International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 6(1): January-February 2016

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences **Review Article……!!!**

Received: 14-01-2016; Revised: 19-02-2016; Accepted: 20-02-2016

REVIEW: BILAYER TECHNOLOGY

Sonawane Pradnya L.[1]*, Zope Janhavi S.[1], Darekar A. B.[1], Saudagar R. B.[2]

1. Department of Pharmaceutics, R. G. Sapkal College of Pharmacy, Anjaneri , Nashik-422213, Maharashtra, India.

2. Department of Pharmaceutical Chemistry , R. G. Sapkal college of Pharmacy , Anjaneri , Nashik-422213, Maharashtra , India.

Keywords:

Bilayer tablet, sustain release, immediate release

For Correspondence:

Sonawane Pradnya L.

Department of Pharmaceutics, R. G. Sapkal College of Pharmacy, Anjaneri , Nashik-422213, Maharashtra, India

E-mail:

pradnya88062@gmail.com

ABSTRACT

In last few decades due to patient convenience and compliance the interest has developed in combination therapy of one or more API' in single dosage form. bilayer formulation can be primarily option to avoid the incompatibility of API's . To produce a good quality bilayer tablet, the machineries should be constructed as per GMP. Various machineries are available to overcome common bilayer problem such as layer separation insufficient hardness, cross contamination between the layers. Some pharmaceutical companies are taking a risk of developing bilayer for variety of reasons like patient compatibility, patient extension, low capital. In bilayer dosage form one layer is immediate release and second layer of sustain release. Immediate release layer is used as initial dose of drug and second layer is used as maintained dose. There are few technologies that are used now a days that are OROS Push pull, L-OROS tm, EM So TROL, DUROS.

INTRODUCTION

Solid dosage form is most preferred route of drug administration by considering this fact various developed and developing countries are moving towards the combination therapy used for treatment of diseases that are requiring long term therapy likewise diabetes ,hypertension , antiplatelet etc. the main objective of designing sustained or controlled drug delivery system is to reduce the frequency of dosing or increase effectiveness of drug by localizing at site of action or providing uniform drug delivery. Among these approaches, the multilayered drug delivery system is gain the much more popularity and particularly the bilayer technology has attracted the manufacturers.

Reasons for development of multilayer tablet dosage form:-

I. The drug delivery rate of single or two different API should be controlled.
II. To acquire more surface area for API in order to achieve swellable/erodible barrier for modified release.
III. Two incompatible API should get separated from each other by utilizing functional properties.

Types of bilayer tablets:-[4]

a) Homogenous.
b) Heterogeneous.

a)Homogenous- both the layers that is immediate release and extended release both are having same contain of drug.

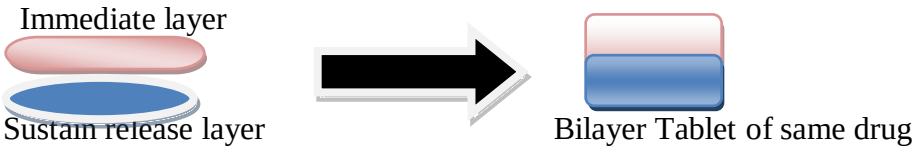

Fig1 : Same drug with different release pattern-homogenous

b)Heterogeneous – In this sequential release of two drug in combination ,separate two in compatible substance.

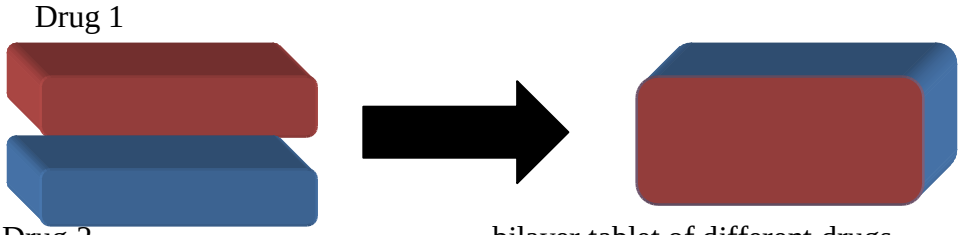

Fig2 :Tablet with different drugs- Heterogenous

Advantages of bilayer technology:-

1) Potency is retained and dose accuracy is ensured.
2) Chemical and physical stability is maintained.
3) Degradation problem of drug is solved.
4) It combines both sustain release and immediate release in same dosage form.
5) Patient convenience and compliance is promoted due to fewer dialy doses as compared to traditional delivery system.
6) Cost is low as compared to the other oral dosage form.

Disadvantages of bilayer technology:-[5,12]

1) Cross contamination may occur between two layers.
2) Insufficient hardness is obtained.
3) Bilayer rotary is costly.
4) Difficulty to swallow the tablet in case of children and unconscious patients.

Various technologies involved in bilayer tablets:-[5,6]

A. OROS push and pull technology.
B. L-OROS tm technology.
C. EN SO TROL technology.
D. DUROS technology.
E. Elan drug technology ‘dual release drug delivery system’.

A. OROS PUSH pull technology

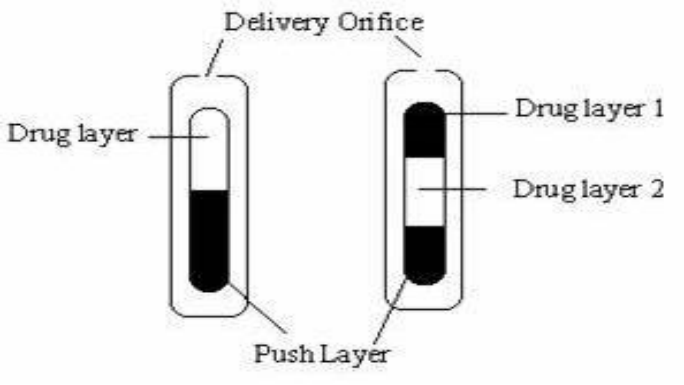

Fig3:Bilayer and trilayer OROS Push pull technology

This system consist of mainly two or three layers among which one or more layers are essential of the drug and other layers 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.

B. Bilayer and trilayer OROS Push pull technology

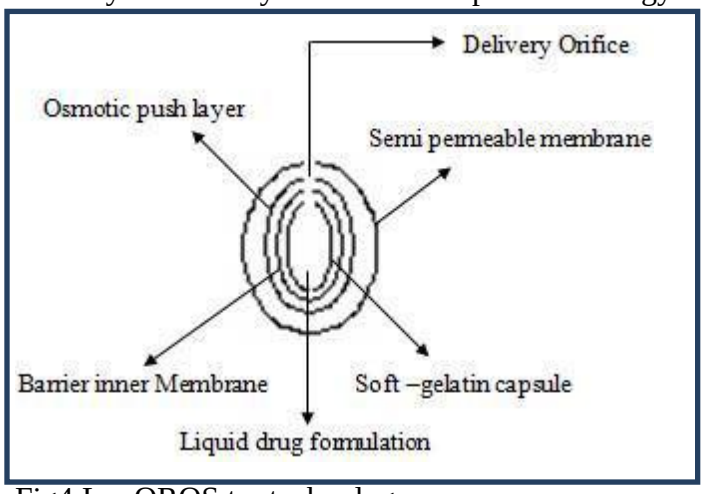

Fig4:L – OROS tm technology

L-OROS tm 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 than a semi permeable membrane ,drilled with an exit orifice.

C.EN SO TROL technology

Fig5: 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 identified enhancer into controller release technologies.

D.DUROS technology

The system consists from an outer cylindrical titanium alloy reservoir (Fig. 3).This reservoir has high impact strength andprotects the drug molecules from enzymes. The DUROS technology is the miniature drug dispensing system that opposeslike a miniature syringe and reglious minute quantity of concentrated form in continues and consistent from over months or year.

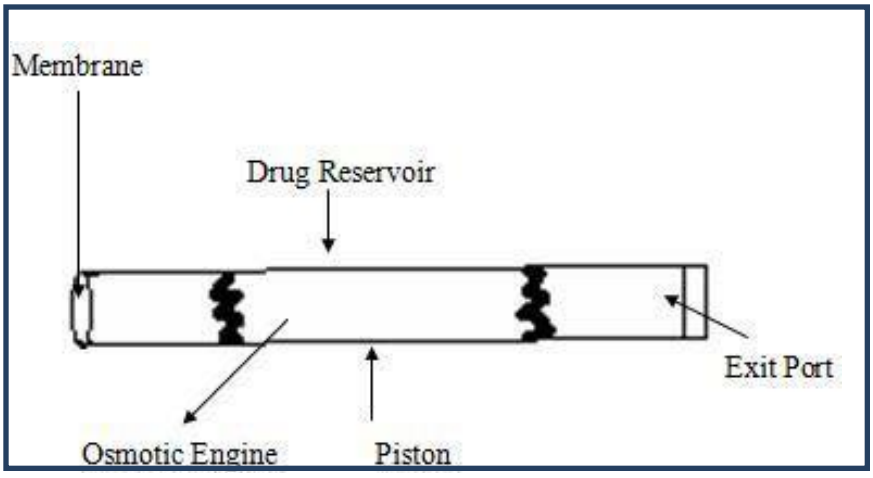

Fig6:DUROS Technology

Bilayer compression process:-[12,13]

Feeder/hopper-1(die filing)

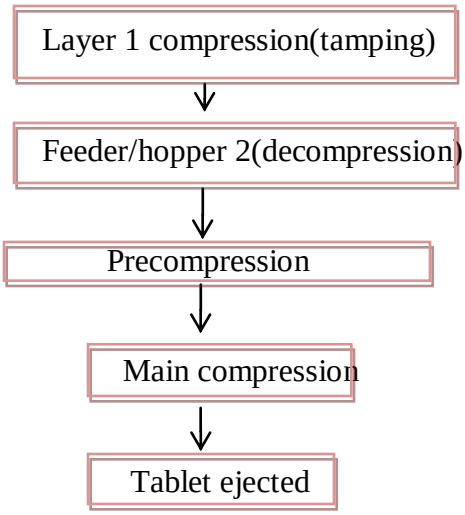

Fig7: flow chart of Bilayer compression process

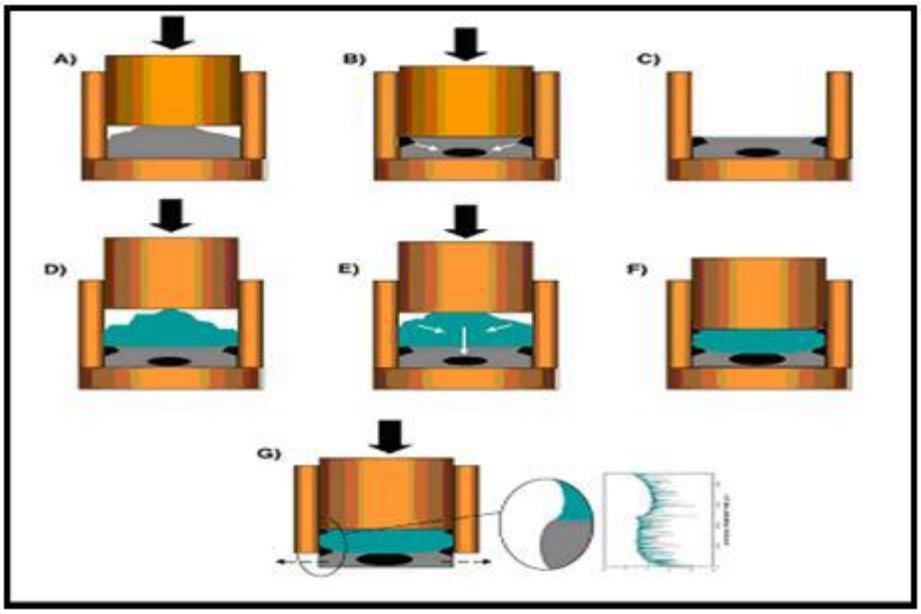

Fig 5 : Bilayer tablet compression.

The two material is compressed in die cavity to produce bilayer. The compression force effects the adhesion and interaction between the two layers. A certain amount of roughness on the surface is required for particles to interlock the second layer. The greater the first layer's compression force, the less will be the surface roughness that may result in reduce adhesion with second layer. To produce certain amount of adequate formulation, certain requirements such as sufficient mechanical strength and desire drug release must be met. At few times it is difficult task to achieve these conditions especially in bilayer tablet formulation where double

compression technique is involved, because of poor flow and compatibility characteristic of drug of the drug which will result in capping and lamination. The compaction of material involves both compression and consolidation. Compression is reduction in bulk volume by eliminating voids and bringing particles into closure contacts. Consolidation is the property of material in which there is increased in the mechanical strength due to bonding.

TYPES OF BILAYER TABLET PRESS:

1. Single sided tablet press.
2. Double sided tablet press or "compression force" controlled tablet press.
3. Bilayer tablet press with displacement monitoring.

1. Single sided tablet press:[7,16]

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

Fig 6 :Single Sided Bi-layer Press

Limitations of Single sided tablet press:

- No weight monitoring/ control of the individual layers.
- No distinct visual separation between the two layers.

Very difficult first-layer tablet sampling and sample transport to a test unit for in-line quality control and weight recalibration.

2. Double sided tablet presses:[7,15]

A double sided press offers an individual fill station, pre–compression and main compression for each layer. In fact the bi-layer tablet will go through four compression stages before being ejected from the press. 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 tablet and correct the die fill depth when required.

Fig7 : ADEPT Double Sided Tablet Press

Advantages:

1. Displacement weight monitoring for accurate and independent weight control of the individual layer.
2. Low compression force exerted on the first layer to avoid capping and separation of the individual layer.
3. Increased dwell time at pre compression of both first and second layer to provide sufficient hardness at maximum turret speed.
4. Maximum prevention of cross contamination between two layers.
5. Maximized yield.

Limitations:

Separation of the two individual layers is due to insufficient bonding between the two layers during final compression of bi-layer tablet. Correct bonding is only obtained when the first layer is compressed at a low compression force so that this layer can still interact with the second layer during final compression. Bonding is too restricted if first layer is compressed at a high compression force. The low compression force required when compressing the first layer unfortunately reduces the accuracy of the weight monitoring/control of the first layer in the case of tablet presses with "compression force measurement". Most of the double sided tablet presses with automated production control use compression force to monitor and control weight. Compression force control system is always based on measurement of compression force at main compression but not at pre-compression.

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 pre compression force. In fact the lower the pre-compression force, the more the monitoring control system and this ideal for good interlayer bonding of the bi-layer tablet.

Advantages:

- Weight monitoring/ control for accurate and independent weight control of the individual layers.
- Low compression force extends on the first layer to avoid capping and separation of the two individual layers.
- Increased dwell time at pre compression of both first and second layer to provide sufficient hardness at maximum turret speed.
- Maximum prevention of cross contamination between the two layers12, 13.tablet.

Evaluation of bilayer tablet:[8,9,10,1,14]

1. General appearance:

It include the visual identity of tablet that may include tablet size, shape, color, absence of odour, taste, surface texture. The size and shape of the tablet can be dimensionally described, monitored and controlled.

2. *Tablet thickness*:

Tablet thickness is an important characteristic in reproducing appearance and also in counting by usingfilling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Thickness of tablet should be recorded by using digital vernier caliper. It is expressed in mm.

3. *Hardness (Crushing strength):*

Hardness indicates the ability of the tablet to withstand mechanical shocks while handling. Hardness of thetablet recorded by Monsanto hardness tester. It is expressed in kg/cm2. The instrument measures the force required to break the tablet when the force generated by a coilspring is applied diametrally to the tablet. The Strong-Cobb Pfizer and Schleuniger apparatus which were later introduced measures the diametrically applied force required to break the tablet. Hardness, which is now more appropriately called crushing strength determinations are made during tablet production and are used to determine the need for pressure adjustment on tablet machine. If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specifications; if it is too soft, it may not be able to withstand the handling during subsequent processing such as coating or packaging and shipping operations. The force required to break the tablet is measured in kilograms and a crushing strength of 4 Kg is usually considered tobe the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10 kg; however, hypodermic and chewable tablets are usually much softer (3 kg) and some sustained release tablets are much harder (10 -20 kg). Tablet hardness have been associated with other tablet properties such as density and porosity. Hardness generally increases with normal storage of tablets and depends on the shape, chemical properties, binding agent and pressure applied during compression.

4. *Friability*:

The ability of the tablet to withstand abrasion in packaging, handling and shipping. Friability is determined by the use of the Roche friabilator. A number of tablets are weighed and placed in theapparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn withinthe apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weightcompared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not

more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked up. Friability is expressed in percentage as:

% Friability = 1- (loss in weight / Initial weight) X 100

5.*Drug content and release:*

To evaluate tablets potential for efficacy, the amount of drug per tablet needs to be monitored from tablet totablet and batch to batch, and a measure of the tablet's ability to release the drug needs to be ascertained.

6. Weight variation:

20 tablets are selected randomly from each batch and weighed individually to check weight variation. Calculate the average weight and compare the individual tablet weight the average. The tablet meet the USP test if no more than 2 tablet are outside the % limit and if no tablet differ by more than 2 times the percent limit. A little variation is allowed in weight of tablet according to U.S.P.

Average weight of tablet	Percent (%) deviation
130 mg or less	±10
>130 mg and <324 mg	±7.5
324 mg or more	±5

7. Stability Study (Temperature dependent):

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

Study	**Storage Conditions**	**Minimum time period covered by data at submission**
Long term*	25°C±2°C/60%RH±5%RH or 30°C±2°C/65%RH±5%RH	12 months
Intermediate**	30°C±2°C/65%RH±5%RH	6 months
Accelarated	40°C±2°C/75%RH±5%RH	6 months

It is upto the applicant to decide whether long term stability studies are performed at 25±2°C/60%RH±5%RH or 30°C±2°C/65%RH±5%RH.If 30°C±2°C/65%RH±5%RH is the long term condition, there is no intermediate condition.

The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability and Dissolution etc.) and drug content. The data obtained fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25°C.

CONCLUSION:

Bilayer technology is beneficial in order to overcome the short coming of single layer tablet. Bilayer technology is suitable to provide the drug in combination, or separate two incompatible substance. Bilayer tablet quality and GMP requirements can vary widely. This explains why many type of different presses are used to produce bilayer tablet. Now a days such technology is used for administration of drugs like anti-platelet, anti-hypertensive, anti-inflammatory, anti-pyretic, to the patient.

REFERENCES

1.Indian Pharmacopoeia, 4th edition, Ministry of Health and Family Welfare, Govt. of India. The controller of publications, New Delhi.1996, A-54.

2.Soma C, Reddy Suryaprakash C, Tabasum SG, Varma V, An overview on bilayer tablets, International journal of pharmacy and technology ,4(2), 2012, 2143-2156.

3.Devtalu SV, Barhate SD, A Review on novel Approaches –Bilayer tablet technology, International journal of pharmaceutical science review and research,21(1),2013, 46-50.

4.Reddy PT, RoaDV, Bilayer technology –an emerging trend: a Review, International journal of research and development in pharmacy and life sciences,3(2),2013,408-410.

5. Panchal HA, Tiwari AK, A Novel Approach of Bilayer Tablet Technology: A Review, International Research Journal of Pharmacy, 3 (5), 2012, 44-49.

6. Pujara ND, Gokani RK, PaunJS, Bilayer Tablet: An Emerging Trend, International Journal of Pharmaceutical Research and Development, 4(04), 2012, 101-112.

7. Soma C, Reddy Suryaprakash C, Tabasum SG, Varma V, An Overview on Bilayer Tablets, International Journal of Pharmacy & Technology, 4 (2), 2012, 2143-2156.

8. Divya A, Kavitha K, Kumar MR, Dakshayani S, Jagadees Singh SD, Bilayer Tablet Technology: An Overview, Journal of Applied Pharmaceutical Science, 01 (08), 2011, 43-47.

9. Singh Manoj K, Prajapati SK, Mahor A, Rajput N, Singh R, Formulation and *In-vitro* Evaluation of Microcrystalline Chitosan Based Buccoadhesive Bilayered Tablets of Repaglinide, International Journal of Pharmaceutical and Biological Archives, 2 (4), 2011, 1282 1290.

10. Lachman L, Lieberman HA, The Theory and Practices of Industrial Pharmacy, CBS publication, New Delhi, 2009, 280- 340.

11. Deshpande R, Govda DV, Bilayer Tablets an Emerging Trends: A Review, International Journal of Pharmaceutical Sciences and Research, 2(10), 2011, 2534-2544.

12. Inman S.J, B.J. Briscoe, K.G. Pitt and C. Shiu, The non-uniformity of microcrystalline cellulose bilayer tablets, Elsevier, 2009, 188, 283–294.

13. Ashish Bhandari, Bilayer tablet oral solid drug delivery system and challenges in the formulation: a review, IJPRD, 2011; May-2012, Vol 4(03), 29 – 44.

14.Kumar HA, Ravithak K, Salvi KA, Jagdesh Singh SD ,Novel Approach of Bilayer Tablet Technology-A Review, International Journal of Pharmaceutical Chemistry and Biological Science ,3(3),2013,887-893.

15. www.pharmatechnologyindex.com/viewad.asp?id=50013105582100076.

16. www.jaguargmc.com/rtm-1.htm

13. www.durect.com

14. http://www.port/ technology.com