Review Article

BILAYER TABLET: A RECENT REVIEW

Prasanthi Teella and NSV. Sushma

Aditya College of Pharmacy, Surampalem, Andhra Pradesh, India.

ABSTRACT

Pharmaceutical industry people are interested to develop a combination of two active pharmaceutical ingredients (API) in a single dosage form I.e Bi layer tablet. Bi layer table is a primary option to avoid incompatibility between two active API by physical separation, simultaneously we are delivering two drugs at a time in a immediate and controlled form, they act as a loading dose and maintainance dose[1]. This review explains how we can manufacture bi layer tablet and its advantages in pharmaceutical field. This article describes the preparation Ezetimibe and Metformin HCl bi layer tablets. Here Ezetimibe acts as an immediate release layer to deliver the drug and Metformin HCl acts as a sustained release layer. In this method immediate release polymers and sustained release polymers (HPMC K15M, HPMC K4M, HPMC K100M) are having very important role.

Keywords: Immediate release, Sustained release, bi layer tablets, loading dose, maintainance dose.

INTRODUCTION

In present scenario all the developed and developing countries moves toward combination therapy for treating multiple diseases[2]. Past few years maximum people were suffering with multiple disease that's why to reduce the problem bi layer tablets preparation was implemented. And we already know oral route is the most preferable and commonly used route for the delivery of drugs[2]. These bi layer tablets having more benefits compared to conventional dosage forms. Bi layer contains immediate and sustained release layers. This immediate release layer contains super disintegrants which releases the drug in fast manner and it also attains onset of action in fast manner, this layer act as a initial dose. Coming to sustained release layer contains release extended polymers releases the drug for an extended period of time, this layers act as a maintenance dose. Both the layers will start the immediate action and it acts for an sustained period of time and cures the problem.

Fig. 1: Bi layered tablets

ADVANTAGES[1]

1. Release of both drugs starts immediately.
2. Combination of incompatible drugs.
3. Combination of different release profiles.
4. Reduce the side effects by using a combination of one drug for this patient.
5. Treat different ailments in the same patient, at the same time and with one pill.
6. Increased patient compliance.
7. Self-administration is possible.
8. Easy to transport from one place to another place.
9. Good physical and chemical stability compared to liquids.

LIMITATIONS OF BILAYERED TABLETS

1. Drugs with poor wetting, slow dissolution properties, optimum absorption in gastro intestinal track (GIT) may be difficult to formulate or manufacture as a tablet that will provide adequate or full drug bio-availability.
2. Difficult to swallow in case of children and unconscious patients.
3. Administration of sustained-release bi-layer tablet does not permit the prompt termination of therapy.
4. Bitter tasting drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating.
5. The physician has less flexibility in adjusting the dose regimens.

GENERAL PROPERTIES OF BI-LAYER TABLET DOSAGE FORMS

1. A bi-layer tablet should have sufficient strength to withstand mechanical shock during its production, packaging, shipping and dispensing.
2. A bi-layer tablet should have elegant product. It is completely free of defects like chips, cracks, discoloration, and contamination.
3. A bi-layer tablet should have the chemical and physical stability to maintain its physical attributes over time.

IDEAL CHARACTERISTICS OF BILAYER TABLETS

1. Drug produces additive/synergistic effect.
2. Drugs having opposite side effects, may reduce the side effect.
3. Incompatible drugs.
4. Low biological half-life (ideal for modified released bi-layer).
5. Unstable at intestinal pH (ideal for bi-layer floating).
6. High first-pass metabolism with low biological half-life (ideal for muco adhesive bi-layer).

MANUFACTURING OF BILAYER TABLETS

Bi layer tablets can be prepared by individual punching of two layers after that we can combine those 2 two layers. Here compaction, compression and consolidation steps are very important.

During preparation of bi layer tablets initially we have to take ingredients for sustained release layer and punch that one after that we adjust the space within the die cavity and place the ingredients of immediate release layer and final punch takes place for attachment of two layers. Here two times

punching takes place that's why the void space between the particles were removed and the tablet maintains some strength and withstands for a long time.

Here two times punching takes place for sustained release layer and one time punching takes place for immediate release layer.

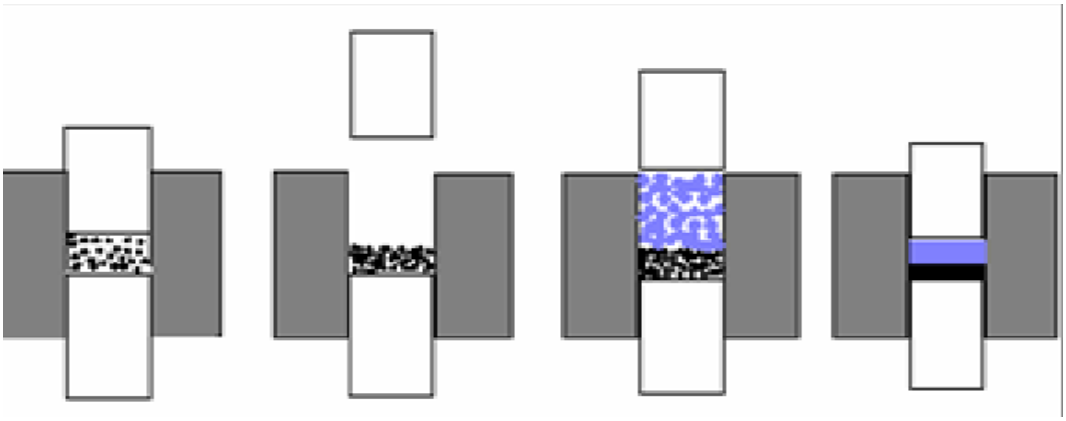

Fig. 2: Production of bi layer tablets[5]

Various approaches used in bi layer tablet preparation[5]

1. Floating drug delivery
2. Bio adhesive systems
3. Swelling systems

- In floating drug delivery system, polymers having low density that's why it was floated in gastro intestinal fluid.
- Bio adhesive systems having viscous material which is having tacky property that's why these systems attached to mucous layer and releases the drug.
- Swelling systems having swellable polymers, by using diffusion procedure these systems release the drug for long time.

EVALUATION TESTS[1,3]

A) Pre compression studies

i. Angle of Repose
ii. Density
    a. Bulk Density
    b. Tapped Density
iii. Carr's Index
iv. Hausner's Ratio

B) Post compression studies

a. Average weight / Weight Variation
b. Thickness
c. Hardness test
d. Friability test
e. Drug content / Assay
f. In vitro dissolution study

A) Precompression studies

Angle of Repose: It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. Angle of Repose of granules was determined by the fixed funnel method. Accurately weighed powder blend was taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and the angle of repose was calculated using the following equation.

$$\text{Angle of repose } (\theta) = \tan^{-1}\left(\frac{h}{r}\right)$$

The angle of repose has been used to characterize the flow properties of solids

Table 1: Angle of repose limits

Flow property	Angle of Repose (Degrees)
Excellent	25-30
Good	31-35
Fair-aid not needed	36-40
Passable-may hang up	41-45
Poor-must agitate, vibrate	46-55
Very poor	56-65

Bulk density (BD): It is the ratio of the total mass of powder to the bulk volume of powder. Weigh accurately 25 g of granules, which was previously passed through 22#sieve and transferred in 100 ml graduated cylinder. Carefully, level the powder without compacting, and read the unsettled apparent volume. Calculate the apparent bulk density in gm/ml by following formula.

Bulk density = Weight of powder/Bulk volume

Tapped density (TD): It is the ratio of the total mass of powder to the tapped volume of powder. Weigh accurately 25g of granules, which was previously passed through 40#sieve and transferred in 100 ml graduated cylinder of tap density tester which was operated for a fixed number of taps until the powder bed volume has reached a minimum, that was calculated by formula.

Tapped density = Weigh of powder/Tapped volume

Carr's Index: Compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's index is as below

Compressibility index = 100 x Tapped density-Bulk density/Tapped density

Hausner's Ratio: Hausner's Ratio is a number that is correlated to the flowability of a powder.

Hausner's Ratio = Tapped density/Bulk density

Table 2: Limits for Compressibility index and Hausner's ratio

Compressibility Index (%)	Flow Character	Hausner's Ratio
<10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59

B) Post compression studies

General appearance*:* The formulated tablets were assessed for its general appearance and observations were made for shape, color, texture, and odor.

Average weight/weight variation: 20 tablets were selected and weighed collectively and individually. From the collective weight, the average weight was calculated. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

$$\text{Average weight} = \text{weight of 20 tablets} / 20$$

$$\% \text{ weight variation} = \frac{\text{Average weight} - \text{weight of each tablet} * 100}{\text{Average weight}}$$

Table 3: Weight variation table for uncoated tablets

Average weight tablet(mg)	% difference allowed
130 or less than	± 10
130-324	± 7.5
More than 324	± 5

Thickness: Thickness of the tablets was determined using a Vernier calipers.

Hardness test: Hardness of the tablet was determined by using the Monsanto hardness tester, the lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

Friability test: This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting.

The initial weight of 20 tablets is taken and these are placed in the friabilator, rotating at 25 rpm for 4mins. The difference in the weight is noted and expressed as a percentage.

It should be preferably between 0.5 to 1.0%

% Friability = [(W1 – W2)/W1] x 100

Where, W1 = weight of tablets before test,

W2 = weight of tablets after test.

Content estimation: Ten tablets were weighed and powdered, a quantity of powder equivalent to 100 mg of drug was transferred to a 100ml volumetric flask and 10ml methanol is added. The drug is dissolved in methanol by vigorously shaking the volumetric flask for 15 minutes. Then the volume is adjusted to the mark with distilled water and the solution is filtered. From prepared solution take 0.1 ml solution in 10 ml volumetric flask and make up to mark with distilled water. The drug content was determined by measuring the absorbance at suitable wavelength after appropriate dilution. The drug content was calculated as an average of three determinations.

Calculate the quantity in mg of drug in the portion taken by the formula

$$\textbf{Assay} = \frac{\text{Test absorbance} * \text{standard concentration} * \text{Average weight} * \%\ \text{purity of drug} * 100}{\text{standard absorbance} * \text{sample concentration} * \text{label claim} * 100}$$

In-vitro Dissolution Study for immediate release layer

900 ml of 0.1N HCL was placed in the vessel and the USP-II apparatus (Paddle method) was assembled. The medium was allowed to equilibrate to temperature of 37˚C±0.5˚C. A tablet was placed in the vessel and was covered; the apparatus was operated up to 60 minutes at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium to maintain sink conditions. Suitable dilutions were done with dissolution medium and were analyzed spectrophotometrically at specific λ max using a UV-spectrophotometer.

Table 4: Dissolution parameters for immediate release layer

Parameter	Details
Dissolution apparatus	USP – type II(Paddle)
Medium	0.1N HCL
Volume	900 ml
Speed	50rpm
Temperature	37˚C±0.5˚C
Sample volume withdrawn	5ml
Time points	5,10,15,30,45 and 60
Analytical method	Ultraviolet-Visible Spectroscopy
λmax	265nm

In Vitro Dissolution Study for bi layer tablet

900 ml of 0.1N HCL was placed in the vessel and the USP-II apparatus (Paddle method) was assembled. The medium was allowed to equilibrate to temperature of 37˚C±0.5˚C. A tablet was placed in the vessel and was covered; the apparatus was operated up to 2 hours at 50 rpm. After completion of 2 hours remove the 0.1N HCL and add 6.8 phosphate buffer then continue the procedure up to 12 hours. At definite time intervals (2,4,6,8,10,12 hours) 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium to maintain sink conditions. Suitable dilutions

were done with dissolution medium and were analyzed spectrophotometrically at specific λ max using a UV-spectrophotometer.

Table 5: Dissolution parameters for bi layer tablets

Parameter	Details
Dissolution apparatus	USP – type II(Paddle)
Medium	0.1N HCl and 6.8 Phosphate buffer
Volume	900 ml
Speed	100rpm
Temperature	37˚C±0.5˚C
Sample volume withdrawn	5ml
Sampling interval points	1,2,3,4,6,8,10 and 12hrs
Analytical method	Ultraviolet-Visible Spectroscopy
λmax	Based on drug

Various advancements in the field of Bi layer tablets[7]

Drug(s)	Dosage Form	Rationale	Ref. No.
Pioglitazone HCl, Gliclazide	Bi layer Tablets	Treatment of Type II Diabetes	20
Losartan potassium	Bi layer tablet	Treatment of hypertension	21
Diclofenac, Cyclobenza-prine	Bi layer tablets	Synergistic effect in pain	22
Amlodipine Besilate Metoprolol Succinate	Bi layer tablets	Synergistic effect in hypertension	23,24
Ibuprofen, Methocarba-mol	Bi layer tablets	Synergistic effect of drugs in back pain	25
Losartan	Bi layer tablets	Biphasic release profile	26
Metformin HCl, Pioglitazone	Bi layer tablets	Synergistic effect in diabetes mellitus	27
Guaifenesin	Bi layer tablets	Biphasic release profile	28
Glipizide, Metformin HCl	Bi layer tablets	To avoid interaction b/w incompatible drugs	29

Applications of bi layer tablet[4]

1. It provides immediate and controlled delivery rate
2. Also provides synergistic property
3. We administered as a fixed dose combination
4. Reducing the dosing frequency, indirectly reduces the side effects

ACKNOWLEDGEMENT

The presenting authors are thankful to principal of Aditya College of Pharmacy for grateful support.

REFERENCES

1. Meraj S, Anjaneyulu M, Anusha C, Vijay shekar reddy. A review article on bilayer tablets. International Journal of Research in Pharmaceutical and Nanosciences. 2013; 2(4): 417-422.
2. Siva sai kiran B, Sambasiva rao P, Raveendrababu G, Venkatkumari M. Bilayer tablets – A Review. International journal of pharmaceutical, chemical and biological sciences. 2015; 5(3) :510-516.
3. Joseph D, Thomas G. A review on current applications of bilayer tablets. Reseach Journal of Pharmacy and Technology. 2019; 12(5): 2539-2544.
4. Venkateswararao S, Priyanka B, Padmalatha K. Bilayer tablet technology: A novel approach. GSC Biological and Pharmaceutical Sciences. 2019; 7(2): 22-28.
5. Rajeswar V, Kishor D, Tushar G. Bilayer tablets for various drugs: A review. Scholars Academic Journal of Pharmacy. 2014; 3(3): 271-279.
6. Panchal HA, Tiwari AK. Novel approach of bilayer tablet technology: An review. Journal of Pharmaceutical Science and Technology. 2012; 4(4): 892-904.
7. Deshpande RD, Gowda DV, Mahammed N, Maramwar. Bilayer tablets - An emerging trend: A review. International Journal of Pharmaceutical Sciences and Research. 2011; 2(10); 2534-2544.
8. Patel M, Ganesh NS, Kavitha, Tamizh M. Challenges in the formulation of bilayered tablets: A review. The International Journal of Periodontics Restorative Density. 2010; 2(10): 30-42.
9. Chinam NP, Arethi BK, Hemant KP, Prakash S, Vimala DM. Design and evaluation of sustained release bilayer tablets of Propranolol hydrochloride. Acta Pharmaceutica. 2007; 57: 479-489.
10. Kumar BV, Prasad G, Ganesh B, Swathi C, Rashmi A, Reddy AG. Development and evaluation of Guaifenesin bilayer tablet. International Journal of Pharmacy and Pharmaceutical Sciences. 2010; 3(3):1122-1128.
11. Sonar SG, Jain DK, More DM. Preparation and in vitro evaluation of bilayer and floating-bioadhesive tablets of Rosiglitazone maleate. Asian Journal of Pharmaceutical sciences. 2007; 2(4): 161-169.
12. Gohel MC, Parikh RK, Nagori SA, Jethwa BA. Fabrication and evaluation of bilayer tablet containing conventional Paracetamol and modified release Diclofenac sodium. Indian Journal of Pharmaceutical sciences. 2010; 72(2): 191-199.
13. Defang O, Shufang N, Wei L. In vitro and in vivo evaluation of two extended release preparations of combination Metformin and Glipizide. Drug Development and Industrial Pharmacy. 2005; 31: 677-685.
14. Galeone F, Fiore G, Arcangeli A, Mannucci E. Gliclazide and metformin combination in patients with type 2 diabetes. Minerva Endocrinol. 1998; 23: 71-75.
15. N.Patel, R.Natarajan, N.N.Rajendran and M.Rangapriya. Formulation and evaluation of immediate release bilayer tablets of Telmisartan and Hydrochlorothiazide. International Journal of Pharmaceutical sciences and nanotechnology. 2011:1477-1482.
16. Ramesh D, Sathish kumar, Guruvaiah, Harani A. Formulation and evaluation of bilayered sustained release matrix tablets of Metformin hydrochloride and Pioglitazone. International journal of Scientific Research. 2010; 5(3): 176-182.
17. Divya A, Kavitha K, Kumar MR, Dakshayani S, Jagadeesh SSD. Bilayer tablet technology - An overview. Journal of Applied Pharmaceutical Science 2011; 01(08): 43-47.

18. Shiyani B, Gattani S, Surana S. Formulation and evaluation of bi-layer tablet of Metoclopramide hydrochloride and Ibuprofen. AAPS Pharmaceutical Science and Technology. 2008; 9(3): 818-827.
19. Wilding IR, Coupe AJ, Davis SS. The role of gamma scientigraphy in oral drug delivery. Advance Drug Delivery Review.1991; 7: 87-117.
20. Sharma SK, Mohan S, Jaimin M, Chauhan BS,Chattarjee A. Formulation and in vitro evaluation of bilayer tablets containing Pioglitazone hydrochloride and Gliclazide for type II diabetes. International Journal of Pharmaceutical Technology and Research. 2014; 6(2): 607-622.
21. Reddy KR, Srinivas N. Formulation and evaluation of bilayer tablets of Losartan potassium. Innovations in Pharmaceuticals and Pharmacotheraphy. 2014; 2(1): 312-320.
22. Jamuna devi V, Sahoo PK, Kailasam P. Formulation and in vitro evaluation of bilayer tablet of Cyclobenzene hydrochloride extended release and Diclofenac potassium immediate release – A novel fixed dose combination. International Journal of Research in Pharmaceutical Sciences. 2011; 2(2): 170-178.
23. Jayaprakash S, Halith SM, Pillai KK, Balasubramaniyam P, Firthouse PUM, Boopathi M. Formulation and evaluation of bilayer tablets of amlodipine besilate and metoprolol succinate. Der Pharmacia Lettre. 2011; 3(4): 143-154.
24. Atram SC, Udavant YK, Salunke RJ, Neb GB, Shahi SR, Gulecha et al., Formulation and evaluation of bilayer tablet containing Metoprolol succinate and Amlodipine besyalte as a molecular drug for antihypertensive theraphy. Journal of Pharmacy Resarch. 2009; 2(8): 1335-1347.
25. Remya PN, Damodaran N, Kumar CVS. Formulation and evaluation of bilayer tables of Ibuprofen and Methocarbamol. International Journal of Pharma Tech Research. 2010; 2(2): 1250-1255.
26. Hiremath D, Goudanavar P, Azharuddin M, Udipi RH, Sarfaraz M. Design and characterization of bilayer controlled release matrix tablets of Losartan potassium. International Journal of Pharmaceutical Research. 2010; 2(4): 34-39.
27. Ramesh A. Formulation and evaluation of bilayer sutained release matrix tablets of Metformin HCl and Pioglitazone. American- Eurasian Journal of Scientific Research. 2010; 5(3): 176-182.
28. Kumar VB, Prasad G, Ganesh B, Swathi C, Rashmi A,Reddy AG. Development and evaluation of Guaifenesin bilayer tablet. International Journal of Pharmaceutical Sciences and Nanotechnology. 2010; 3(3): 1122-1128.
29. Kadam VV, Waghmare MU, Venkatpurwar VP, Pokharkar VB. Preparation and evaluation of Glipizide-Metformin HCl sustained release bilayer tablet. Available from www.scientificipca.org/paper/2009/09/15/2009 09151256230A.doc
30. Jitendra R, Amruthkar, Mohan, G.Kalaskar, Varsha, G.Shrivastav, P.G.Yeole. Bilayer tablet formulation of Metformin hydrochloride and Gliclazide: A novel approach in the treatment of diabetes. International Journal of Pharmaceutical Research and Development. 2009; 1: 1-11.