Bilayer Floating Tablets for Gastroretentive Drug Delivery System

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Received March 15, 2013; accepted May 19, 2013

ABSTRACT

Oral delivery of the drug is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in the formulations but has a drawback of non-site specificity and short gastric residence time. In recent years, scientific and technological advancements have been made in the development of novel drug delivery systems by overcoming physiological troubles such as short gastric residence times and unpredictable gastric emptying times. Among several approaches of floating systems, Bilayer floating technology is considered as promising approach. It combines the principle of bilayer technology and floating mechanism. The combined principle of bilayer floating tablet helps to release initial dose from the immediate release layer to reach the plasma concentration and then the floating layer absorbs gastric fluid forming an impermeable colloidal gel barrier on its surface, maintains a bulk density less than unity and thereby remains buoyant in stomach providing steady state concentration of drug in system. This review focuses on bilayer floating tablet technology a new era of gastro retentive drug delivery system, its advantages over conventional tablets and it also summarizes the bilayer tablet presses used in the industry, formulation design and evaluation parameters of bilayer floating tablets.

KEYWORDS: Novel drug delivery systems; floating drug delivery systems (FDDS); Floating layer and immediate release layer.

Introduction

The conventional oral drug delivery has been known for decades was the most widely utilized route of administration among all the routes. It remains as the preferred route of administration in the discovery and development of new drug candidates. The popularity of oral route was attributed to patient acceptance, ease of administration, accurate dosing, cost effective manufacturing methods and generally improved shelf life of the product (Chien, 1992).

Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian Pharmacopoeia, Pharmaceutical tablets are solid, flat or biconvex shaped, unit dosage form, prepared by compressing a drug or a mixture of drugs, with or without diluents. They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration. It was the most popular dosage form and 70% of the total medicines are dispensed in the form of Tablet.

An ideal drug delivery system should be able to show either spatial or temporal delivery of drugs. Spatial delivery relates to targeting a drug to a specified organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An appropriately designed extended release dosage form shows either spatial or temporal delivery of drugs.

An effective oral drug delivery depends upon gastric emptying time, gastro-intestinal transit. However, it possess several physiological limitations such as variable GI transit and gastric emptying time leading to non-uniform absorption profiles, incomplete drug release and short residence time of dosage form in the stomach. One of the oral drug delivery system which meant to prolong the residence time of dosage form in the stomach is Gastro-retentive drug delivery system (GRDDS). The successful development of gastro-retentive drug delivery systems requires an understanding of two aspects of the system, namely:

1. The physiochemical characteristics of the drug
2. Anatomy and physiology of GIT and characteristics of dosage forms.

Good fundamental understanding of the anatomic and physiological characteristics of the human GIT is required to modulate the gastrointestinal transit time of a drug through FDDS for maximal gastrointestinal absorption of drugs and site-specific delivery.

Anatomy and Physiology of Stomach

Anatomy

The stomach is J-shaped organ located in the upper left hand portion of the abdomen just below the
diaphragm. It occupies a portion of the epigastric and left hypochondriac region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Due to its small surface area very little absorption takes place from the stomach. (Toratora et al., 2010 and Guyton et al., 1996). Anatomy of the stomach was shown in Figure 1.

Fig. 1. Anatomy of the stomach.

Anatomically the stomach is divided into 4 main regions:
1. Cardia
2. Fundus
3. Body and
4. Antrum (pylorus).

The main function of the Fundus and body is storage, whereas that of cardia is mixing or grinding. The fundus adjusts the increased volume during eating by relaxation of the fundus muscle fibers. The fundus also exerts a steady pressure on the gastric contents pressing them towards the distal region, to pass through pyloric sphincter into the small intestine. The pylorus (antrum) is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.

Physiology

Various physiological factors like the absorption ability, presystemic clearance, gastric motility, gastrointestinal transit time and gastrointestinal emptying time will have an influence on the bioavailability of drug from the dosage form.

Absorption ability

The absorption capability of various segments of gastrointestinal tract differs from each other, i.e. most of the absorption takes place in small intestine and lesser extent in colon and stomach. Unless drugs are absorbed equally both in colon and small intestine, the duration of action for most of the drugs being less than 3-8 hours. This would be the major limiting factor for sustained release and controlled release drug delivery systems.

Presystemic clearance

For drugs that are absorbed equally well throughout the gastrointestinal tract bioavailability was significantly reduced by the site-specific changes in presystemic clearance. Degradation of the drug also occurs due to hydrolysis in the stomach, enzymatic digestion, metabolism in the brush border of gut wall and by microorganisms. Such degradation may lead to high variation in plasma drug concentration and poor absorption of drug in to the systemic circulation.

Gastric motility

Gastric emptying occurs during fasting as well as fed states. During the fasting state an interdigestive series of electrical events take place, which cycles through stomach and intestine every 2 to 3 hours. This is called the Interdigestive myoelectric cycle or Migrating myoelectric cycle (MMC), which is further divided into four phases as described by Wilson and Washington. (Wilson KRW et al., 1996 and Wilson CG et al., 1989) The Interdigestive myoelectric cycle was shown in Figure 2.

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
2. Phase II (Pre-burst phase) lasts for 40 to 60 minutes with intermittent contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of two consecutive cycles.

Fig. 2. Interdigestive myoelectric cycle or migrating myoelectric cycle (MMC).

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.

There is a marked difference between motility in the fasting state and the fed state: the motoric activity in the fasting state, termed Interdigestive myoelectric motor complex (IMMC), is a 2-h cycle of peristaltic activity that is generated in the stomach and progresses to the ileocecal junction. Its aim was to clear the stomach and small intestine of indigested debris, swallowed saliva and sloughed epithelial cells.
Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically two complications that of short gastric residence time and unpredictable gastric emptying rate. (Wong, 2000 and Desai et al., 1993)

Gastrointestinal Transit Time

Food content remains in each segment of the gastrointestinal tract for different periods of time. The resident time for both liquid and solid foods in each segment of the gastrointestinal tract is as reported by park (Table 1).

<table>
<thead>
<tr>
<th>Segment</th>
<th>Liquid</th>
<th>Solid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>10-30 min</td>
<td>1 – 3 hrs</td>
</tr>
<tr>
<td>Duodenum</td>
<td>&lt; 60 sec</td>
<td>&lt; 60 sec</td>
</tr>
<tr>
<td>Jejunum and Ileum</td>
<td>3 hrs ± 1.5 hrs</td>
<td>4 hrs ± 1.5 hrs</td>
</tr>
<tr>
<td>Colon</td>
<td>--------</td>
<td>20 – 50 hrs</td>
</tr>
</tbody>
</table>

Various factors affecting the gastric emptying time are:

State of the stomach: Gastric emptying time depends upon the fed state of the stomach, which increases the gastric emptying time as compared to an unfed state.

Circadian rhythms: These are increased in daytime and less during night and also affect the gastric retention time (GRT).

Size of the dosage form: Greater the energy content of the meal (carbohydrate and high fat content), longer the duration of emptying.

Density of the oral dosage form: The density of the gastric fluid is reported to be 1.2 g/cm³. The density of the dosage form should be less than this for the buoyancy so that it is retained in the stomach for longer period of time.

Diseased state: State of the stomach also affects the environment for the dosage form in case of ulcers, flatulence and spasms.

Drug therapy: Plays an important role in gastric emptying e.g. prokinetic drugs like cisapride and mosapride increase the gastric emptying time.

Age: Increase in age decreases the gastric motility thereby increasing the gastric emptying time.

Posture: It was seen that the supine posture on the right side showed better results than on the left side. (Mojaverian et al., 1988 and Mazer et al., 1988)

Gastro-Retentive Drug Delivery System (GRDDS)

Gastro-retentive drug delivery systems (GRDDS) or Hydro-dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Prolonged gastric retention improves oral bioavailability of drug, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. GRDDS has applications for local drug delivery to the stomach and proximal small intestines. Thus Gastric retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

Drug Candidates Suitable for Grdds

Appropriate candidates for controlled release gastro retentive dosage forms are (Ami1 et al., 2012):

1. Drugs that have narrow absorption window in GI tract, e.g. riboflavin, levodopa, p-aminobenzoic acid, furosemide etc.
2. Drugs those are locally active in the stomach e.g., antacids and misoprostol etc.
3. Drugs that exhibit low solubility at high pH values e.g. Verapamil, Chlordiazepoxide, cinnarizine etc.
4. Drugs that disturb normal colonic microbes (e.g. antibiotics used for the eradication of Helicobacter pylori, such as tetracycline, clarithromycin, amoxicillin)
5. Drugs that degrade in the colon, e.g. Ranitidine HCl and metronidazole and captopril.
6. Drugs which cause gastric irritation e.g. NSAID's

Drugs those are Unsuitable for Grdds

1. Drugs that have limited acid solubility e.g. Phenytoin etc.
2. Drugs that suffer instability in gastric environment e.g. Erythromycin etc.
3. Drugs intended for selective release in the colon e.g. 5-Amino salicylic acid, Corticosteroids etc. (Ami1 et al., 2012)

Factors Affecting Gastric Residence Time of Grdds

Formulation Factors

Size of Formulation

Retention of floating dosage forms in stomach depends on the size of tablets. Small tablets are emptied from the stomach during the digestive phase, but large ones are expelled during the house keeping waves (Oth et al., 1992).

Density

Density is the main factor affecting the gastric residence time of dosage form. A buoyant dosage form having a density less than that of the gastric fluid (< 1.0 g/ml) floats, since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period. However, the floating force kinetics of such dosage form has shown that the bulk density of a dosage form is not the most appropriate parameter for describing its buoyancy capabilities (Gergogiannis et al., 1993).
Shape

The shape of dosage form is one of the factors that affect its gastric residence time. Six shapes (ring, tetrahedron, cloverleaf, string, pellet, and disk) were screened in vivo for their gastric retention potential. The tetrahedron (each leg 2 cm long) rings (3.6 cm in diameter) exhibited nearly 100% retention at 24 hr (Cargill et al., 1988).

Viscosity grade of polymer

Drug release and floating properties of FDDS are greatly affected by viscosity of polymers and their interaction. Low viscosity polymers (e.g., HPMC K100 M) were found to be more beneficial than high viscosity polymers (e.g., HPMC K4M) in improving floating properties. In addition, a decrease in the release rate was observed with an increase in polymer viscosity (Li et al., 2003).

Idiosyncratic Factors

Gender

Women have slower gastric emptying time than do men. Mean ambulatory GRT in males (3.4±0.4 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface (Patel et al., 2007).

Age

Low gastric emptying time is observed in elderly than do in younger subjects. Intra-subject and inter-subject variations are also observed in gastric and intestinal transit time. Elderly people, especially those over 70 years have a significantly longer GRT (Mojaverian et al., 1988).

Posture

Upright position: An upright position protects floating dosage forms against postprandial emptying because the dosage form remains above the gastric contents irrespective of its size. Floating dosage forms show prolonged and more reproducible GRTs while the conventional dosage form sink to the lower part of the distal stomach from where they are expelled through the pylorus by pyloric peristaltic movements (Timmermans et al., 1989).

Supine position: This position offers no reliable protection against early and erratic emptying. In supine subjects large dosage forms (both conventional and floating) experience prolonged retention. The gastric retention of floating forms appear to remain buoyant anywhere between the lesser and greater curvature of the stomach. (Chawla et al., 2003).

Concomitant Intake of Drugs

Drugs such as Prokinetic agents (e.g., Metoclopramide and cisapride), Anti-Cholinergics (e.g., atropine or propantheline), Opiates (e.g., codeine) may affect the performance of FDDS. The co-administration of GI-motility decreasing drugs can increase gastric emptying time (Chawla et al., 2003).

Feeding Regimen

Gastric residence time increases in the presence of food, leading to increased drug dissolution of the dosage form at the most favourable site of absorption. A GRT of 4-10 h has been reported after a meal of fats and proteins (Muller-Lissner et al., 1981)

Classification of Gastro-Retentive Drug Delivery System

Gastro Retentive drug delivery systems are classified based on the mechanism of drug release. The classification of GRDDS is as follows. (Bardonett et al., 2006 and Nayak et al., 2010)

<table>
<thead>
<tr>
<th>Classification of Gastro-Retentive Drug Delivery System</th>
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<tbody>
<tr>
<td>High density Floating Bio-adhesive Swelling &amp; Expanding</td>
</tr>
</tbody>
</table>

High density systems

These systems, which have a density of ~3 g/cm³, are retained in the rugae of stomach and capable of withstanding its peristaltic movements. The only major drawback with these systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and achieve required density of 2.4-2.8 g/cm³. Diluents such as barium sulphate (density= 4.9), zinc oxide, titanium oxide, and iron powder must be used to manufacture such high-density formulation.

Swelling and expanding systems

These systems are also called as “Plug type system”, since they exhibit tendency to remain logged in the pyloric sphincters. These polymeric matrices remain in the gastric cavity for several hours even in fed state (Figure 3).

![Fig. 3. Swellable tablet in stomach](image-url)
By selection of polymer with the proper molecular weight and swelling properties controlled and sustained drug release can be achieved. Upon coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is a result of the presence of physical-chemical cross links in the hydrophilic polymer network. These cross link prevents the dissolution of polymer and thus maintains the physical integrity of the dosage form. A high degree of cross linking retards the swelling ability of the system and maintains its physical integrity for prolonged period. On the other hand, a low degree of cross linking results in extensive swelling followed by the rapid dissolution of polymer.

**Bio/Muco – Adhesive Systems**

Bio-adhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug absorption in a site specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Gastric mucoadhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastroretentive force. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan and gliadin etc.

**Floating systems**

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal (Figure 5) (Shah et al., 2009).

Fig. 5 Mechanism of floating systems.

To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side (Figure 5 (b)). This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intra-gastric buoyancy capability variations.

\[
F = F_{buoyancy} - F_{gravity} = (D_f - D_s) g v
\]  

Where,

- \( F \) = Total vertical force
- \( D_f \) = Fluid density,
- \( D_s \) = Object density,
- \( v \) = volume and
- \( g \) = acceleration due to gravity
Types of Floating Drug Delivery Systems

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in the development of FDDS (Singh et al., 2010, Garg et al., 2008, Klausner et al., 2003, Whitehead L et al., 2010, Gopalakrishnan S et al., 2011 and Yyas SP et al., 2003).

Non-Effervescent Systems

Colloidal gel barrier system

Sheth and Tossounian first designated this ‘hydro-dynamically balanced system’. Such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption. This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloids, e.g., hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose (HPMC), polysaccharides and matrix-forming polymer such as polycarbophil, polyacrylate and polystyrene. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface.

Micro porous compartment system

This technology is based on the encapsulation of a drug reservoir inside a Micro porous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the flotation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

Alginate beads

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40°C for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hours.

Hollow microspheres / Microballoons

Hollow microspheres loaded with drug in their outer polymer shelf were prepared by a novel emulsion solvent diffusion method. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40°C. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The micro balloon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 h.

Gas Generating (Effervescent) Systems

Effervescent systems include use of gas generating agents, carbonates (sodium bicarbonate) and other organic acid (citric acid and tartaric acid) to produce carbon dioxide (CO2) gas, thus reducing the density of the system and making it to float on the gastric fluid. These effervescent systems further classified into two types.

Intra gastric single layer floating system

These are formulated by mixing the CO2 generating agents and the drug with in the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

Intra gastric bilayered floating tablets

A bi-layer tablet contain two layer one immediate release layer which releases initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

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 pill like balloon and float as the density decreases.

Volatile Liquid / Vacuum Containing Systems

Intragastric Floating Gastrointestinal Drug Delivery System

This system can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a micro porous compartment (Figure 6).

Fig. 6. Intra gastric floating gastrointestinal drug delivery device.
Inflatable Gastrointestinal Delivery Systems

In these systems an inflatable chamber is incorporated, which contains liquid that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in floating position. The drug continuously released from the reservoir into the gastric fluid (Figure 7).

Fig. 7. Inflatable gastrointestinal delivery system.

Intragastric Osmotically Controlled Drug Delivery System

It is comprised of an osmotically controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components: drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapor and liquid and it has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi-permeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semi-permeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and turns in forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release in solution form through the delivery orifice. The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach (Figure 8).

Fig. 8. Intragastric osmotically controlled drug delivery system.

Advantages of FDDS

1. The Floating systems are advantageous for drugs meant for local action in the stomach. E.g. antacids.
2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence FDDS may be useful for the administration of aspirin and other similar drugs.
3. Administration of prolonged release floating dosage forms such as tablet or capsules will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid and it would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
4. Gastric retention will provide advantages such as the delivery of drugs with narrow absorption window in the small intestinal region.
5. When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.
6. By formulating floating drug delivery system of a drug, the dose of drug can be reduced. (Sawicki 2001; Babu et al., 1990)

Disadvantages of FDDS

1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
3. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
4. Some drugs present in the floating system cause irritation to gastric mucosa.

**Brief Discussion on Bi-Layer Floating Tablets**

The term Bilayered tablets refers to tablet containing subunits that may be either the same (homogeneous) or different (heterogeneous). Bilayer tablets allows for designing and modulating the dissolution and release characteristics. These tablets are composed of two layers of granulation compressed together. They have appearance of a sandwich because the edges of each layer are exposed. (Patel M et al., 2010)

Bilayer Floating tablets are prepared with one layer of drug for immediate release which releases initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach (Figure 9 and Figure 10) (Shrikant et al., 2012 and Ostwal et al., 2012).

**Advantages of Bilayer-Floating tablets over conventional tablets**

1. Better patient compliance, therapeutic efficacy and provide good treatment efficiency
2. Reduced dosing intervals, number of dosing and number of dosage form
3. Incompatible drugs are given by separating these drugs by inert materials
4. The fluctuations in plasma drug concentration are minimized, and concentration- dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.
5. The efficacy of the medications administered utilizing the sustained release principle of floating formulation has been found to be independent of the site of particular medicaments.
6. Drugs that have poor bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

**Press Designed for Quality Bi-layer Tablets**

Several pharmaceutical companies are currently developing bi-layer tablets for a variety of reasons like to improve patient compliance, to reduce number of doses of drug, to decrease capital investment etc. The development and production of quality bi-layer tablets needs to be carried out on purpose-built tablet presses to overcome common bi-layer problems, such as layer-separation, insufficient hardness, inaccurate individual layer weight control, cross contamination between the layers, reduced yield, etc.

**Ideal properties for bilayer tablets press:**

To produce a quality bilayer 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,
- Preventing cross-contamination between the two layers,
- Producing a clear visual separation between the two layers and high yield, Accurate and individual weight control of the two layers

**Bi-Layer Compression Basics:**

(a) Initial layer die filling and compaction.
(b) Initial layer compaction showing the predominant stress transmission profile.
(c) Density profile of initial layer before die filling of the final layer.
(d) Final layer die filling and compaction.
(e) Final layer compaction showing the predominant stress transmission profile.
(f) Density profile of bilayer tablet before ejection.
Ejection of a bilayer tablet, dashed arrows show the postulated radial expansion due to energy dissipation (Aulton, 2002) (Figure 11).

**Bi-Layer Tablet Presses used in Industry**

Bilayer tablets are prepared by compressing two different blends fed into a die succession, one on the top of another, in layers. Each layer comes from separate fed frame with individual weight control (Divya et al., 2011). Rotary tablet press can be set up for two layers.

**RoTab Bilayer**

Compactest bilayer rotary tablet press on the market is with highly sophisticated R&D and production functions. Noise and vibration is reduced for optimum operation in the lab. This tablet press is easy to maintain by its automatical punch lubrication and with interval setting. It is optimized for operation with only one occupied punch station and easy sampling for first layer (weight adjustment). Optifiller for 1st and 2nd tablet layer with special dust extraction rails helps to minimize cross-contamination and a touch screen display allows operating and controlling the machine easily by the operator and visualizes all machine parameters such as compaction forces, speeds, tablet production etc. (Figure 12)

**Piccola Bilayer Tablet Press**

This rotary press was designed to represent two layer tablet production conditions at small scale, according to the needs of new product development. The Piccola Bilayer tablet press is a 10 station rotary tablet press. The press uses standard B or D tooling, which allows the employment of the same punches used in tablet production. The Piccola Bi-layer tablet press, with its larger turret diameter, pre-compression, and variable speed allow for realistic scale up to larger rotary presses. The dual paddle feed system helps maintain uniform die fill and represents production equipment. (Figure 13).

**TABLE 2**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>B-tooling</th>
<th>D-tooling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Stations</td>
<td>9-14</td>
<td>9-13</td>
</tr>
<tr>
<td>Motor Horsepower</td>
<td>5HP</td>
<td>5HP</td>
</tr>
<tr>
<td>Maximum tablet diameter</td>
<td>16 mm</td>
<td>25 mm</td>
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<tr>
<td>Maximum compression force 1st layer</td>
<td>10 Ton</td>
<td>10 Ton</td>
</tr>
<tr>
<td>Maximum compression force 2nd layer</td>
<td>10 Ton</td>
<td>10 Ton</td>
</tr>
<tr>
<td>Depth of Fill</td>
<td>18.5 mm first layer</td>
<td>18.5 mm first layer</td>
</tr>
<tr>
<td>Upper punch penetration</td>
<td>2-8 mm</td>
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<tr>
<td>Max Production Rate</td>
<td>42,000 TPH</td>
<td>39,000 TPH</td>
</tr>
</tbody>
</table>

**Mini Bi-Layer Press (for compression of double layer tablet)**

It is designed to represent two-layer tablet productions at a small scale. Its larger turret diameter & variable speed allows for realistic scale up to large rotary presses. It has two forces feeder system which helps to
maintain uniform die fill and represents production equipment. Pressure compensation hydraulic system is present to regulate the pressure and tablet thickness & weight adjustment settings are present outside the machine. It was designed as per cGMP norms. Lower punch seal is present to avoid jamming of the lower punches and transparent Guards at compression zone with safety switches are present.

**KORSCH XM 12 Bi-Layer Tablet Press**

It is a small-scale press which is ideal for product development, scale-up, clinical trials, and midrange production. The bi-layer execution, single-layer conversion kit, and exchangeable turret offers unprecedented flexibility. The XM 12 Bi-Layer Tablet Press offers a new standard in GMP with extreme accessibility to the compression zone and combinations of quick disconnects and smooth surfaces permit fast cleaning and changeover. The XM 12 Bi-Layer Tablet Press features a retractable second layer feeder that permits automated first layer sampling at production speeds. The first layer sampling capability also offers a hardening feature, in which the main compression station will automatically compress the first layer tablet for in-process measurement. The two feeders are configured with an integrated dust extraction manifold, which cleans the die table and completely eliminates any potential for cross-contamination.

**MODUL™ P rotary tablet press with Bi-layer ECM40**

GEA Courtys's MODUL™ P, the smallest tablet press in the MODUL™ range, is now available with an Exchangeable Compression Module (ECM) for bi-layer tablet (bilayer) production. The MODUL™ P with bi-layer ECM is the first press to enter the market that enables continuous bi-layer tabletting on a small scale. It is the perfect solution to your bi-layer formulation development, clinical trial and other small-scale production needs.

**Compression Force of Bilayer Tablets**

Since the material in the die cavity is compressed twice to produce a bi-layer tablet, compressed first with layer one followed by both the layers, the compression force affects the interfacial interaction and adhesion between the two layers. A certain amount of surface roughness of the initial layer is required for particle interlocking and adhesion with the second layer. As the surface roughness of the first layer is reduced, the contact area for the second layer is significantly reduced at the interface and makes the adhesion weaker. Immediately after final compaction, the compressed second layer may release the stored elastic energy unevenly and may produce crack on the first layer which could act as a stress concentrator and eventually making the tablet interface weaker. This may result in capping or de-lamination of the tablet along the interface either during manufacturing or immediately after the level of compression. The compression force used in the first layer compaction determines the degree of surface roughness of the first layer. The higher the first layer compression force, the lesser the surface roughness resulting in reduced adhesion with the second layer. Therefore, for a given final compression force the strength of interfacial adhesion decreases with the increasing first layer compression force. It implies that the extent of plastic/elastic deformation of the first layer has profound effect on the strength of the interface. Thus, understanding the interaction and adhesion behaviour between different layers composed of various ingredients with differing physico-chemical properties during compaction is critical to understand the failure mechanisms of bi-layer tablets. Understanding of material attributes of the excipients and API that undergoes compression and compaction is decisive in predicting the interaction.

**Immediate Release Tablets**

Immediate release tablets are designed to disintegrate and release the drug in absence of any controlling features such as coatings or other formulation techniques. Despite a rising interest in controlled-release drug delivery systems, the most common tablets are those intended to be swallowed whole, disintegrating and releasing their medicaments rapidly in the gastrointestinal tract (Anisul et al., 2006).

A disintegrant is a substance in a tablet formulation that enables the tablet to break up into smaller fragments upon contact with gastrointestinal fluids. Such a rapid rupture of the tablet matrix increases the surface area of the tablet particles, thereby increasing the rate of absorption of the active ingredient and producing the desired therapeutic action. The proper choice of disintegrant and its consistency of performance are critical to formulation development of immediate release tablets. In the past, starch was one of the most widely used, inexpensive, and effective tablet disintegrant. A high concentration of starch is required to bring about effective disintegration. Scientists search for disintegrating agents with efficient disintegrating properties at relatively low concentrations has led to the development of some new compounds with excellent disintegrating properties.

**Superdisintegrants**

Generally used at a low level in the solid dosage form, typically 1–10% by weight relative to the total weight of the dosage unit (Table 3).

**TABLE 3**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Name</th>
<th>Brand Name</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Crospovidone</td>
<td>Kollidon, Polyplasdone XL</td>
<td>BASF, ISP's</td>
</tr>
<tr>
<td>2</td>
<td>Crosscarmellose</td>
<td>Ac-Di-Sol</td>
<td>FMC Bio Polymer</td>
</tr>
<tr>
<td>3</td>
<td>Sodium starch glycolate</td>
<td>Primojel</td>
<td>DMV International</td>
</tr>
</tbody>
</table>
Floating Tablet

Mechanism of drug release (Matrix diffusion controlled release system)

In this system, rate of drug delivery is controlled by molecular diffusion of the drug molecules across the barrier medium within or surrounding the delivery system. The rate limiting step in these formulations is liquid penetration into the matrix unless channeling agents are included to promote the permeation of the polymer matrix by water. This allows drug dissolution and diffusion from the channels created in the matrix. A controlled release matrix system consists of active agent and the polymer matrix or matrices that regulate its release.

In selecting polymeric matrix the following design criteria should be considered: Molecular weight and chemical functionality of the polymer must allow the proper diffusion and release of the specific active agent. Polymer functional group should not react with the chemicals incorporated with the active agent. It must not decompose on storage or during the useful shelf life of the device and it must be easily manufactured or fabricated into the desired product and should allow incorporation of large amount of active agent in the product without sacrificing its mechanical properties. The cost of the polymer should not be high. In this type of preprogrammed drug delivery system the drug reservoir was prepared by homogenously dispersing drug particles in a rate controlling polymer matrix fabricated from either hydrophobic or a hydrophilic polymer. The drug dispersion in the polymeric matrix is accomplished either by Blending a therapeutic dose of finely ground drug particles with a liquid polymer or a highly viscous base polymer, followed by cross linking of the polymer chains, or Mixing drug solids with a rubbery polymer at an elevated temperature. The resultant drug-polymer dispersion is then molded or extruded to form a drug delivery device of various shapes and sizes designed for specific application. It can also be fabricated by dissolving the drug and the polymer in a common solvent, followed by solvent evaporation at an elevated temperature and / or under a vacuum. The rate of drug release from this polymer matrix diffusion controlled drug delivery system is time dependent and is defined at steady state by

\[ Q_{t/2} = \left( \frac{2ACRD_p}{\Delta t} \right)^{1/2} \]

Where \( A \) is the initial drug loading dose in the polymer matrix;
\( C_R \) is the drug solubility in the polymer, which is also the drug reservoir concentration in the system,
\( D_p \) is the diffusivity of the drug molecules in the polymer matrix.

The release of drug molecules from this type of controlled release drug delivery systems is controlled at a preprogrammed rate by controlling the loading dose, polymer solubility of the drug and its diffusivity in the polymer matrix (Figure 14).

Preparation of drug embedded matrix tablet by the direct compression of a blend of drug retardant materials and additives is one of the least complicated approaches for delivery of drug in a temporal pattern into the systemic circulation. A wide array of polymers has been employed as drug retarding agents.

Materials used as retardants in matrix tablets are classified by three categories (Table 4).

<table>
<thead>
<tr>
<th>S.No</th>
<th>Matrix Characteristics</th>
<th>Materials</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Insoluble inert materials</td>
<td>Polyethylene, Polyvinylchloride, Methacrylate, Methacrylate-co-polymer, Ethyl cellulose etc.</td>
</tr>
<tr>
<td>2</td>
<td>Insoluble Erodible materials</td>
<td>Carnauba wax, Stearylalcohol, Stearicacid, Polyethylene glycol etc</td>
</tr>
<tr>
<td>3</td>
<td>Hydrophilic materials</td>
<td>Methylcellulose, Hydroxyethylcellulose, Sodium carboxymethylcellulose, Sodium alginate, Carboxyl polyethylene, Hydroxy propyl methyl cellulose.</td>
</tr>
</tbody>
</table>

Formulation Design of Bilayer Floating Tablets

The bilayer floating tablet was prepared by direct compression (or) wet granulation (or) dry granulation method. Development of bilayer floating tablet was carried out in three stages:

Stage I: Immediate release tablets and Floating tablets (two layers of bilayer floating tablet) were formulated separately using different concentration of Super disintegrants and polymers in different ratios.

Stage II: Optimization of individual layers by in-vitro studies and statistical methods.

Stage III: Bilayer Floating tablet was prepared using optimized formulae.

Preparation of Bilayer Floating tablet:

From the optimized immediate release and floating layer, Bilayer floating tablets was prepared. First the extended release layer was pre-compressed on compression machine and then immediate release layer was loaded on top of pre-compressed layer and punched on compression machine automatically.
Evaluation Parameters

Trial batches of different formulations of immediate release tablets, Floating tablets and Bilayer floating tablets were prepared and evaluated for the following parameters.

Pre-Compression Evaluation Parameters

Angle of repose (θ)

Angle of repose was determined using fixed funnel method. The blend was poured through a funnel than can be raised vertically until a maximum cone height (h) was obtained (Bhavesh et al., 2008) Radius of the heap (r) was measured and the angle of repose (θ) was calculated using the formula,

\[ \theta = \tan^{-1} \left( \frac{h}{r} \right) \]

Bulk density

Bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (V) and mass of the powder (M) was determined (Bhavesh S et al., 2008). The bulk density was calculated using formula,

\[ \text{Bulk Density} = \frac{M}{V} \]

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume occupied in the cylinder (Vt) and the mass (M) of the blend was measured (Bhavesh et al., 2008). The tapped density was calculated using formula,

\[ \text{Tapped Density} = \frac{M}{V_t} \]

Hausner's ratio

The Hausner's ratio is an indirect index of ease of powder flow (Bhavesh et al., 2008). It is calculated by following formula,

\[ \text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \]

Compressibility index

The simplest way for measurement of free flow of powder is compressibility, which is an indication of the ease with which a material can be induced to flow (Bhavesh et al., 2008). It is given by compressibility index (I) which is calculated as follows,

\[ I = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \]

Post-Compression Evaluation Parameters

General Appearance

The morphological characterization of bilayer floating tablets includes size, shape and colour. Presence or absence of odour, taste and surface texture was determined organoleptically (Mehta et.al., 1997).

Thickness

The control of physical dimension of the tablet such as thickness is essential for consumer acceptance and to maintain uniformity of tablet weight. (Gerbino PP, 2005) Thickness of the bilayer floating tablets was tested using calibrated dial-caliper (Mitutoyo, Japan) in mm. The tablet thickness was controlled within a ± 5% variation.

Hardness test

The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of the formulation was determined using Monsanto or Pfizer hardness tester. It is expressed in kg/cm² (Gerbino, 2005). Six tablets according to USP Guidelines were randomly picked and analyzed for hardness. For bilayer floating tablets the hardness is in the range of 5-7 kg/cm²

Friability test

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 (Gerbino, 2005). The following formula can be used to calculate friability:

\[ F = \frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}} \times 100 \]

% Friability of tablets less than 1% are considered acceptable.

Weight variation test

Various standard procedures are there for weight variation test in various official books (Gerbino, 2005). One of the standard procedure according to USP is:

Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation is allowed in the weight of a tablet by U.S. Pharmacopoeia. The allowed percentage deviation in weight variation is given in Table 5

<table>
<thead>
<tr>
<th>Average weight of a tablet</th>
<th>Percentage deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>130 mg or Less</td>
<td>±10</td>
</tr>
<tr>
<td>More than 130 mg and less than 324 mg</td>
<td>±7.5</td>
</tr>
<tr>
<td>324 mg or More.</td>
<td>±5</td>
</tr>
</tbody>
</table>

In vitro disintegration time

The process of breakdown of a tablet into smaller particles is called as disintegration. The in vitro disintegration time of a tablet was determined using
disintegration test apparatus as per IP specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 1.2 (simulated gastric fluid) maintained at 37 ± 2 °C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 1.2 maintained at 37 ± 2 °C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded (Gerhino PP, 2005).

**Floating property study**

The time taken for dosage form to emerge on surface of medium is called as buoyancy lag time (BLT). Duration of time by which the dosage form constantly emerges on surface of medium called Total floating time (TFT) (Nurten OZ et al., 2010).

Tablets were placed in a 400 ml flask of pH 1.2, time needed to go upward and float on surface of the liquid and floating duration were determined.

**Water uptake study**

The swelling of the polymers can be measured by their ability to absorb water and swell. The swelling property of the formulation was determined by various techniques. The water uptake study of the tablet was done using USP dissolution apparatus II. (Mahesh DC et al., 2006). The medium used was distilled water, 900 ml rotated at 50 rpm. The medium was maintained at 37±0.5 °C throughout the study. After a selected time intervals, the tablets were withdrawn, blotted to remove excess water and weighed. Swelling characteristics of the tablets were expressed in terms of water uptake (WU) as:

\[ WU (\%) = \frac{\text{Weight of swollen tablet} - \text{initial weight of tablet}}{\text{initial weight of tablet}} \times 100 \]

**In vitro dissolution studies**

Dissolution of the tablets was carried out on USP XXIII dissolution type II apparatus using paddle. The tablet was fixed to the paddle by hydration mechanism. Dissolution medium was filled in a dissolution vessel and the temperature of the medium was set at 37 ± 0.5°C. The withdrawn samples were diluted filtered and analyzed on UV spectrophotometer. Percentage cumulative drug release was calculated (Patel et al., 2006).

**X-Ray/Gamma scintigraphy**

For in vivo studies, X-Ray/Gamma Scintigraphy is the main evaluation parameter for floating dosage form. In each experiment, the animals are allowed to fast overnight with free access to water, and a radiograph is made just before the administration of the floating tablet to ensure the absence of radio-opaque material. Visualization of dosage form by X-ray is due to the inclusion of a radio-opaque material. The formulation is administered by natural swallowing followed by 50 ml of water. The radiographic imaging is taken from each animal in a standing position, and the distance between the source of X-rays and the animal should be kept constant for all imaging, so that the tablet movement could be easily noticed. Gastric radiography was done at 30-min time intervals for a period of 5 h using an X-ray machine.

Gamma scintigraphy is a technique whereby the transit of a dosage form through its intended site of delivery can be non-invasively imaged in vivo via the judicious introduction of an appropriate short lived gamma emitting radioisotope. The inclusion of a γ-emitting radionuclide in a formulation allows indirect external observation using a γ-camera or scintiscanner. But the main drawback of γ-sciintigraphy are the associated ionizing radiation for the patient, the limited topographic information, low resolution inherent to the technique and the complicated and expensive preparation of radiopharmaceutical (Whitehead L et al., 1998 and Gansbeke BV et al., 1991).

**Pharmacokinetic studies**

Pharmacokinetic studies include AUC (Area under Curve), Cmax, and time to reach maximum plasma concentration (Tmax) were estimated using a computer. Statistical analyses were performed using a Student t test with p, 0.05 as the minimal level of significance (Klausner EA et al., 2003).

**Specific Gravity**

Displacement method is used to determine the specific gravity of floating system using benzene as a displacing medium

**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 (Table 6).

<table>
<thead>
<tr>
<th>Study</th>
<th>Storage condition</th>
<th>Minimum time period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long term</td>
<td>25 °C ± 2°C/60% RH ± 5% RH</td>
<td>12 months</td>
</tr>
<tr>
<td>Intermediate</td>
<td>30 °C ± 2°C/65% RH ± 5% RH</td>
<td>6 months</td>
</tr>
<tr>
<td>accelerated</td>
<td>40 °C ± 2°C/75% RH ± 5% RH</td>
<td>6 months</td>
</tr>
</tbody>
</table>

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.

**List of the drugs Fabricated as a Bilayer Floating Tablets**

List of drugs are given in the Table 7.
TABLE 7
List of drugs, super disintegrants and polymers fabricated as bilayer floating tablets.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Drug</th>
<th>Immediate Release Layer (Super Disintegrants)</th>
<th>Floating Layer (Rate Controlling Polymers)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Metformin Hydrochloride</td>
<td>Sodium Starch glycolate (SSG), Microcrystalline cellulose (MCC)</td>
<td>HPMC K4M, HPMC K15M</td>
<td>Chandira et al., 2012</td>
</tr>
<tr>
<td>2</td>
<td>Amoxicillin trihydrate</td>
<td>Sodium Starch glycolate (SSG)</td>
<td>HPMC K4M, HPMC K15M, Sodium CMC</td>
<td>Patil et al., 2011</td>
</tr>
<tr>
<td>3</td>
<td>Ciprofloxacin HCl</td>
<td>Sodium Starch glycolate (SSG), Cross povidone</td>
<td>HPMC K100M, HPMC K15M, Carbopol 934p</td>
<td>Patel et al., 2012</td>
</tr>
<tr>
<td>4</td>
<td>Famotidine</td>
<td>Cross carmellose sodium</td>
<td>HPMC K4MCR, HPMC K100LV, Sodium alginate</td>
<td>Barhate et al., 2010</td>
</tr>
<tr>
<td>5</td>
<td>Ranitidine</td>
<td>----</td>
<td>HPMC K4M, HPMC K100, HPMC E15, Carbopol 934</td>
<td>Kumar et al., 2010</td>
</tr>
<tr>
<td>6</td>
<td>Tramadol Hydrochloride</td>
<td>Cross carmellose sodium, Microcrystalline cellulose (MCC), Spray dried Mannitol</td>
<td>HPMC K4M, HPMC K15M, HPMC K100, Sodium alginate, PEO</td>
<td>Sarfaraz et al., 2012</td>
</tr>
<tr>
<td>7</td>
<td>Domperidone maleate</td>
<td>Sodium Starch glycolate (SSG), Cross carmellose sodium, Microcrystalline cellulose (MCC), Cross povidone</td>
<td>HPMC K100M</td>
<td>Kumar et al., 2011</td>
</tr>
<tr>
<td>8</td>
<td>Metoprolol Succinate (IRL), Trimetazidine HCl (FL)</td>
<td>Sodium Starch glycolate (SSG)</td>
<td>Ethyl cellulose, xanthan gum, HPMC K100M, HPMC K4M</td>
<td>Santhanalakshmi et al., 2011</td>
</tr>
<tr>
<td>9</td>
<td>Indomethacin</td>
<td>AvicelPH-112, Aerosil</td>
<td>HPMC K4M</td>
<td>Jitendra et al., 2011</td>
</tr>
<tr>
<td>10</td>
<td>Rosiglitazone maleate</td>
<td>Sodium Starch glycolate (SSG), Cross carmellose sodium, Microcrystalline cellulose (MCC)</td>
<td>HPMC K100M</td>
<td>Patil et al., 2012</td>
</tr>
<tr>
<td>11</td>
<td>Captopril</td>
<td>----</td>
<td>HPMC K4M, HPMC K15M, HPMC K100, Carbopol 934p</td>
<td>Rahman et al., 2006</td>
</tr>
<tr>
<td>12</td>
<td>Ziprasidone HCl (IRL), Trihexyphenidyl HCl (FL)</td>
<td>Microcrystalline cellulose (MCC), Aerosil, Colloidal silicon dioxide</td>
<td>HPMC K4M, HPMC K15M</td>
<td>Dinakaran et al., 2011</td>
</tr>
<tr>
<td>13</td>
<td>Baclofen</td>
<td>Sodium starch glycolate</td>
<td>HPMC K4M</td>
<td>Krishna et al., 2011</td>
</tr>
<tr>
<td>14</td>
<td>Trimetazidine dihydro-chloride</td>
<td>Sodium starch glycolate, Cross povidone</td>
<td>HPMC K15M, HPMC K100M, Carbopol 971p</td>
<td>Biswal et al., 2011</td>
</tr>
<tr>
<td>15</td>
<td>Trifluoperazine HCl</td>
<td>Sodium starch glycolate, Microcrystalline cellulose (MCC), Aerosil</td>
<td>HPMC K100M, Carbopol 934p, Eudragit RS100</td>
<td>Gahiwa et al., 2012</td>
</tr>
<tr>
<td>16</td>
<td>Lovastatin (IRL), Atenolol (FL)</td>
<td>Tablettose 80, Sodium starch glycolate (SSG)</td>
<td>Xanthan gum, HPMC K100M</td>
<td>Kulkarni et al., 2009</td>
</tr>
<tr>
<td>17</td>
<td>Cefuroxime axetil</td>
<td>Sodium citrate, Tulsion T-339</td>
<td>HPMC K4M</td>
<td>Dhumal et al., 2006</td>
</tr>
<tr>
<td>18</td>
<td>Celfpodoxime proxetil</td>
<td>Sodium starch glycolate (SSG)</td>
<td>HPMC, Hydroxy propyl cellulose (HPC), Carbopol 934P</td>
<td>Borkar et al., 2010</td>
</tr>
<tr>
<td>19</td>
<td>Losartan potassium (IRL), Metformin HCl (FL)</td>
<td>Sodium starch glycolate (SSG)</td>
<td>Ethyl cellulose, HPMC K4M, HPMC K100M</td>
<td>Kumar et al., 2012</td>
</tr>
</tbody>
</table>

*IRL - Immediate release layer
*FL - Floating layer

Conclusion

From the above review we can conclude that bilayer floating approach - a new scenario of gastro retentive drug delivery systems can be used for various potential active agents with narrow absorption window, e.g. anti diabetics, anti hypertensives, anti histaminics, anti emetics, NSAID’s, antibiotics, antiviral and antifungal agents, which are absorbed from very specific regions of GI tract. The development of narrow absorption window and short bioavailability drugs has been halted due to the lack of appropriate pharmaceutical technologies. To overcome those drawbacks, Pharmaceutical industries are trying to prepare one of the most economic and conventional dosage form like bilayer floating tablets which is considered as one of the best approaches. Bilayer Floating technology provide one of the important design approach where incompatible drugs with different indications and same drug with different release rates (Immediate release and sustained release) can be incorporated in a single unit. Some of the unresolved critical issues related to the rational development of bilayer floating drug delivery system include, the quantitative efficiency of floating delivery systems in the fasted and fed states and the correlation between
prolonged gastric residence time and Pharmacokinetic characteristics. However, bilayer floating technology is one of the promising approaches for drugs with shorter biological half-life, narrow absorption window and shorter bioavailability.

References


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