ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 10, Issue, 06(H), pp. 33255-33267, June, 2019

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Research Article

A REVIEW: ON BILAYER FLOATING TABLET AS MULTIFUNCTIONAL APPROCH OF GASTRO RETAINTIVE DRUG DELIVERY SYSTEM

***Das S R., Panigrahi B.B and Pani M.K**

Department of Pharmaceutics, Indira Gandhi Institute of Pharmaceutical Sciences, Bhubaneswar

DOI: http://dx.doi.org/10.24327/ijrsr.2019.1006.3638

ARTICLE INFO

Article History:
Received 4th March, 2019
Received in revised form 25th April, 2019
Accepted 18th May, 2019
Published online 28th June, 2019

Key Words:

Bi-layered Floating Tablet , Bioavailability. GRDDS.

ABSTRACT

To make an overview on multifunctional activities of Gastro Retaintive Drug delivery System.(GRDDS) This review deals with study upon recent literatures on needs, advantages and disadvantages , ,suitable and unsuitable drugs, pharmacokinetic aspect, mechanism, approaches, list of polymers and other ingredients used, in vitro and in vivo evaluation, literature survey, marketed products, patented formulations, applications, limitations, and future aspect of Floating Drug Delivery System. Incorporation of drugs in bilayer floating tablet remain in gastric region for several hours would significantly prolong the gastric residence time of drug and improve the bioavailability and reduce the drug waste and enhance the solubility of drugs that are less soluable in high environment. Bilayer tablet is a new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. It also may be extensively used to improve therapy with several important drugs.

INTRODUCTION

Floating systems, first described by Davis in 1968 (Biswal B *et al*, 2011) Bilayer floating drug delivery system is combined principle of bilayer tablet as well as floating mechanism.(Maggi L *et al*,2005)

Bi-layer tablets have been developed to achieve controlled delivery of different drugs with pre-defined release profiles. In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bilayer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance. Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles (immediate release with extended release). (Laforce C *et al*,2008)

Bilayer tablets contain immediate and sustained release layer. Immediate release layer delivers the initial dose, it contains superdisintegrants which increase drug release rate and start onset of action whereas sustained release layer float due to gas generating agent and releases drug at sustained manner for prolonged period . (Biswal B *et al*, 2011) Incorporation of drug in controlled release gastroretentive dosage forms which can remain in the gastric region for several hours would significantly prolong the gastric residence time of drugs and improve bioavailability, reduce drug waste and enhance the solubility of drugs that are less soluble in high pH environment.(Lende LK *et al*, 2013)

The biphasic system is used mostly when maximum relief needs to be achieved quickly and it is followed by a sustained release phase. It also avoids repeated administration of drug. Coronary vasodilator, antihypertensive, antihistaminic, analgesic, antipyretics and antiallergenic agents are mainly used for this system. The biphasic system may contain one or two drugs for immediate release and sustained release layer. (Biswal B *et al*, 2011)

This review is an attempt to illustrate the application of Bilayer tablet by releasing the medicaments immediately for patient relief and also maintaining the therapeutic level to a extended period of time by controlling the release of drug in a sustained manner for better patient compliance and acceptability

Needs of Bilayer Floating Tablet

(Laforce C *et al* ,2008, Maggi L *et al*,2005, Park C.R *et al* 2002, Kulkarni A *et al,* 2009, Panchel HA *et al,* 2012, Nirma J *et al*, 2008)

- ✓ To administer fixed dose combinations of different APIs.
- ✓ Prolong the drug product life cycle.
- ✓ Fabricate novel drug delivery systems such as chewing device, buccal/ mucoadhesive delivery systems, and

Corresponding author:* **Das S R
Department of Pharmaceutics, Indira Gandhi Institute of Pharmaceutical Sciences, Bhubaneswar

floating tablets for gastro-retentive drug delivery.

- ✓ For the administration of fixed dose combinations of different APIs, prolong the drug
- ✓ Product life cycle, buccal/mucoadhesive delivery systems; fabricate novel drug deliver systems such as chewing device and floating tablets for gastro-retentive drug delivery.
- ✓ Controlling the delivery rate of either single or two different active pharmaceutical ingredients
- ✓ 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.
- ✓ To separate incompatible Active pharmaceutical ingredient (APIs) from each other, to control the release of API from one layer by utilizing the functional property of the other layer (such as, osmotic property).

Advantages (Poddar SS et al, 2004, Liu L et al, 2008, Despande RD et al 2011)

- ✓ They are used as an extension of a conventional technology.
- ✓ Potential use of single entity feed granules.
- ✓ Separation of incompatible components.
- ✓ Patient compliance is enhanced leading to improved drug regimen efficacy.
- ✓ Patient convenience is improved because fewer daily doses are required compared to
- ✓ Traditional delivery system.
- ✓ Maintain physical and chemical stability.
- ✓ Retain potency and ensure dose accuracy
- ✓ Better patient compliance is achieved due to its ease of administration.
- ✓ It maintains constant blood level.
- ✓ Site specific drug delivery is achieved for the drugs such as furosemide and riboflavin which are formulated as floating system.
- ✓ Overall other oral routes these are microbiologically and chemically stable.
- ✓ Due to higher dose precision and lesser content variation they are the most compatible oral dosage form.
- ✓ They offer the most flexible dosage form.
- ✓ Masking of bitter taste and bad odor by coating.
- ✓ Swallowing of tablets is easy.
- ✓ Lesser cost compared to other oral dosage forms.
- ✓ These are the most lighter and compact
- ✓ Tablet is a unit dosage form and they offer the greatest compatibilities of all oral dosage forms for the greatest dose precision and the least content variability.
- ✓ The cost is approximately lower than any other oral dosage form.
- ✓ These are very compact in nature.
- ✓ In genera the packaging procedure for tablets are easier and cheaper.
- ✓ Swallowing of tablets is very easy.
- ✓ They are better suited to large scale production.
- ✓ Chemically, mechanically and microbiologically tablets are very stable.

Disadvantages (Martindale W et al, 1996)

- ✓ Adds complexity and bilayer rotary presses are expensive.
- ✓ Insufficient hardness, layer separation, reduced yield.
- ✓ Individual layer weight control.
- ✓ Cross contamination between the layers.
- ✓ Increased fluid levels are required in the stomach so that the system float properly.
- ✓ Drugs with solubility and stability problem in stomach cannot be formulated as floating dosage form.
- ✓ Irritation producing drugs on gastric mucosa can be formulated as floating dosage form.
- ✓ Capping is the major problem in bilayer tablets
- ✓ Separation of layer occurs due to insufficient bonding and reduction in yield occurs.
- ✓ There are chances of cross contamination between two layers.
- ✓ Due to low density and amorphous nature of some drugs, compacts do not form because they resist compression
- ✓ There is less control over weight of individual layer.
- ✓ Swallowing problem in case of children and unconscious patients.
- ✓ Bioavailability problem occurs in case of poor wetting and less dissolution properties.
- ✓ Sometimes encapsulation or coating is required for the drugs that are oxygen sensitive, bitter tasting and with bad odour

***Need of Bilayer Floaying Tablets* (Singh PK *et al* 2011)**

- ✓ To control the delivery rate of either single or two different active pharmaceutical ingredients.
- ✓ For the administration of fixed dose combination of drug, prolong the product life cycle, buccal/ muco adhesive delivery systems, fabricate novel drug delivery system such as chewing device and floating tablets for gastro retentive drug delivery systems.
- ✓ To separate incompatible active pharmaceutical ingredients from each other, to control the release of API from one layer by utilizing the functional property of other layer (such as osmotic property..
- ✓ To modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable /erodible for modified release.
- ✓ For the administration of fixed dose combinations of different APIs, prolong the drug product life cycle, buccal /mucoadhesive delivery systems; fabricate novel drug deliver systems such as chewing device and floating tablets for gastro-retentive drug delivery
- ✓ Controlling the delivery rate of either single or two different active pharmaceutical ingredients
- ✓ 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.
- ✓ To separate incompatible Active pharmaceutical ingredient (APIs) from each other, tocontrol the release of API from one layer by utilizing the functional property of the other layer (such as, osmotic property *limitations* (Vijaya C *et al*)

Delamination

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

Cross-Contamination

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

Production yields

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

Cost

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

***Drug Suitable For* Bi Layer Floating Tablet (Sharma Ar *Et Al* , 2014)**

Table 1

sl no	conditions	examples
1	That disturb colonic microbes(Helicobacter pylori)	Antibiotics,Metoprostol
2	Drug that degrade the colon	Ranitidine,MetforminHcl
3	Drugs absorbe rapidly in GIT	Metronidanzole,Tetracycline
4	Drugs with narrow absorption of window	Cyclosporin,Methoxitrate
5	Drugs which are poorly soluble in alkaline pH	Forosemide,Diazepam,Veraprimil
6	Drugs that primarily absorb in stomach	Amoxilline
7	Drugs acting locally in stomach	Antacid

Drugs Not Suitable for Bi Layer Floating Tablet (Badoni A Et Al, 2012)

Table 2

sl no	conditions	examples
1	Drugs with very limited acid solubility	Phenytoin
2	Drugs that suffer instability in GIT pH	Erythromycin,Rebiprazole,Clarithromycin
3	Drug that selectively release in colon	Corticosteroids

Pharmacokinetic Aspect of *Bi Layer Floating Tablet (Kumar Mr Et Al 2013)*

Absoption window

he candidates for GRDDS are molecules that have poor colonic absorption but are characterized by better absorption properties at upper part of GIT.

Enhance bioavailability

Compound having narrow absorption window having the possibility of continuous administration of the compound at specific site.

Enhance first pass biotransformation

Pre-systemic metabolism of the tested compound is increased when the drug is presented to metabolic enzyme (Cytochrom p450) in a sustained manner

Improve bioavailability due to reduced P-glycoprotein activity in t6he duodenum

The drugs that P-gp substrate do not undergoes oxidative metabolism. GRDDS may elevate absorption compaired to immediate and CR dosage form.

Reduce frequency of dosing

For drugs with relatively short biological half life ,sustained and slow input from GRDDS result flip-flop pharmacokinetic and enable reduced dosing freequency.

Targeted therapy for local elements in upper GIT tract

The prolonged and sustained administration of the drug from GRDDS to the stomach may produce local therapy in the stomach and small intestine.

Pharmacodynamic aspect of bi layer floating tablet : (jamini m et al , 2007)

- ✓ Reduce fluctuation of drug concentration
- ✓ The fluctuations in drug effects are minimized and concentration dependent adverse effects that
- ✓ are associated with peak concentration can be prevented.
- ✓ Improved selectively in receptor activation-
- ✓ Minimization of fluctuation in drug concentration also make it possible to obtain certain selectively in the elicited pharmacological effect of drugs that activate different type of receptors at different concentration.
- ✓ Reduced counter activity of the body-
- ✓ Slow input of drug into the body was shown to minimize the counter activity leading to higher drug efficiency.
- ✓ Extended time over critical (effective) concentration-
- ✓ Clinical response is not associated with peak concentration. but rather with duration of time over critical therapeutic concentration
- ✓ Minimize adverse activity of colon-
- ✓ The pharmacodynamnic aspect provide the rationale for GRDDS formulation for beta-lactumantibiotics that are only absorbed from the small intestine and due to presence at colon it develop of microorganism's resistance,

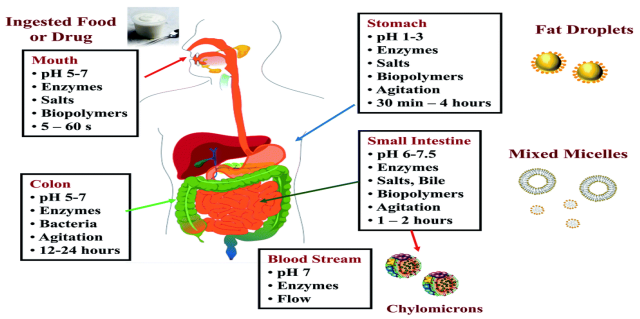

Figure 1 Regulation of acid secretion [28]

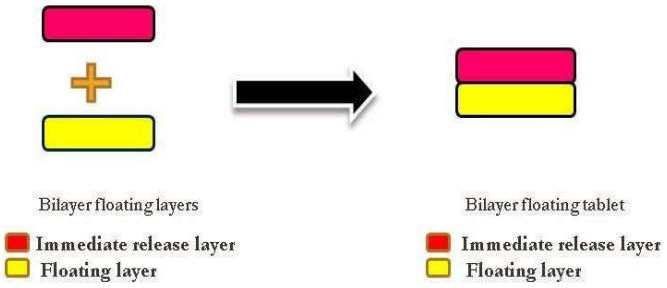

Figure 2 Bilayer Floating tablet (Karudumpala S *et al* ,2013)

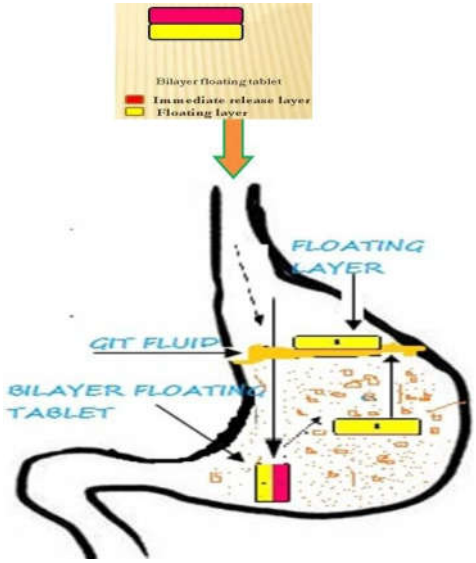

Figure 3 Mechanism of Bilayer floating tablet (Karudumpala S *et al* ,2013)

Methodology of Bilayer Floating Tablet

- ✓ -Oros ® Push Pull Technology
- ✓ L-Oros Tm Technology
- ✓ -DUROS Technology
- ✓ -Elan Drug Technologies‟ Dual Release Drug Delivery System
- ✓ EN SO TROL Technology
- ✓ Rotab Bilayer
- ✓ Geminex Technology
- ✓ PRODAS or Programmable Oral Drug Absorption System

OROS® Push Pulls Technology

This system consist of mainly two or three layer among which the one or more layer are essential of the drug and other layer are consist of push layer. The drug layer mainly consists of drug along with two or more different agents. So this drug layer comprises of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core .(Dev A *et al* , 2012)

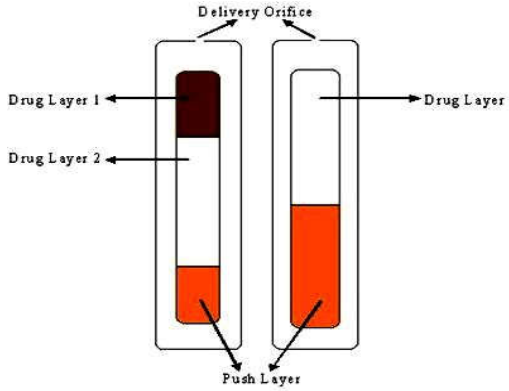

Figure 4 Bilayer and Trilayer OROS Push Pull Technology

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 then a semi permeable membrane, drilled with an exit orifice [31]

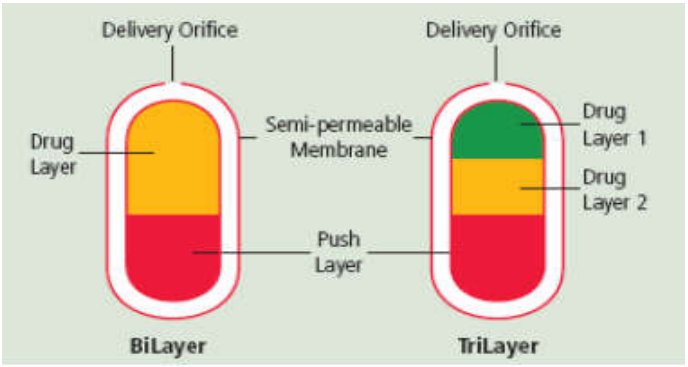

Figure 5 L-OROS TM Technology

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 [32]

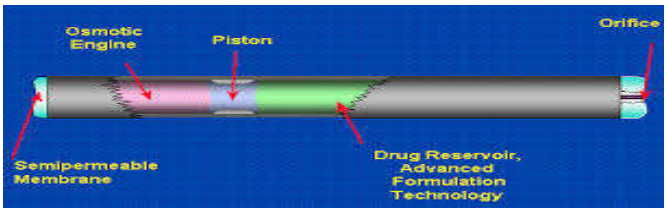

Figure 6 DUROS Technology.

Elan Drug Technologies' Dual Release Drug Delivery System

The DUREDASTM Technology provides combination release of drugs together and different release pattern of single drug i.e. it provides sustained release as well as immediate release. This technology provides various advantages i.e. two drug components provide tailored release and its another benefit is that it consists of bilayered tablet technology in which it contains modified as well as immediate release pattern in one

tablet. In these different controlled release formulations are combined together.

EN SO TROL Technology

An integrated approach is used by Shire laboratory for drug delivery system which focuses on identification and incorporation of enhancer which is identified to form optimized dosage form in controlled release system. By this enhancement in solubility is achieved

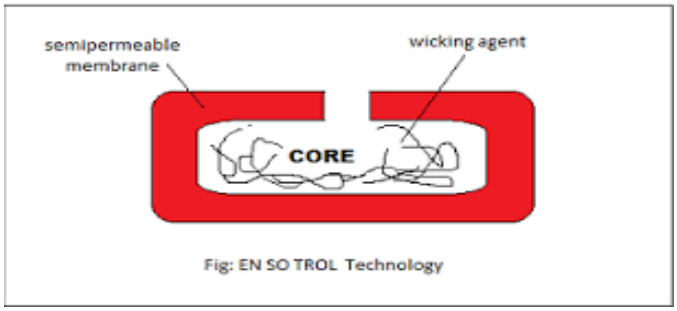

Figure 7 ENSOTROL Technology

RoTab Bilayer

RoTab bilayer when using is switched to production mode. Dose and compression force is automatically regulated by adjusting filling speed and die table. Hardness is also regulated when required (Solakhia TM *et al* 2012)

Geminex Technology

In this drug delivery system at different times more than one drug can be delivered. This technology basically increases the therapeutic efficacy of the drug by decreasing its side effects. It is useful to both industry as well as patient as in single tablet it provides delivery of drug at different rate (Pranapalli B K *et al* 2012)

PRODAS or Programmable Oral Drug Absorption System

(Elan Corporation) is a multiparticulate drug delivery technology that is based on the encapsulation of controlled release minitablets in the size range of 1.5 to 4 mm in diameter. This technology represents a combination of multiparticulate and hydrophilic matrix tablet technologies and thus provides the benefits of both these drug delivery systems in one dosage form. Minitablets with different release rates can be combined and incorporated into a single dosage form to provide the desired release rates. These combinations may include immediate release, delayed release, and/or controlled release mini tablets (Patwekar SL *et al* 2012)

List of Polymers and Other Ingredients Used in Grdds

(Kumar MR *et al* ,2013, Aslam R *et al* 2014 , Kumar R *et al*,2016)

Table 3 List of polymers and other ingredients used in GRDDS

Sl No	Category	Materials
1	POLYMERS	Cellulose polymers-HPMC K4M,HPMCK15,HPMC K 100, HPMC 4000,HPMC K4,HPC-M,HPC-L,HPC-H,HPC-M,Ethyl cellulose. Methyl cellulose. Eudragit- Eudragit s 100,Eudragit RL, Eudragit-s,Eudragit-RS Alginates- Calcium alginate, Sodium alginate etc Others-Propylean foam, Poly methyl Metha crylate ,PVA, Polycarbonate, Metolose S.M 100,PVP, Polyox, Acrylic polymer, Carbopol, Pectine.
2	*Inert fatty materials (5% to 75%)*	Bees wax ,Long chain fatty alcohols,Gelucires39/01and 43/01
3	*Effervescent agents*	Sodium bicarbonate, Citric acid, Tatraric acid, Di Sodium Glycin carbonate, Citric Acid, Citroglycin,
4	*Low density materials Buoyancy increasing agents (upto 80%)*	Glycin palmitosterate, Glyceryl behenate, Polypropelene low powder(Accurel MP 1000)
5		Ethyl cellulose
6	*Release rate accelerants (5% to 60%)*	Lactose, Mannitol, etc
7	*Release rate retardants(5% to 60%)*	Di-calcium phosphate, Talc, Magnesium stearate,

Preparation of Granules

Preparation of granules of IR Layer :(Priyal S *et al,* 2013)

The Immidiate release IR layer were prepared by wet granulation method. The required ingredients were weighed accurately and passed through 40 mesh. The sieved materials were then mixed well in a poly bag for about 30 minutes. The surfactants, SLS and polysorbate80 were dissolved in cold and hot water respectively to use as granulating fluid. To moisten the blend, either water or surfactant solution was used as granulating fluid. The wet mass was granulated in RMG granulator. The granules were then dried in a Retsch rapid dryer at 60^0C for about 60 minutes until the % LOD becomes less than 3%. The dried granules were then passed through 40 mesh and then lubricated by mixing with the lubricant (which was previously passed through 60 mesh) in a polybag for about 15 minutes. The flow properties of the lubricated granules were determined.

Preparation of granules of SR Layer (Rudnic EM *et al* ,1996)

The floating sustained release SR layer were prepared by wet granulation method. The drug and polymer which were previously passed through 40 mesh were mixed thoroughly in a polybag for 20 minutes. The blend was moistened with granulating fluid *i.e.,* water and IPA (1:9 parts). The wet mass was passed through 24 mesh and then dried in a tray dryer at 50^0C for about 50 minutes until the % LOD becomes less than 2%. The dried granules were passed through 30 mesh and mixed with sodium bicarbonate in a polybag for 10 minutes. To this talc (previously passed through 60mesh) was added and mixed well for 10 minutes. The flow properties of the lubricated granules were evaluated.

Flow Properties of Lubricated granules

The lubricated granules obtained from wet granulation of Sucralfate and Metoprolol Succinate with different excipients are evaluated for flow properties like bulk density, tapped density etc.

Bulk density and Tapped density (g/ml)

The previously weighed pure drug or granules (W) were placed separately into a graduated measuring cylinder and the initial (bulk) volume (V_B) was noted. It was placed in the tapped density tester USP and subjected to constant tapping at a rate of 200drops/min until the difference between the initial and final volumes should be less than 2%. It was recorded as the final (tapped) volume (V_T) and various flow properties were calculated with the following formulae.

Bulk density, $\rho B = \frac{W}{VB}$ Tapped density, $\rho T = \frac{W}{VT}$

Compressibility Index

It was calculated by using the following formula

Carr's Index or Compressibility Index (CI) = $1-\frac{\rho B}{\rho T} * 100$

The CI value below 15% indicates good flow of the powder and above 30% indicates poor flow property of the powder.

Hausner's Ratio*:* It is calculated by the following formula;

Hausner's Ratio= $\frac{\rho T}{\rho B}$

The Hausner's ratio below 1.25 indicates good flow property and above 1.25 indicates poor flow property of the powder.

Angle of Repose (Θ)

It was determined by using a funnel whose tip was fixed at a constant height (H) of 2.5cm from horizontal surface. The granules and the powder were passed separately through the funnel until the tip of the conical pile touches the tip of the funnel. The radius of the base of the conical pile is measured as R (cm). It is determined with the formula;

Angle of repose (θ) = Tan^{-1} (height /radius).

Table 3 Normal value of angle of repose

Angle of repose	Powder flow
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very poor

Acclerater stability study of Lubricated Granules

Acclerated stability study is done of lubricated granules 10 gm of each formulations of at 45^0C and 75% RH for a period of 3 months. The granules were packed in 85mm HDPE bottles with an oxygen adsorbent, and a desiccant containing silica gel with cotton as filler. The granules were withdrawn after the regular interval of stability period, and evaluated for physical properties.

Preparation of Bilayer Tablets (Rudnic EM *et al* ,1998, Breech AJ *et al* , 1998 , Kalam MA *et al*,2012, Albert S *et al,* 2007,Li SP *et al* , 1995)

Bilayer floating tablet can be prepared using methods like direct compression, dry granulation, and wet gra nulation method. Layers was also prepared using combination of methods

Bi-layer tablets are tablet, made by compressing two different granulations fed into a die succession, one on top of another, in layers. Each layer comes from a sep- arate feed frame with individual weight control. Rotary tablet press can be set up for two or three layers. More are possible but the design becomes very special.

Bilayer tablets can be prepared by combining of fast release layer and various formulations of controlled release layer. (F After the compression upper punch was lifted and the blend of powder for imme- diate release layer was poured into the die, containing initially compressed matrix tablet on RIMEK multi sta- tion punching machine using 12.5 mm flat punches, with the hardness of 6.5 kg/cm2.

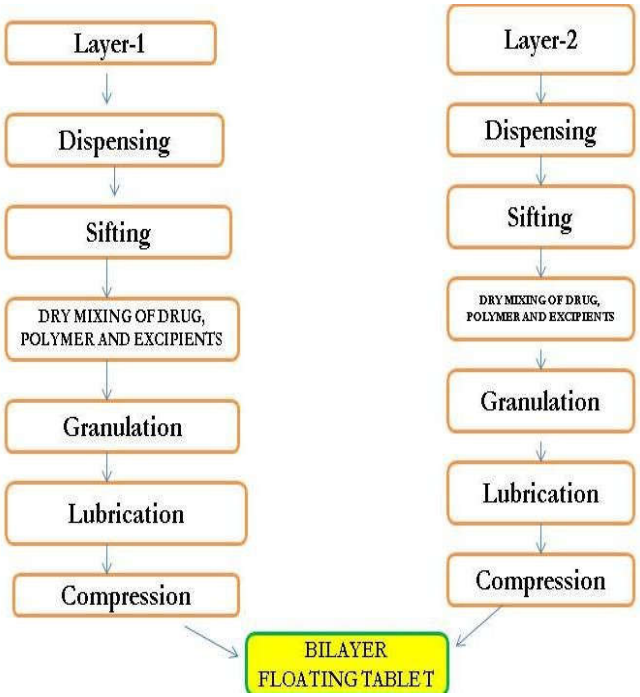

Figure 8 Preparation of Bilayer floating tablet

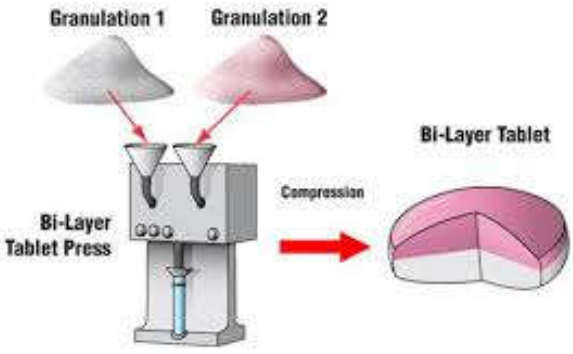

Figure 9 Manufacturing process of Bi Layer floating tablet

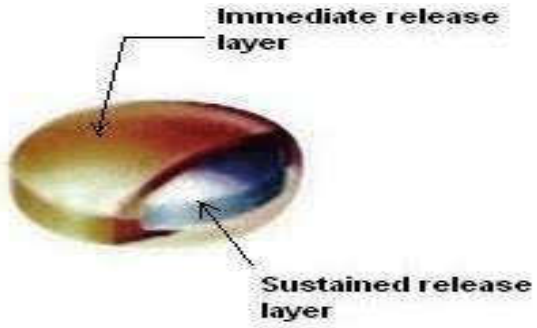

Figure 10 Digramatic pregentation of Bilayer Floating Tablet

Figure 11 Shematic diagram of Bilayer Floating Tablet

Bilayer tablets are prepared with one layer of drug for immediate release with the second layer designed to release drug later, either as a second dose or in an extended release form. 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

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 table.

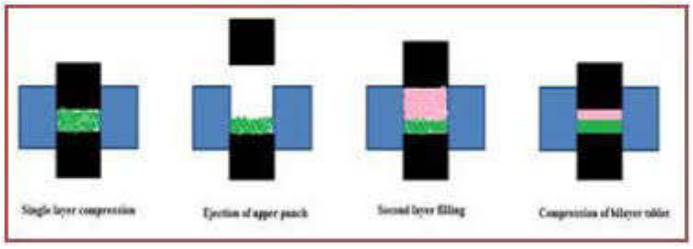

Figure 12 Preparation of bilayer tablet Compaction

***General properties of Bi-Layer Tablet Dosage Forms* (Shukla S *et al*, 2013)**

1. A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration, and contamination.
2. Should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
3. 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. Must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

Types of Bilayer Tablet Press [46,47]

- ✓ Single sided tablet press.
- ✓ Double sided tablet press.
- ✓ Bilayer tablet press with displacement monitoring.

Single sides 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 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.

Double Sided Tablet 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 the main compression of the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance tablets and correct the die fill depth when required.

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 pre- compression force.

Figure 13 Single sides press

Figure 14 Double Sided Tablet Press

Figure 15 Bilayer tablet press with displacement

Evaluation of Bilayer Floating Tablet (Kumar R Et Al, 2016)

Evaluation of a drug product is a tool to ensure

- ✓ Performance characteristics
- ✓ Control batch to batch quality

Apart from routine tests like general appearance, hardness and friability, drug content, weight variation, uniformity of content, disintegration time, drug release, etc., GRDDS need to be evaluated for gastroretentive performance by carrying out specific tests.

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

Weight Variation Test: **(IP** ,1996)

Twenty tablets are selected and weighed individually. Then the average weight and standard deviation is calculated. Test passes when not more than two tablets deviate from average weight.

Table 4 Limit of Weight Variation

Weight	% Variation
Less than 80 mg	10%
80-250 mg	7.5%
Above 250 mg	5%

Hardness

Expressed in kg/cm^2 and it is checked using Monsanto hardness tester by randomly picking three tablets. Hardness helps in knowing ability of the tablet to withstand mechanical shock during handling of tablets (Gahiwade HP *et al,* 2012)

Friability: (USP 2000)

Ten tablets are selected and weighed and then placed in friabilator apparatus which rotates at 25 rpm speed for 4 minutes. After 4 minutes tablets are weighed again.

%F= [1-(Wt/W)]*100

W – Initial weight of tablet
Wt - Weight of tablet after revolution.
If % Friability of tablets is less than 1% is considered acceptable

Tablet Density*:* (Chaudhuri S *et al*, 2012)
It is an important parameter in case of floating tablets. If density is less than (1.004) gastric fluid, the tablets will float. It is calculated by using formula:

V=πr2h d = m/v
r = Radius of tablet
h = crown thickness (g/cc) m = Mass of tablet

In Vitro Evaluation (Kumar R *et al,* 2016)

Floating systems

a. Floating lag time: It is determined in order to assess the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. These parameters can be measured as a part of the dissolution test
b. Floating time: Test for buoyancy is usually performed in SGF Simulated Gastric Fluid maintained at 370C.The time for which the dosage form continuously floats on the dissolution media is termed as floating time .
c. Specific gravity or density: Density can be determined by the displacement method using Benzene as displacement medium.
d. Resultant weight: Now we know that bulk density and floating time are the main parameters for describing buoyancy. But only single determination of density is not sufficient to describe the buoyancy because density changes with change in resultant weight as a function of time. For example a matrix tablet with bicarbonate and matrix polymer floats initially by gas generation and entrapment but after some time, some drug is released and simultaneously some outer part of matrix polymer may erode out leading to change in resultant weight of dosage form.

The magnitude and direction of force or resultant weight (up or down) is corresponding to its buoyancy force (Fbuoy) and gravity force (Fgrav) acting on dosage form

Swelling systems

a. Swelling index: After immersion of swelling dosage form into SGF at 370C, dosage form is removed out at regular interval and dimensional changes are measured in terms of increase in tablet thickness or diameter with time.
b. Water uptake: It is an indirect measurement of swelling property of swellable matrix. Here dosage form is removed out at regular interval and weight changes are

determined with respect to time. So it is also termed as Weight Gain.

Water uptake = WU = (Wt – Wo) * 100 / Wo Where, Wt = Weight of dosage form at time t; Wo = Initial weight of dosage form II)

In vitro dissolution test

In vitro dissolution test is generally done by using USP apparatus with paddle and GRDDS is placed normally as for other conventional tablets.

a. But sometimes as the vessel is large and paddles are at bottom, there is much lesser paddle force acts on floating dosage form which generally floats on surface. As floating dosage form not rotates may not give proper result and also not reproducible results. Similar problem occur with swellable dosage form, as they are hydrogel may stick to surface of vessel or paddle and gives irreproducible results. In order to prevent such problems, various types of modification in dissolution assembly made are as follows
b. To prevent sticking at vessel or paddle and to improve movement of dosage form, method suggested is to keep paddle at surface and not too deep inside dissolution medium.
c. Floating unit can be made fully submerged, by attaching some small, loose, non- reacting material, such as few turns of wire helix, around dosage form. However this method can inhibit three dimensional swelling of some dosage form and also affects drug release.
d. Other modification is to make floating unit fully submerged under ring or mesh assembly and paddle is just over ring that gives better force for movement of unit
e. In previous methods unit have very small area, which can inhibit 3D swelling of swellable units, another method suggest the change in dissolution vessel that is indented at some above place from bottom and mesh is place on indented protrusions, this gives more area for dosage form. In-spite of the various modifications done to get the reproducible results, none of them showed correlation with the in vivo conditions. So a novel dissolution test apparatus with modification of Rossett-Rice test apparatus was proposed

In vivo evaluation: (Kumar R *et al*, 2016)

Radiology: X-ray is widely used for examination of internal body systems. Barium Sulphate is widely used Radio Opaque Marker. So, BaSO4 is incorporated inside dosage form and X-ray images are taken at various intervals to view gastric residence (GR).

Scintigraphy*:* Similar to X-ray, emitting materials are incorporated into dosage form and then images are taken by scintigraphy. Widely used emitting material is Tc99.

Gastroscopy**:** It is peroral endoscopy used with fiber optics or video systems. Gastroscopy is used to inspect visually the effect of prolongation in stomach. It can also give the detailed evaluation of GRDDS.

Magnetic marker monitoring: In this technique, dosage form is magnetically marked with incorporating iron powder inside, and images can be taken by very sensitive bio-magnetic measurement equipment. Advantage of this method is radiation less and so, not hazardous.

Ultrasonography: Used sometimes, not used generally because it is not traceable at intestine.

C ^{13}Octanoic acid breath test: In stomach due to chemical reaction, octanoic acid liberates CO2 gas which comes out in breath. The important Carbon atom which will come in CO2 is replaced with 13C isotope. So time up to which 13CO2 gas is observed in breath can be considered as gastric retention time of dosage form. As the dosage form moves to intestine, there is no reaction and no CO2 release. So this method is cheaper than other.

Patent on Floating Bilayer Tablet (Greg RK *et al* ,2015)

Table 5

Drug	Patent application number
Ciprofloxacin, Acyclovir, Ofloxacin	US Patent Appln 2006013876
Heparin and Insulin	US Patent Appln 2008153779
Acyclovir, Ganciclovir, Ritonavir, Minocycline, Cimetidine, Ranitidine, Captopril, Methyldopa, Selegiline, Fexofenadine, Bupropion, Orlistat & Metformin	US Patent 6120803
Ciprofloxacin	US Patent Appl 2003232081
Calcitriol, combined with delayed release of a bisphosphonate	
calcium resorption inhibitor such as alendronic acid and its salts and hydrates	US Patent Appl 2007104786

Literature Review

Commercially Marketed Bilayer Tablets (Aryal S *et al,*2008, Quali A *et al*,)

Table 7

Product Name	Chemical Name	Developer
ALPRAXPLUS	Sertraline, Alprazolam	Torrent Pharmaceutcals Ltd.
Glycomet®-GP2Forte	Metformin hydrochloride, Glimepiride	USV Limited
Newcold Plus	Levocetrizine hydrochloride, Phenylpropanolamine, Paracetamol	Piramal Healthcare Ltd.
DIAMICRON®XRNEX500	Gliclazide, Metformin hydrochloride	Serdia® Pharmaceuticals (India) Pvt. Ltd.
DIUCONTIN-K®20/250	Furosemide, Potassium chloride	T.C. Health Care Pvt. Ltd.
TRIOMUNE 30	Nevirapine, Lamivudine, Stavudine	Cipla Ltd.
PIOKIND®-M15	Pioglitazone, metformine hydrochloride	Psychotropics India Ltd.
Revelol®-Am 25/5	Metoprolol succinate, Amlodipine besilate	Ipca Laboratories Ltd.

Table 6

Sl no	Formulations	Drugs in (ir) layer	Drugs in (sr) layer	Rationel	Ref no
1	Bilayer Gastroretentive Matrix Tablet	Atorvastatin,	Atenolol	Treatment of hypertension and hypercholesterolemia	Swati s et,al ,2014
2	Gastro-Retentive Floating Bilayer Tablets	Nifedipine	Vinpocetin	Treatment of hypertension and angina pectoris	Kurudumpala S et al, 2013
3	Sustained Bilayer tablets	Aspirin,	Isosorbide 5-mono-nitrate	Treatment of pain, fever and other inflammatory conditions	Hu.L et al, 2014
4	Bilayer Tablets	Pioglitazone HCL	Gliclazide	Treatment of Type II Diabetes	Sharma SK , et al 2014
5	Bilayer tablet	Losartan	potassium	Treatment of hypertension	Reddy K.R et al 2014
6	Bilayer tablets	Trimetazidine HCL	clopidogrel bisulphate	Cytoprotective anti-ischemic, platelet inhibitor in acute coronary syndromes,	Saif AA et al 2014
7	Bilayer tablets	Diclofenac,	Cyclobenza-prine	Synergistic effect in pain	Jamunadevi V et al,2011
8	Bilayer buccal tablets	Granisetron HC1	Metoprolol	To overcome bioavailability problem, reducing side effects	Swamy PV et al ,2011
9	Bilayer tablets	Metformin HC1,		Synergistic effect in diabetes	Pattnaik DP , et al 2011
10	Bilayer floating tablets	Indomethacin		Biphasic drug release	Jain J et al, 2011
11	Bilayer tablets	Metformin HC1,	AtorvastatinCalcium	To develop polytherapy for the treatment of NIDDS & hyperlipidemia	Neem MA et al ,2010
12	Bilayer tablets	Cefixime Trihydrate,	Dicloxacilline Sodium	Synergistic effect in bacterial infections	Mohindeen S et al, 2011
13	Bilayer tablets	Piracetam,	Vinpocetin	Synergistic effect in Alzheimer disease	Kumar GV et al ,2011
14	Bilayer tablets	MetforminHCL	Pioglitazone	Synergistic effect in diabetes mellitus	Jadav RT et al 2011
15	Bilayer buccal tablets	Atenolol		To overcome bioavailability problem, reducing side effects and frequency of administration	Rajendra NN et al 2011
16	Bilayer tablets	Cefuroxime Axetil	Potassium Clavulanate	Synergistic effect against microbial infections and to minimize dose dependent side effects	Shrisand SB et al 2011
17	Bilayer tablets	Amlodipine Besilate	Metoprolol Succinate	Synergistic effect in hypertension	Parmar CK et al ,2011
18	Bilayer tablets	Diclofenac Sodium,	Paracetamol	Synergistic effect in pain	Jayaprakash S etal,2011
19	Bilayer tablets	Ibuprofen,	Methocarba-mol	Synergistic effect of drugs in back pain	Atram SC et al 2009
20	Bilayer buccal tablets	Atorvastatin	Calcium	To overcome bioavailability problem, reducing side effects and frequency of administration	Musle k et al 2011
21	Bilayer tablets	Paracetamol	Diclofenac	Synergistic effect of drugs in pain	Remya PN et al ,2010
22	Bilayer tablets	Losartan		Biphasic release profile	John As et al, 2010
23	Bilayer tablets	Metformin HCL	Pioglitazone	Synergistic effect in diabetes mellitus	Gohel Mc et al ,2010
24	Bilayer tablets	Guaifenesin		Biphasic release profile	Hiremath D et al ,2010
25	Bilayer tablets	Tramadol,	Acetaminophen	Synergistic effect of drugs in pain	Ramesh A et al, 2010
26	Bilayer floating tablets	Atenolol,	Lovastatin	Synergistic effect in hypertension and biphasic release profile	Kumar VB et al 2010
27	Bilayer tablets	Montelukast,	Levocetrizine	To improve the stability of drugs in combination	Naeem MA et al,2010
28	Bilayer tablets	Salbutamol,	Theophylline	Synergistic effect of drugs in asthma	Kulkarni A et al, 2009
29	Bilayer tablets	Glipizide,	Metformin HCl	To avoid interaction b/w incompatible drugs	Rathod RT et al ,2009
30	Bilayer tablets	Telmisartan	Hydrochlor- thiazide	To minimize contact b/w hydrochlorothiazide & basic component of telmisartan	Nagaraju R et al,2009
31	Bilayer tablets	Amlodipine,	Atenolol	To improve the stability of drugs in combination	Kadam VV et al ,2009
32	Bilayer tablets	Misorostol,	Diclofenac	To minimize contact b/w drugs	Friedl T et al,

Herbal Drugs Delivered By Bilayer Floating Tablet (Nirav R *et al*,2012, Liao J *et al,* Oong SLP *et al*, Doshi MM *et al)*

Forskolin

A normal root extract from the coleus forskolin was developed. These formulations contain different grades of HPMC polymer.

The drug is used as anti- obesity agent reducing fat in body muscles. it may en- hence fat loss without loss of muscle mass .

Black myrobalan

The aqueous exctract of black myrobalan (terminalia chebula Retz) has been shown to have uniform anti- bacterial activity against ten clinical strains of H pyroli.

Giner root (Zingiber officinale Rose.)

It has been used traditionally for the treatment of gastrointestinal ailments such as motion sickness, dyspepsia and hyperemesis gravidarum and is also reported to have chemopreventative activity in animal models.

Turmeric

Curcumin derived from turmeric has been shown to prevent gastric and colon cancers in rodents

Licorice

In the recent study at the institute of medical microbi- ology and virology, Germany, researchers identified that licorice extract produced a potent effect against a strains of H.pylori 6- Berbirine has wide ver

Berberine

Berberine has wide variety of activity against bacteria, viruses, fungi, protozoans, and helminthes

CONCLUSION

Bilayer tablet is improved beneficial technology to overcome the shortcoming of single layered tablet. Bilayer tablets provide one of the important design approaches where incompatible drugs, with different indication, and same drug with different release rate can be incorporated in a single unit. Bilayer tablet is suitable for sequential release of one or 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 Bilayer is used to provide systems for the ad- ministration of drugs, which are incompatible and pro- vide controlled release tablet preparations by provid- ing surroundings or multiple swelling layers.

Acknowledgement

I would like to express my special thanks of gratitude to my Guide Dr Bibhuti Bhusan Panigrahi and Co Guide Dr Monoj Kumar Pani as well as The Principal who gave me a golden opportunity to proceed on my research work on the topic which helped in enhancement of my knowledge and ability.I am really thankful to them.

Secondly i would like to thank my parents, my family and supporting staffs who helped me a lot in fulfilment of the work. Finally i would like to thank to God for blessing of further proceed.

References

1. Biswal B. 2011. Design development and evaluation of trimetazidine dihydrochloride floating bi layer MR tablets.IRJP, 2(7) 92-97.
2. Pethkar SV, Suggala V, Gholap S, Salunke R, Jain Hemantkumar, Swain Kapileswar . 2016. Review on Bilayer floating tablet .WJPPR 5(2) 1411-23.
3. Lende LK, Banarjee S.K, Gandhave MV, Gaikwad D.D, Gaykar AJ . 2013 .Review on: Bilayer floating tablet.AJPRD .1(1) 31-39
4. Garg RK . 2015.Bilayer floating tablet Technology : an Overview . IJPPR 3(3) 302-322.
5. LaForce C., Gentile D.A., Skoner D.P. 2008. A randomized, double-blind, parallel group, multicenter, placebo-controlled study of the safety and efficacy of extended-release guaifenesin/ pseudoephedrine hydrochloride for symptom relief as an adjunctive therapy to antibiotic treatment of acute respiratory infections. Postgrad. Med.; 120: 53–59.
6. Maggi L., Segale L., Conti S., Ochoa Machiste E., Conte U. 2005. Preparation and evaluation of release characteristics of 3TabGum, a novel chewing device. Eur. J. Pharm. Sci.;4: 487– 493.
7. Park C.R., Munday D.L. 2002. Development and evaluation of a biphasic buccal adhesive tablet fo nicotine replacement therapy. Int. J. Pharm.; 237: 215–226.
8. Kulkarni A, Bhatia M; 2009.Development and evaluation of bilayer floating tablets of atenolol and lovastatin for biphasic release profile. *Iranian Journal of Pharmaceutical Research,*; 8(1): 15-25.
9. Panchel HA, Tiwari AK; 2012.A Novel approach of bilayer tablet technology-A review.; 3(5): 44-49.
10. Nirmal J, Saisivam S, Peddanna C, Muralidharan S, Godwinkumar S, Nagarajan M .2008. Bilayer tablets of atorvastatin calcium and nicotinic acid: formulation and evaluation. Chem Pharm Bull., 56(10):1455-1458.
11. Poddar SS, Abdul S.2004.A flexible technology for modified release of drugs: multilayered tablets. Journal of Control Release97(3): 393– 405.
12. Liu L, Xu X.2008.Preparation of bilayer-core osmotic pump tablet by coating the indented core tablet. International Journal of Pharmacy, 225–230.
13. Deshpande RD, Gowda DV, Mohamad N, Marambar DN.2011 ."Bi-Layer Tablets- An Emerging Trend: A Review", *International Journal of Pharmaceutical Science and Research*, 2534-44.
14. Martindale W, Reynolds JEF.1996. Martindale The Extra Pharmacopoeia. 31st edition, The Pharmaceutical Press, London,: 936–37.
15. Singh PK, Kumar S, Shukla VK, Sharan G, Verma P, Dev S.2011.Bilayer and Floating- Bioadhesive Tablets: Innovative Approach to Gastroretension",Journal of Drug Delivery & Therapeutics, 1, 32-35.
16. SinghPK, Kumar S, ShuklaVK, Sharan G, Verma P, Dey S, 2011.Bilayer and floating – Bioadhesive tablets: Innovative approach to gastroretension. *Journal of Drug Delivery and Therapeutics*, 1(1), 32-35.
17. Sowmya C, Suryaprakash Reddy C, Tabasum SG, Varma V. 2012.An overview on bi-layer tablets. IJPT, 2(4), 2143-56.
18. Naisarg D Pujara, Ronak K Gokani, Jalpa S Paun. 2012, Bilayer tablet – An Emerging Trend. IJPRD, 4(4), 102-11.
19. Kulkarni A, Bhatia M. 2009. Development and evaluation of bilayer floating tablets of atenolol and lovastatin for biphasic release profile. *Iranian Journal of Pharmaceutical Research*, 8(1): 15-25.
20. Panchel HA, Tiwari AK . 2012. A Novel approach of bilayer tablet technology-A review; 3(5): 44-49.
21. Nirmal J, Saisivam S, Peddanna C, Muralidharan S, Godwinkumar S, Nagarajan M; 2008 .
22. Bilayer tablets of atorvastatin calcium and nicotinic acid: formulation and evaluation. Chem Pharm Bull.,; 56(10):1455-58.
23. 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.
24. Sharma AR, Khan A. 2014. Gastroretaintive drug delivery system : An approach to enhance gastric retenti on for prolonged drug release., IJPSR;5(4):1095-1106.
25. Presentation on Gastro Retaintive Drug Delivery system.2015. Avilable at:https://www.slideshare.net/NadiaJawaid/presentation-grdds. Accessed Feb 17.
26. Badoni A, Ojha A, Gnanaranjan G ,Kothiyal P. 2012 .Review on Gastro retaintive drug delivery system: The Pharma Innovation.,1(8):32-42.
27. Kumar M R, Satyanarayan B, Paladugu N D,Kondavasmi N, Muddasar S, Pasha S I, Vemireddy S,Poloju D. 2013 .A Compressive review on Gastro retaintive drug delivery system: Acta Chim. Pharm.Indica ., 3(2):149-164.
28. Jamini M, Rana A.C, Tanwar Y.S. 2007.Formulation and Evaluation of Famotidine Floating Tables. Current Drug Delivery., (4) : 51-55.
29. Role of pH and Pka in Drug absorption.2015 Science of Drugs. Avilable at: https://drugs-bd.blogspot.com/2015/04/role-of-ph-and-pka-in-drug-absorption.html. Accessed April 12,2015.
30. Karudumpala S, Chetty M, Gnanaprakash K, Venkatesh B, Sankar P . , 2013. A review on bilayer floating tablets ., Int. J. Res. Pharm.Sci; 4(2) : 354-360.
31. Dev A, Gopal NV , Shekar L, Ramarav B, Rao JV, Karunakar K, Surendra Y, . 2012 .AReview of Novel Approach in Bilayer Tablet Technology International *Journal of Pharmaceutical, Biological and Chemical Sciences*, 1, 01 – 08.
32. Panchan HA, Tiwari AK. 2012, A Novel Approach of Bilayer Tablet Technology: AReview". .International Research Journal of Pharmacy. 3, 44-49.
33. Pujar ND, Gokani RK, Paun JS. 2012 .Bilayer Tablet – An Emerging Trend". *International Journal of Pharmaceutical Research and Development*., 4, 102 – 11.
34. Solakhia TM, Kosta AK, Agarwal S, Gupta D.2012.Bi-Layer Tablets: An Emerging Trend". *International Journal of Pharmaceutical & Biological Archives*. 3, 499-506.
35. Parnapalli Mand Arshad BK. . 2012, Recent Apporaches in Bilayered Technology: Review". *International Journal of Pharmaceutical Science and Research* .3, 4681-4688.
36. Patwekar SL, Baramade MK. 2012. Controlled Release Approach To Novel Multiparticulate. Drug Delivery System". *International Journal of Pharmacy and Pharmaceutical Sciences*., 4, 757-63.
37. Kumar M R, Satyanarayan B, Paladugu N D,Kondavasmi N, Muddasar S, Pasha S I, Vemireddy S,Poloju D. 2013 .A Compressive review on Gastro retaintive drug delivery system: Acta Chim. Pharm.Indica.3(2):149-164.
38. Aslam R, Mehmood Y, Khan S, Yousaf H, 2014 .Technique and polymer Used to design Gastroretaintive Drug delivery system. WJPPS.3(12) : 97-110.
39. Kumar R, Mohon K .2016. A compressive review on Gastroretaintive drug delivery system.IAJPS .,3(2) :115-128.
40. NilawarPS,WankhadeVP,Badnag DB.2013. An emerg- ing trend on bilayer tablets. *International journal of pharmacy and pharmaceutical science research* 3(1): 15-21.
41. Rudnic EM, Kottke MK.1996. Tablet dosage form. In Banker GS, Rhodes CT editors; Modern Pharmaceutics. 3rd edition, New York: Marcel Dekker Inc.
42. Breech AJ, Lucisano LJ, Franz RM; 1998.Investigation into substrate cracking of a film coated bilayered tablet. J Pharm Pharmacol.40(4): 282- 283.
43. Kalam MA, Humayun M, Parvez N, Yadav S, Garg A, Amin S *et al*.; Release kinetics of modified
44. Pharmaceutical dosage forms: 2007. A Review, Continental J. Pharmaceutical Sciences; 1: 30 – 35.
45. Li SP, Karth MG, Feld KM, Pendharkar CM, Willams RO; 1995. Evaluation of Bilayer tablet machines. A Case study. Drug Dev Ind Pharm. 21(5): 571-590.
46. Shukla S, PandyaV , Bhardia P, Jonwal N, Bhatt D; 2013.Bi-layer Tablet system – An Innovative trend, Asian J Pharm Res.3(2): 49-56.
47. Available from http://www.elan.com/
48. Available from http://en.wikipedia.org/wiki/bi-layer_tablet_press
49. Kumar R, Mohon K .2016. A compressive review on Gastroretaintive drug delivery system.IAJPS ., 3(2) :115-128.
50. Indian Pharmacopoeia.2nd edn, Published by the Controller Publication, Delhi, 1996, 736.
51. Gahiwade HP, Patil MV, Thakare BW, Vinod MT, Patil VR. 2012, Formulation and In-vitro evaluation of Trifluperazine HCl bilayer floating tablets. *International Journal of Pharma and BioScience*. 2, 166-172.
52. The United States Pharmacopoeia, United states Pharmacopoeial convention, Inc., Rockville, MD2000, 19-44.
53. Chaudhari S, Bawaskar M, Shirsat A. 2012, "Formulation and Evaluation of bilayer Floating tablets of Carvedilol Phosphate". *Journal of Drug Delivery and Therapeutics*. 2, 9-19.
54. Formulation and Evaluation of Fixed-Dose Combination of Bilayer Gastroretentive Matrix Tablet Containing Atorvastatin as Fast-Release and Atenolol as Sustained-Release. Available from http://dx.doi.org/1m 0.1155/2014/396106 .
55. Karudumpala S, Gnanaprakash K, Venkatesh B, Sankar P, Balaji G, Vidya Sagar N; 2013. Formulation and Evaluation of Gastro- Retentive Floating Bilayer Tablets of Nifedipine. AJADD, 1(3): 341-357.
56. Hu L, Hu Q, Kong D; 2014.Formulation and in vitro evaluation of Aspirin and Isosorbide 5-mono-nitratesustained bilayer tablets. IJPSR.5(3): 799-804.
57. Sharma SK, Mohan S, Jaimin Mi, Chauhan BS, Chatterjee.2014. A; Formulation and In-Vitro Evaluation of Bilayer Tablets containing Pioglitazone HCl and Gliclazide for Type II Diabetes. Int J Pharm Tech Res 6(2): 607-622.
58. Reddy KR, Srinivas N; 2014 .Formulation and evaluation of bilayered tablets of losartan potassium. Innovations in Pharmaceuticals and Pharmacotherapy,; 2(1): 312-320.
59. Saif AA, Alburyhi MM, Noman MA, a Ala`a Almaktari MA.2014. Formulation and evaluation of trimetazidine hydrochloride and clopidogrel bisulphate multi-unit solid dosage forms Journal of Chemical and Pharmaceutical Research6(2): 421-426.
60. Jamunadhevi V, Sahoo P K, Kailasam P; 2011.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.2(2):170-178.
61. Swamy PV, Kinagi MB, Biradar SS, Gada SN, Shilpa H; 2011.Formulation design and evaluation of bilayer buccal tablets of granisetron hydrochloride. Ind J Pharm Edu Res. 45(3): 242-47.

62. Pattanayak DP, Dinda SC; 2011.Bilayer tablet formulation of Metformin HCl and Glimepiride:A novel approach to improve therapeutic efficacy. Int J Drug Discovery Herb Res.1(1): 1-4.
63. Jain J, Marya BH, Mittal RP, Patel M.2011. Formulation and evaluation of indomethacin bilayer sustained release tablets. Int J Pharm Tech Res; 3(2):1132-38.
64. Mohindeen S, Jyothi B, Pavani S, Satyanarayana T, Kumar SP, Krishna NS. 2011.Formulation and evaluation of bilayered tablets of metformin hydrochloride and atorvastatin calcium. Int J Pharm Sci Rev Res., 10(2): 130-134.
65. Kumar GV, Babu KA, Ramasanay C.2011. Formulation and evaluation of bilayered tablets of cefixime trihydrate and dicloxacillin sodium. Int J PharmTech Res; 3(2): 613-618.
66. Jadhav RT, Patil PH, Patil PR; 2011. Formulation and evaluation of bilayered tablets of piracetam and vinpocetine. J Chem Pharm Res; 3(3): 423-431.
67. Rajendran NN, Natarajan R, Subhashini R, Patel H; 2011.Formulation and evaluation of sustained release bilayer tablets of metformin HCl and pioglitazone HCl. Int J Curr Pharm Res. 3(3): 118-122.
68. Shirsand SB, Swamy PV, Keshavshetti G; 2011.Design and evaluation of atenolol bilayer buccal tablets. J Pharm Sci 1(1): 4-10.
69. Parmar CK, Pednekar PP.2011.Development and evaluation of bilayer tablets of cefuroxime axetil and potassium clavulanate. Int J Pharm Res Dev .3(7): 16-23.
70. Jayaprakash S, Halith SM, Pillai KK, Balasubramaniyam P, Firthouse PUM, Boopathi M.2011. Formulation and evaluation of bilayer tablets of amlodipine besilate and metprolol succinate. Derr pPharmacia Lettre, 3(4):143-154.
71. Atram SC, Udavant YK, Salunke RJ, Neb GB, Shahi SR, Gulecha BS *et al*.2009. Formulation and evaluation of bilayer tablet containing Metoprolol succinate and Amlodipine besylate as a model drug for anti hypertensive therapy. J Pharm Res.2(8):1335-1347.
72. Musle K, Payghan SA, Disuza JI .2011.Fomulation, evaluation and development of bilayer tablet. Int J Pharm Res Dev. 3(10): 80-87.
73. Remya PN, Damodharan N, Kumar CVS; 2010.Formulation and evaluation of bilayered tablets of ibuprofen and methocarbamol. Int J Pharm Tech Res.2(2): 1250-55.
74. John AS, Sathesh B P R, Divakar G, Jangid MK, Purohit KK.2010. Development and evaluation of buccoadhesive drug delivery system for Atorvastatin calcium. J Curr Pharm Res.1: 31-38.
75. Gohel MC, Parikh RK, Nagori SA, Jethwa BA; 2010. Fabrication and evaluation of bi-layer tablet containing conventional paracetamol and modified diclofenac sodium. Indian J Pharm Sci. 72(2):191-196.
76. Hiremath D, Goudanavar P, Azharuddin M, Udupi RH, Sarfaraz M. 2010;.Design and characterization of bilayer controlled release matrix tablets of losartan potassium. Int J Pharm Res. 2(4): 34-39.
77. Ramesh A. 2010. Formulation and evaluation of bilayer sustained release matrix tablets of Metformin HCl and Pioglitazone. Amer-Euras J Sci Res; 5(3):176-182.
78. Kumar VB, Prasad G, Ganesh B, Swathi C, Rashmi A, Reddy AG; 2010. Development and evaluation of guaifenesin bilayer tablet. Int J Pharm Sci Nanotech.,; 3(3):1122-28
79. Naeem MA, Mahmood A, Khan SA, Shahiq Z.2010.Development and evaluation of controlled release bilayer tablets containing microencapsulated tramadol and acetaminophen. Trop J Pharm Res.9(4): 347-54
80. Kulkarni A, Bhatia M.2009. Development and evaluation of regioselective bilayer floating tablets of atenolol and lovastatin for biphasic release profile. Iranian J Pharm Res 8:15-25.
81. Rathod RT, Misra D. 2009. FDC of montelukast with levocetirizine: Focus on bilayer technology. J Indian Med Assoc.107(8): 562-564.
82. Nagaraju R, Kaza R; 2009.Formulation and evaluation of bilayer sustained release tablets of salbutamol and theophylline. Int J Pharm Sci Nanotech; 2(3): 638-46.
83. Kadam VV, Waghmare MU, Venkatpurwar VP, Pokharkar VB; Preparation and evaluation ofglipizide-metformin HCl sustainedrelease bilayertablet.Availableat-www.scientificipca.org/paper/2009/09/15/2009 09151256230A.doc
84. Friedl T, Schepky G inventors; Boehringer Ingelheim USA Corporation, assignee. Bilayer pharmaceutical tablet comprising telmisartan and a diuretic and preparation thereof. US patent 0227802A1
85. Aryal S, Skalko-Basnet N; 2008 .Stability of amlodipine besylate and atenolol in multicomponent tablets of mono-layer and bi- layer types. Acta Pharm. 58: 299-308.
86. Ouali A, Azad AK, inventors; Pharmascience Inc, assignee. Stabilized pharmaceutical composition of nonsteroidal anti-inflammatory agent and a prostaglandin. US patent US6287600 B1.
87. Nirav R, Ajay T, Gaurang P, Vishal V. 2012. The Floating Drug Delivery System And IT`S Impact On Calcium Channel Blocker: A Review Article. *International Journal of Pharmaceutical Research and Development* 3,107 – 131.
88. LiaoJ, Liu P, Dinh S inventors; Emisphere Technologies, assignee. Gastric retention and controlled release delivery system. US Patent Appl US 2008153779, 2008.
89. Wong SLP, Dong L, Edgren ED, Theeuwes F, Gardner IP, Jao F, Wan JJ, Inventors; Alza Corporation, assignee. Prolonged release active agent dosage form adapted for gastric retention. US Patent US 6120803, 2000.
90. Doshi MM, Joshi MD, Mehta .P, inventors, JB. Chemicals & Pharmaceuticals Ltd Pharmaceutical composition for controlled drug delivery system. US Patent Appl US 2003232081,

How to cite this article:

Das S R., Panigrahi B.B and Pani M.K., 2019, A Review: on Bilayer Floating Tablet as Multifunctional Approch of Gastro Retaintive drug Delivery System. *Int J Recent Sci Res.* 10(06), pp. 33255-33267.
DOI: http://dx.doi.org/10.24327/ijrsr.2019.1006.3638