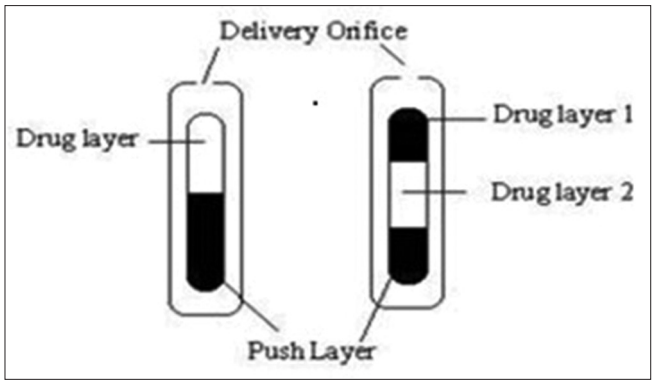

Figure 2: OROS® push-pull technology

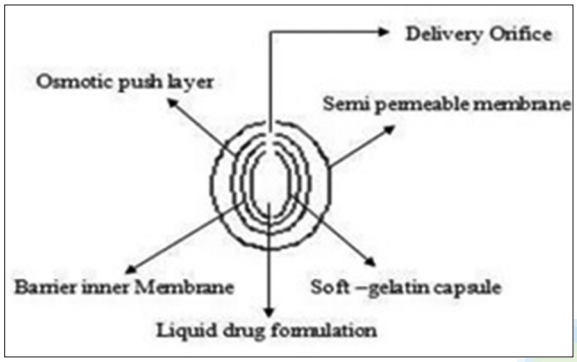

Figure 3: L-OROS™ technology

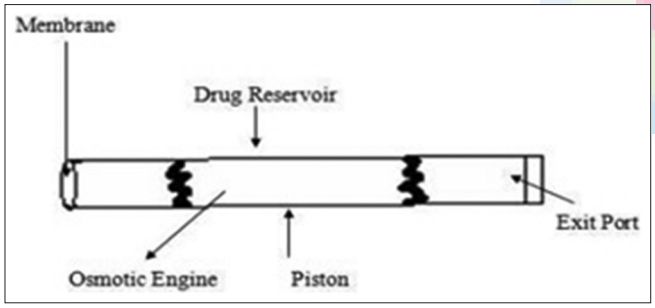

Figure 4: DUROS technology

Benefits offered by the DUREDAS™ technology include:

- Bilayer tableting technology
- Trim 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.

The DUREDAS™ system can easily be manipulated to allow incorporation of two CR formulations in the bilayer. Furthermore, two different release rates can be achieved from each side. In this way, further prolongation of sustained release can be achieved. Typically, an immediate release granulate is first compressed followed by the addition of a CR element, which is compressed onto the initial tablet. This gives the characteristic bilayer effect to the final dosage form. A further extension of the DUREDAS™ technology is the production of CR combination dosage forms whereby two different drugs are incorporated into the different layers and drug release of each is controlled to maximize the therapeutic effect of the combination. Both immediate release and CR combinations of the two drugs are possible. A number of combination products utilizing this technology approach have been evaluated.

The DUREDAS™ technology was initially employed in the development of a number of over-the-counter (OTC) CR analgesics. In this case, a rapid release of analgesic is necessary for a fast onset of therapeutic effect. Hence, one layer of the tablets is formulated as immediate releases granulate. By contrast, the second layer of the tablet, through use of hydrophilic polymers, releases drug in a controlled manner, to prolong the action or to produce the action in synergism to that of immediate layer. The CR is due to a combination of diffusion and erosion through the hydrophilic polymer matrix.[20]

Various Advancements in bilayer technology has been shown in Table 1.

METHOD OF EVALUATION OF BILAYER MATRIX TABLETS

Characterization of bilayer tablet granules

Particle size distribution

The particle size distribution can be measured using sieving method or by stage oculometer microscope.

Angle of repose

The diameter of the powder cone was measured and the angle of repose was calculated using the following equation:

$$\text{Tan } \theta = h/r \quad (1)$$

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

Moisture sorption capacity

All disintegrate have capacity to absorb moisture from atmosphere which can affect moisture sensitive drugs. Moisture sorption capacity determination is performed by taking 1 g of blend uniformly distributed in Petri dish and keeping it in the stability chamber at 37 ± 1°C and 100% relative humidity for 2 days and then investigating for the amount of moisture uptake by difference between weights.

Density

The loose bulk density (LBD) and tapped bulk density (TBD) are determined for the flow property assessments and are calculated using the following formulas:

LBD ¼ weight of the powder = volume of the packing (2)

TBD ¼ weight of the powder = tapped volume of the Packing (3)

Table 1: Lists of various advances made in bilayer technology

Author	Drug (s)	Dosages form	Rationale	Method	Year	Ref. no.
Jamunadhevi *et al.*	Diclofenac cyclobenzaprine HCl	Bilayer tablets	Synergistic effect in pain	Wet granulation	2011	25
Swamy *et al.*	Granisetron HCl	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects	Direct compression	2011	26
Pattanayak *et al.*	Metformin HCl glimipiride	Bilayer tablets	Synergistic effect in diabetes	Wet granulation	2011	27
Jain *et al.*	Indomethacin	Bilayer floating tablets	Biphasic drug release	Wet granulation	2011	28
Mohindeen *et al.*	Metformin HCl Atorvastatin Calcium	Bilayer tablets	To develop polytherapy for the treatment of non-insulin-dependent diabetes mellitus and hyperlipidemia	Wet granulation	2011	29
Kumar *et al.*	Cefixime trihydrate Dicloxacilline sodium	Bilayer tablets	Synergistic effect in bacterial infections	Wet granulation	2011	30
Jadhav *et al.*	Piracetam Vinpocetin	Bilayer tablets	Synergistic effect in alzheimer disease	Wet granulation	2011	31
Rajendran *et al.*	Metformin HCl Pioglitazone	Bilayer tablets	Synergistic effect in diabetes mellitus	Wet granulation and direct compression	2011	32
Shirsand *et al.*	Atenolol	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects, and frequency of administration	Direct compression	2011	33
Parmar *et al.*	Cefuroxime axetil Potassium clavulanate	Bilayer tablets	Synergistic effect against microbial infections and to minimize dose-dependent side effects	Dry granulation	2011	34
Musle *et al.*	Diclofenac sodium Paracetamol	Bilayer tablets	Synergistic effect in pain	Wet granulation	2011	35
Remya *et al.*	Ibuprofen Methocarbamol	Bilayer tablets	Synergistic effect of drugs in back pain	Wet granulation	2010	36
Gohel *et al.*	Paracetamol Diclofenac	Bilayer tablets	Synergistic effect of drugs in pain	Wet granulation	2010	37
Ramesh *et al.*	Metformin HCl Pioglitazone	Bilayer tablets	Synergistic effect in diabetes mellitus	Dry and wet granulation	2010	38
Naeem *et al.*	Tramadol Acetaminophen	Bilayer tablets	Synergistic effect of drugs in pain	Coacervation via temperature change	2010	39
Rathod *et al.*	Montelukast Levocetrizine	Bilayer tablets	To improve the stability of drugs in combination	Wet granulation	2009	40
Kadam *et al.*	Glipizide Metformin HCl	Bilayer tablets	To avoid interaction between incompatible drugs	Wet granulation	2009	41
Friedl *et al.*	Telmisartan Hydrochlorthiazide	Bilayer tablets	To minimize contact between hydrochlorthiazide and basic component of telmisartan	Wet granulation	2009	42
Bakuridze *et al.*	Ascorbic acid Cyanocobalamine	Double layer suppositories	To avoid interaction between incompatible vitamins	Using suppository base	2008	43
Ouali *et al.*	Misorostol Diclofenac	Bilayer tablets	To minimize contact between drugs	Wet granulation	2007	44
Kohlrausch *et al.*	Telmisartan Simvastatin	Bilayer tablets	To minimize contact between simvastatin and telmisartan	Wet granulation	2006	45
De-fang *et al.*	Metformin Glipizide	Bilayer tablets	Synergistic effect of drugs in diabetes	Wet granulation	2005	46

Compressibility

The compressibility index of the granules is determined by Carr's compressibility index.[21,22]

$$C = 100 \times (1 - \rho B/\rho T) \quad (4)$$

Hausnser's ratio

T is calculated by the formula,

$$H = \rho T/\rho B \quad (5)$$

Where ρB is the freely settled bulk density of the powder and ρT is the tapped density of the powder.[23]

Evaluation of bilayer tablet

Tablet thickness and size

Thickness and diameter of tablets are important for uniformity of tablet size. Thickness and diameters is measured using vernier caliper and the standard deviation (SD) is reported accordingly.

Tablet hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation, and handling before usage depends on its hardness. In general, the hardness of tablets is measured by Monsanto hardness tester. The hardness is reported in kg/cm^2.

Friability

Friability gives the measurement of tablet strength. Electrolab EF-2 friabilator (United States Pharmacopoeia (USP)) are generally used for testing the friability. According to Indian Pharmacopoeia (IP), 20 tablets are weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of 6 inches with each revolution. After 4 min/100 revolutions, the tablets are dusted and reweighed and the percentage loss in tablet weight is determined.[21]

% loss = [(Initial wt. of tablets − Final wt. of tablets)/Initial wt. of tablets] × 100 (6)

Uniformity of weight

Twenty tablets are selected at random and the average weight is calculated. Weight variation test should comply with IP standards.[23]

Dissolution studies

Bilayer tablets are subjected to *in vitro* drug release kinetic studies in simulated gastric and intestinal fluids to assess their ability in providing the desired immediate/controlled drug delivery. At different time intervals the definite sample size are withdrawn and replaced with drug-free dissolution medium. The samples withdrawn are analyzed spectrophotometrically using multicomponent mode of analysis for the release of the drug components and the *in vivo-in vitro* correlations (IVIVC) are established to facilitate efficacy of the product.[24]

REFERENCES

1. Bankar GS, Anderson NR. Tablets. In: Leon L, Liberman HA, Kaing JL, editors. The Theory and Practice of Industrial Pharmacy. 3rd ed. Varghese Publishing House; 1987. p. 293-303.
2. Nangia A, Molloy T, Fahie BJ, Chopra SK. Novel regulated release system based on geometric configuration. Proc Int Sym Con Rel Bio Mat 1995;22:294-5.
3. Chidambaram N, Porter W, Flood K, Qiu Y. Formulation and characterization of new layered diffusional matrices for zero-order sustained release. J Control Release 1998;52:149-58.
4. Conte U, Maggi L, Columbo P, La Manna A. Multi-layered hydrophilic matrices as constant release devices (Geomatrix Systems). J Control Release 1993;26:39-47.
5. Abdul S, Poddar SS. A flexible technology for modified release of drugs: Multi layered tablets. J Control Release 2004;97:393-405.
6. Podczeck F, Drake KR, Newton JM, Haririan I. The strength of bi-layered tablet. Eur J Pharm Sci 2006;29:361-6.
7. Inman SJ, Briscoe BJ, Pitt KG. Topographic characterization of cellulose bilayered tablets interfaces. Chem Eng Res Des 2007;85:1005-12.
8. Jitendra R, Mohan A, Kalaskar G, Shrivastav VG, Yeole PG. Bilayer tablet formulation of metformin hydrochloride and gliclazide: A novel approach in the treatment of diabetes. Int J Pharma Res Dev 2009;1:1-11.
9. Gunsel WC. Compression-coated and layered tablets. In: Lieberman HA, Lachman L, editors. Phramaceutical Dosage Forms: Tablets. Marcel Dekker.
10. Bogan RK. Treatment options for insomania--pharmacodynamics of zolpidem extended-release to benefit next day performance. Postgrad Med 2008;120:161-71.
11. Kulkarni A, Bhatia M. Development and evaluation of bilayer floating tablets of atenolo and lovastatin for biphasic release profile. Iranian J Pharm Res 2009;8:15-25.
12. Nirmal J, Saisivam S, Peddanna C, Muralidharan S, Godwinkumar S, Nagarajan M. Bilayer tablets of atorvastatin calcium and nicotinic acid: Formulation and evaluation. Chem Pharm Bull (Tokyo) 2008;56:1455-8.
13. Efentakis M, Peponaki C. Formulation study and evaluation of matrix and three-layer tablet sustained drug delivery systems based on carbopols with isosorbite mononitrate. AAPS PharmSciTech 2008;9:917-23.
14. Phaechmud T. Variables influencing drug release from layered matrix system comprising hydroxypropyl methylcellulose. AAPS PharmSciTech 2008;9:668-74.
15. LaForce C, Gentile DA, Skoner DP. A randomized, double blind, parallel group, multicenter, placebo-controlled study of the safety and efficacy of ER guaifensein/pseudoephedrine HCl for symptom relief as an adjunctive therapy of antibiotic treatment of acute respiratory infections. Postgrad Med 2008;120:53-9.
16. Maggi L, Segale L, Conti S, Ochoa Machiste E, Conte U. Preparation and evaluation of release characteristics of 3TabGum, a novel chewing device. Eur J Pharm Sci 2005;4:487-93.
17. Park CR, Munday DL. Development and evaluation of biphasic buccal adhesive tablet for nicotine replacement therapy. Int J Pharm 2002;237:215-26.
18. Sungthongjeen S, Srimornsak P, Puttipipatkhachorn S. Design and evaluation of floating multilayered coated tablets based on gas formation. Eur J Pharm Biopharm 2008;69:255-63.
19. Kale SS, Saste VS, Prajkta L, Ughade, Dheeraj T, Bhaviskar, *et al*. Bilayer tablet: Review. Int J Pharm Sci Rev Res 2011;9:25-30.
20. Available from: http://www.port/technology.com [Last accessed on July 1, 2012].
21. The Indian Pharmacopoeia. 4th ed, Vol. 2. The Controller of Publication, Govt. of India, Delhi, 1996. p. A82-A85.
22. The United States Pharmacopoeia, United States Pharmacopoeial Convention, Inc., Rockville: 2000. p. 1944.
23. Singh BN, Kim KH. Floating drug delivery systems an approach to oral controlled drug delivery via gastric retention. J Control Release 2000;63:235-59.
24. Atram SC, Udavant YK, Salunke RJ, Neb GB, Shahi SR, Gulecha BS, *et al*. Formulation and evaluation of bilayer tablet containing Metoprolol succinate and Amlodipine besylate as a model drug for anti hypertensive therapy. J Pharm Res 2009;2:1335-47.
25. Jamunadhevi V, Sahoo PK, 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;2:170-8.
26. Swamy PV, Kinagi MB, Biradar SS, Gada SN, Shilpa H. Formulation design and evaluation of bilayer buccal tablets of granisetron hydrochloride. Ind J Pharm Edu Res 2011;45:242-7.
27. Pattanayak DP, Dinda SC. Bilayer tablet formulation of metformin HCl and glimepiride: A novel approach to improve therapeutic efficacy. Int J Drug Discov Herb Res 2011;1:1-4.
28. Jain J, Marya BH, Mittal RP, Patel M. Formulation and evaluation of indomethacin bilayer sustained release tablets. Int J PharmTech Res 2011;3:1132-8.

29. Mohindeen S, Jyothi B, Pavani S, Satyanarayana T, Kumar SP, Krishna NS. Formulation and evaluation of bilayered tablets of metformin hydrochloride and atorvastatin calcium. Int J Pharm Sci Rev Res 2011;10:130-4.
30. Kumar GV, Babu KA, Ramasanay C. Formulation and evaluation of bilayered tablets of cefixime trihydrate and dicloxacillin sodium. Int J PharmTech Res 2011;3:613-8.
31. Jadhav RT, Patil PH, Patil PR. Formulation and evaluation of bilayered tablets of piracetam and vinpocetine. J Chem Pharm Res 2011;3:423-31.
32. Rajendran NN, Natarajan R, Subhashini R, Patel H. Formulation and evaluation of sustained release bilayer tablets of metformin HCl and pioglitazone HCl. Int J Curr Pharm Res 2011;3:118-22.
33. Shirsand SB, Swamy PV, Keshavshetti GG. Design and evaluation of atenolol bilayer buccal tablets. RGUHS J Pharm Sci 2011;1:4-10.
34. Parmar CK, Pednekar PP. Development and evaluation of bilayer tablets of cefuroxime axetil and potassium clavulanate. Int J Pharm Res Dev 2011;3:16-23.
35. Musle K, Payghan SA, Disuza JI. Fomulation, evaluation and development of bilayer tablet. Int J Pharm Res Dev 2011;3:80-7.
36. Remya PN, Damodharan N, Kumar CV. Formulation and evaluation of bilayered tablets of ibuprofen and methocarbamol. Int J PharmTech Res 2010;2:1250-5.
37. Gohel MC, Parikh RK, Nagori SA, Jethwa BA. Fabrication and evaluation of bi-layer tabletcontaining conventional paracetamol and modified diclofenac sodium. Indian J Pharm Sci 2010;72:191-6.
38. Ramesh DS, Guruvaiah, Harani A. Formulation and evaluation of bilayer sustained release matrix tablets of Metformin HCl and Pioglitazone. Amer-Euras J Sci Res 2010;5:176-82.
39. Naeem MA, Mahmood A, Khan SA, Shahiq Z. Development and evaluation of controlledrelease bilayer tablets containing microencapsulated tramadol and acetaminophen. Trop J Pharm Res 2010;9:347-54.
40. Rathod RT, Misra D. FDC of montelukast with levocetirizine: Focus on bilayer technology. J Indian Med Assoc 2009;107:562-4.
41. Kadam VV, Waghmare MU, Venkatpurwar VP, Pokharkar VB. Preparation and evaluation of glipizide-metformin HCl sustained release bilayer tablet [online]. 2009 [Last cited on 2009 Sep 15]. Available from: http://www.scientificipca.org/paper/2009/09/15/200909151256230A.doc [Last accessed on 2011 Jul 1].
42. Friedl T, 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. Bakuridze AD, Maglakelidze GM, Kurdiani NG, Tsagarejshvili NT, Berashvili DT. Technology of vitamins containing double layer suppositories. Georgian Med News 2008;158:49-51.
44. Ouali A, Azad AK, inventors; Pharmascience Inc, assignee. Stabilized pharmaceutical composition of nonsteroidal antiinflammatory agent and a prostaglandin. WO 2000/056339. 2007 Jan 03.
45. Kohlrausch A, inventor; Boehringer Ingelheim International GmbH, assignee. Bilayer tablet of telmisartan and simvastatin. US patent 0078615 A1. 2006 Apr 13.
46. De-fang O, Shu-fang N, Jin M, Xing-gang Y, Zhi-quan S, Wei-san P. Compound metformin/glipizide bilayer extended release tablets: Development and *in vitro* release. 2005;14:169-72.

How to cite this article: Sharma SK, Mohan S, Jaimini M, Tiwari R. Polytherapeutic approach using bilayer matrix technology. Asian J Pharm 2014;8:133-8.

Source of Support: Nil. **Conflict of Interest:** None declared.