WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 4, Issue 01, 529-548. Review Article ISSN 2277– 7105

BI-LAYER TABLET TECHNOLOGY-OPENING NEW WAYS IN DRUG DELIVERY SYSTEM: AN OVERVIEW

Manisha D. Bhadange[1*], A. B. Darekar[1], R B. Saudagar[2]

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

[2.] Department of Pharmaceutical chemistry. G. Sapkal College of Pharmacy, Anjaneri, Nashik-422213, Maharashtra, India

Article Received on
25 October 2014,

Revised on 20 Nov 2014,
Accepted on 15 Dec 2014

***Correspondence for Author**
Manisha D. Bhadange
Department of Pharmaceutics, R. G. Sapkal College of Pharmacy, Anjaneri, Nashik-422213, Maharashtra, India.

ABSTRACT

Bi-layer tablet could be a new era for successful development of controlled release formulation along with various features to provide successful drug delivery. Bi-layer tablets may be primary option to avoid chemical incompatibilities between APIs by physical separation and to enable the development of different drug release profiles. Therefore bilayer tablet is totally different facet for medicine, anti-inflammatory, Anti hypertension, Anti diabetic, and analgesic. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. within the case of bilayered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper no adhesive layer its delivery occurs into the whole oral cavity.

KEYWORDS: Bi-layer tablet, GMP needs, API, tablet press.

INTRODUCTION

In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a very indefinite quantity kind (bi-layer tablet) has hyperbolic within the pharmaceutical industry, promoting patient convenience and compliance. Bi-layer tablets will 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). Bilayer tablet technology is improved beneficial technology to overcome the shortcoming of the single layered tablet. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose needed or providing uniform drug delivery.

NEED OF BILAYER TABLETS

1. For the administration of fixed dose combinations of various APIs, prolong the drug Product life cycle, buccal/mucoadhesive delivery systems; fabricate novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery.
2. Controlling the delivery rate of either single or two totally 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 one another, to control the release of API from one layer by utilizing the functional property of the other layer (such as, diffusion property).

ADVANTAGES OF THE BILAYER TABLET

1. Bi-layer execution with discretionary single-layer transformation pack .
2. Cost is lower compared to all other oral dosage form.
3. Most noteworthy synthetic and microbial stability over all oral dosage form.
4. Frightful odour and bitter taste can be masked by coating technique.
5. Adaptable 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

1. Some medicines resist compression into dense compacts, due to amorphous nature, low density character.
2. Bitter tasting drugs, drugs with associate with nourishing 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 could be troublesome to formulate or manufacture as a tablet that may still provide adequate or full drug bioavailability.

IDEAL CHARACTERSTICS 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 with stand 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.

Table-I: Various Types of Tablets

A) Oral Tablets for Ingestion	
➢ Standard compressed tablets	
➢ Multiple compressed tablets	
a. Layered tablets	
b. Compression coated tablets	
c. Inlay tablets	
➢ Modified release tablets	
➢ Delayed action tablets	
➢ Targeted tablets	
a. Floating tablets	b. Colon targeted tablets
➢ Chewable tablets	
B) Tablets Used In the Oral Cavity	
➢ Buccal tablets	
➢ Sublingual tablets	
➢ Troches and lozenges	
➢ Dental cones	
C) Tablets Administered By Other Routes	
➢ Implantation tablets	
➢ Vaginal tablets	
D) Tablets Used To Prepare Solution	
a. Effervescent tablets	b. Dispersible tablets
c. Hypodermic tablets	d. Tablet triturates

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

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

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

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

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.

PREPARATION OF BILAYER TABLETS

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 associate extended release

form. 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 elimination.

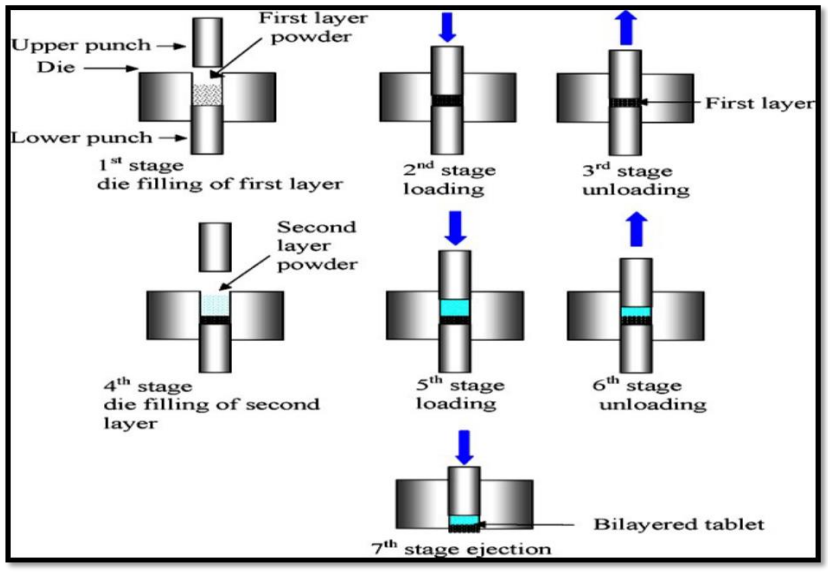

Fig 1: Preparation of bilayer tablet Compaction

Bi-layer tablets quality and GMP-requirements

- To produce a quality bi-layer tablet, in a validated and GMP way,

  It is important that the selected press is capable of:

- Preventing capping and separation of the two individual layers that constitute the bi-layer tablet.

- Providing sufficient tablet hardness
- Preventing cross-contamination between the two layers
- Producing a clear visual separation between the two layers.
- High yield.
- Accurate and individual weight control of the two layers. These requirements seem obvious but are not as easily accomplished as this article aims to demonstrate.

VARIOUS TECHNIQUES FOR BILAYER TABLETS

A) OROS® push pulls Technology

This system accommodates primarily 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 primarily 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 diffusion agent. A semi permeable membrane surrounds the tablet core (Figure 2).

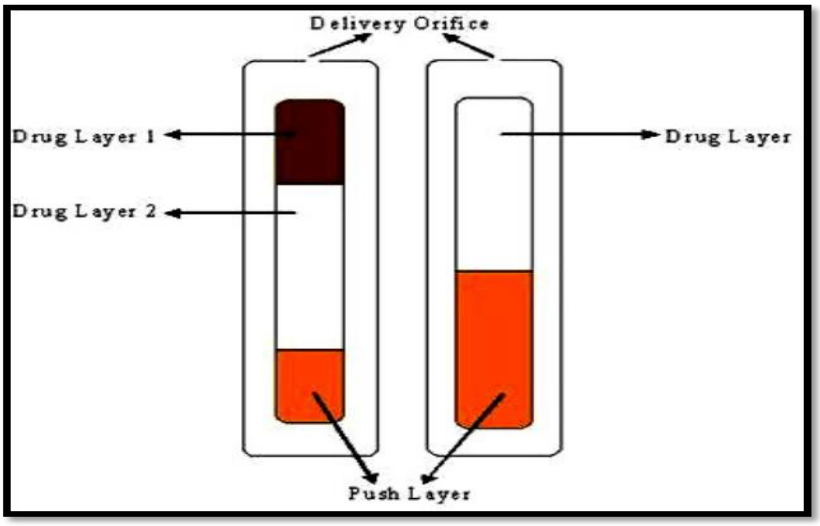

Fig. 2: Bilayer and trilayer OROS push pull technology

B) 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 (Fig.3).

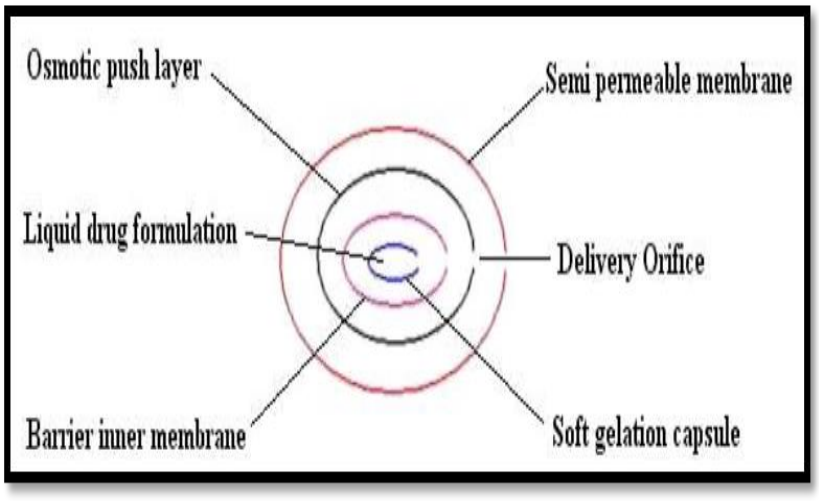

Fig.3: L–OROS TM Technology

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).

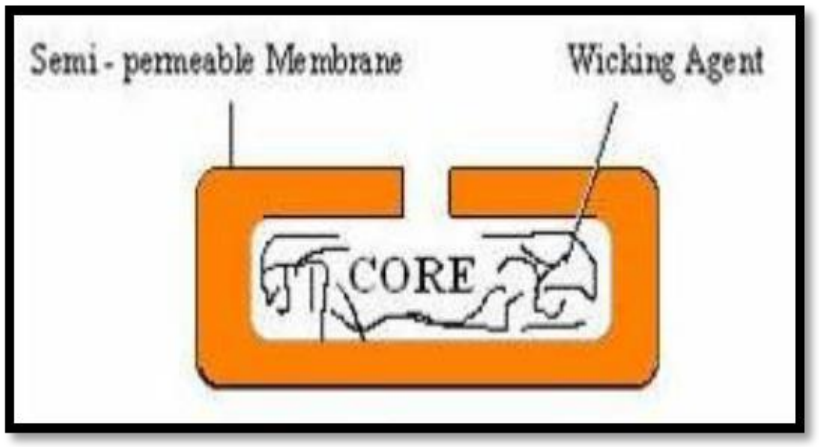

Fig: 4: EN SO TROL Technology

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 tabletting 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.

Benefits offered by the DUREDAS™ technology include

1) Bilayer. Tabletting .technology.

2) Tailayred. Release rate of .two .drug. Components.

3) Capability. Of .two. Different. CR. Formulations .combined.

4) Capability for immediate release and modified release components in one tablet

5) Unit .dose tablet.

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).

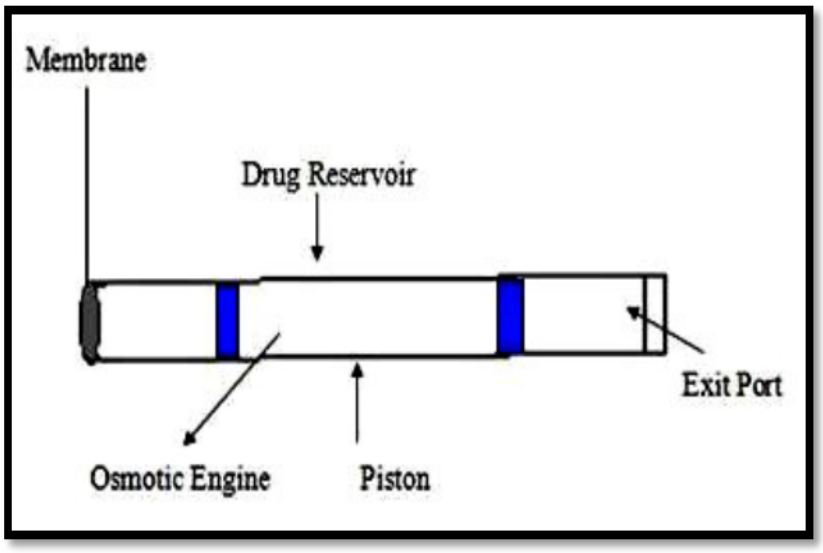

Fig. 5: DUROS Technology

VARIOUS APPROACHES USED IN THE BILAYER TABLET

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)

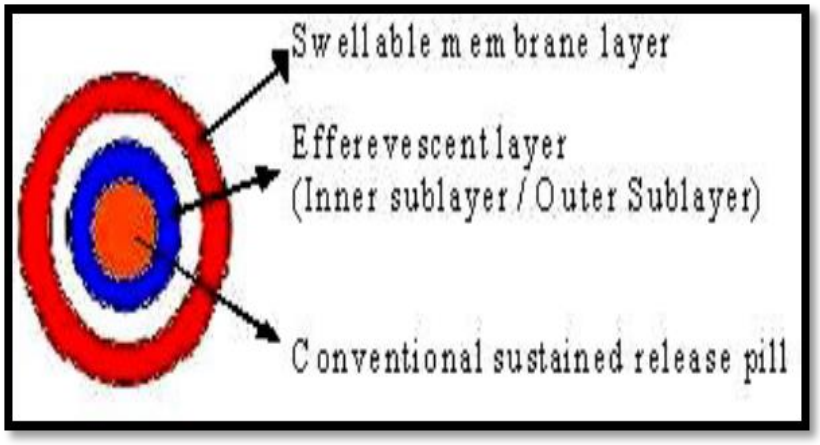

Fig. 6: Multiple units of oral FDDS

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 little on administration thus as not to make ingestion of the dosage form difficult (e.g., but more or less 23mm 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 straight forward 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-2.

Table-II: 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]
Metoprolol Succinate	Bilayer tablets	Synergistic effect in hypertension	[28]
Diclofenac Sodium Paracetamol	Bilayer tablets	Synergistic effect in pain	[29]
Methocarba-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 Levocetrizine	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]
Metoprolol Succinate Amlodipine Besilate	Bilayer tablets	Synergistic effect in hypertension	[41]
Telmisartan Hydrochlorthiazide	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]
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]

CHARACTERIZATION OF BILAYER TABLET

- **Particle size distribution**

The particle size distribution was measured using sieving method

- **Photo-microscope Study**

Photo-microscope image of TGG and GG was taken (X450 magnifications) by photomicroscope

- **Angle of Repose**

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

Tan Ø=h/r

Where, h and r are the height and radius of the powder cone.

- **Moisture Sorption Capacity**

All disintegrates have capacity to absorb moisture from atmosphere which affects moisture sensitive drugs. Moisture sorption capacity was performed by taking 1 g of disintegrate uniformly distributed in Petri-dish and kept in stability chamber at 37±1°C and 100% relative

humidity for 2 days and investigated for the amount of moisture uptake by difference between weights.

- **Density**

The loose bulk density (LBD) and tapped bulk density (TBD) were determined and calculated using the following formulas.

LBD ¼ weight of the powder=volume of the packing ð2Þ

TBD ¼ weight of the powder=tapped volume of the packing ð3Þ

- **Compressibility**

The compressibility index of the disintegrate was determined by Carr's compressibility index.

C = 100 x (1-ÞB/ÞT)

(Indian Pharmacopoeia, 1996; United States Pharmacopoeia, 2000:1944).

- **Hausnser's ratio**

It is calculated by the formula,

H=ρT/ρB

Where ρB is the freely settled bulk density of the powder,

And ρT is the tapped density of the

Powder (Atram et al., 2009).

Evaluation of Bilayer Tablets

1. General Appearance

The general appearance of a tablet, its visual identity and overall "elegance" is essential for consumer acceptance. Includes in are tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

2. Size and Shape

The size and shape of the tablet can be dimensionally described, monitored and

Controlled.

3. Tablet thickness: Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes

the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

4. Weight variation

Standard procedures are followed as described in the official books.

5. Friability

Friction and shock are the forces that the majority usually cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator. A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared 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. Normally, when capping occurs, friability values are not calculated. A thick tablet may have less tendency to cap where as thin tablets of huge diameter often show extensive capping, thus indicating that tablets with greater thickness have reduced internal stress the loss in the weight of tablet is the measure of friability and is expressed in percentage as:

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

6. Hardness (Crushing strength): The resistance of tablets to capping**,** abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness**.** The small and portable hardness tester was manufactured and introduced by Monsanto in the Mid 1930s. It is now Designated as either the Monsanto or Stokes hardness tester. The instrument measures the force required to break the tablet when the force generated by a coil spring 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 to be 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.

7. Dissolution Studies: Bilayer tablets were subjected to in vitro drug release studies in simulated gastric and intestinal fluids to assess their ability in providing the desired controlled drug delivery. Drug release studies were carried out using USP dissolution test apparatus I at 100 rpm, 37±0.5°C, and pH 1.2 buffer (900 ml) (i.e. 0.1 N HCl) for 2 hours, since the average gastric emptying time is about 2 hours. The dissolution medium was replaced with pH 6.8 phosphate buffer (900ml) and experiment continued for another 10 hours. At different time intervals, 5ml of the samples were withdrawn and replaced with 5ml of drug-free dissolution medium. The samples withdrawn were analyzed by UV spectrophotometer using multi component mode of analysis.

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. 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 is 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.

Table-III: Temperature dependant Stability study by ICH Guideline.

Study	Storage Condition	Minimum time period covered by data at Submission
Long Term	$25^0c \pm 2^0c$ / 60% RH ± 5 % RH or $30^0c \pm 2^0c$ /65% RH ± 5% RH	12 Months
Intermediate	$30^0c \pm 2^0c$ /65% RH ± 5% RH	6 Months
Accelerated	$40^0c \pm 2^0c$ / 75 % RH ± 5% RH	6 Months

*It is up to the applicant to decide whether long term stability are performd at $25^0c \pm 2^0c$ / 60% RH ± 5 % RH or $30^0c \pm 2^0c$ /65% RH ± 5% RH. ** If $30^0c \pm 2^0c$ /65% RH ± 5% RH is the long- term condition, there is no intermediate condition.

CONCLUSION

Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. There is various application of the bilayer tablet it consist of monolithic partially coated or multilayered matrices. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose. The preparation of tablets in the form of multi layers is used to provide systems for the administration of drugs, which are incompatible and to provide controlled release tablet preparations by providing surrounding or multiple swelling layers. 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 tabletting 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. Micheal AE, Modified release per oral dosage forms, Pharmaceutics – The Science of Dosage form Design, Churchill LivingSton New York, p. 575.
2. Banker S, Gilbert J, Rhodes T. Christopher, Modern Pharmaceutics, Marcel Dekker, Inc., New York, p.575.
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, 2012; 3(5).
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 tabletting Q & A. CSC Publishing.

7. Jan Vogeleer 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; 19: 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.;1995:142–145.
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. 369.
12. Martindale, the Extra Pharmacopoeia, 31st ed.The Pharmaceutical Press, London; 1996:936–937.
13. Bogan R K. Treatment options for insomnia - Pharmacodynamics of zolpidem extended release to benefit next-day performance. Postgrad Med 2008; 120: 161–71.
14. Patel G M and Patel D H. Formulation and evaluation of once a day regioselective dual component tablet of atorvastatin calcium and metoprolol succinate. Int J PharmTech Res 2010; 2 (3):.1870-82.
15. Indian Pharmacopoeia. The Controller of Publication. Delhi. 1996; (2):735.
16. Lachman L, Liberman H and Kanig J. The theory and practice of industrial pharmacy, 3rd edn. Varghese Publishing House, Mumbai. 1987:297.
17. Herrmann H, Kuhl A, Maier-Lenz H, Influence of the time of dosage of isosorbide mononitrate on objective and subjective angina pectoris parameters,Arzeim.-Forsch./Drug Res, 1988; 38:694–698.
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 Glimepiride: 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, Balasubramaniyam P, Firthouse P U M and Boopathi M. Formulation and evaluation of bilayer tablets of amlodipine besylate and metoprolol succinate. Derr pharmacia Lettre, 2011; 3(4):143-54.
29. Musle K, Payghan S A and Disuza J I. Fomulation, 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, Udupi 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 D S, Guruvaiah and Harani 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: URL: www.scientificipca.org/paper/2009/09/15/200909151256230A.doc [accessed on 1 July 2011].
41. Atram S C, Udavant Y K, Salunke RJ, 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. Anti-malarial 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. Dhumal R S, Rajmane S T, Dhumal 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, Jin M, Xinggang Y, Zhi-quan S and Wei-san P. 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.