International Journal of Pharmaceutical Archive-3(5), 2014, 424-438
Available online through www.ijpaonline.info ISSN 2319-7226

REVIEW ARTICLE

REVIEW ON FLOATING DRUG DELIVERY SYSTEM

Richa Joshi* and Sayantan Mukhopadhyay

Grd (PG) Institute of Management and Technology,
Department of Pharmacy, Rajpur Road, Dehradun- 248001, Uttrakhand, India.

(Received on: 27-04-14; Revised & Accepted on: 17-05-14)

ABSTRACT

The main aim of controlled release dosage form is to maintain the drug concentration within the therapeutically effective range needed for treatment of disease. Controlled release floating drug delivery system is a drug which locally release in stomach. At absorption site drug absorption is limited by gastric retention time of a drug. Review focused on approaches, selection of drug & polymers, preparation technique, their evaluation with their application and recent development.

Key words: *Oral drug delivery systems, floating drug delivery system, gastric retention time, fasted state.*

INTRODUCTION

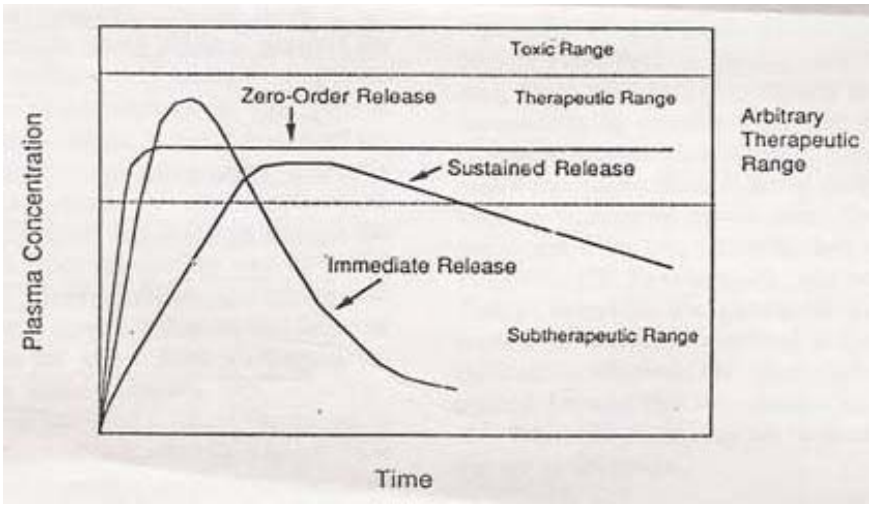
Among novel drug delivery systems, rate controlled oral drug delivery system forms an important area.[1]Oral route is the most popular and convenient route for various drugs.[2] Oral route generally consider an ideal drug delivery system that will possess two main properties:

a) It should be in a single dose for prolonging action.
b) It should be deliver the active drug directly to the target site.[2]
c) It provide good bioavailability and which makes the dosage form reproducible.[4]

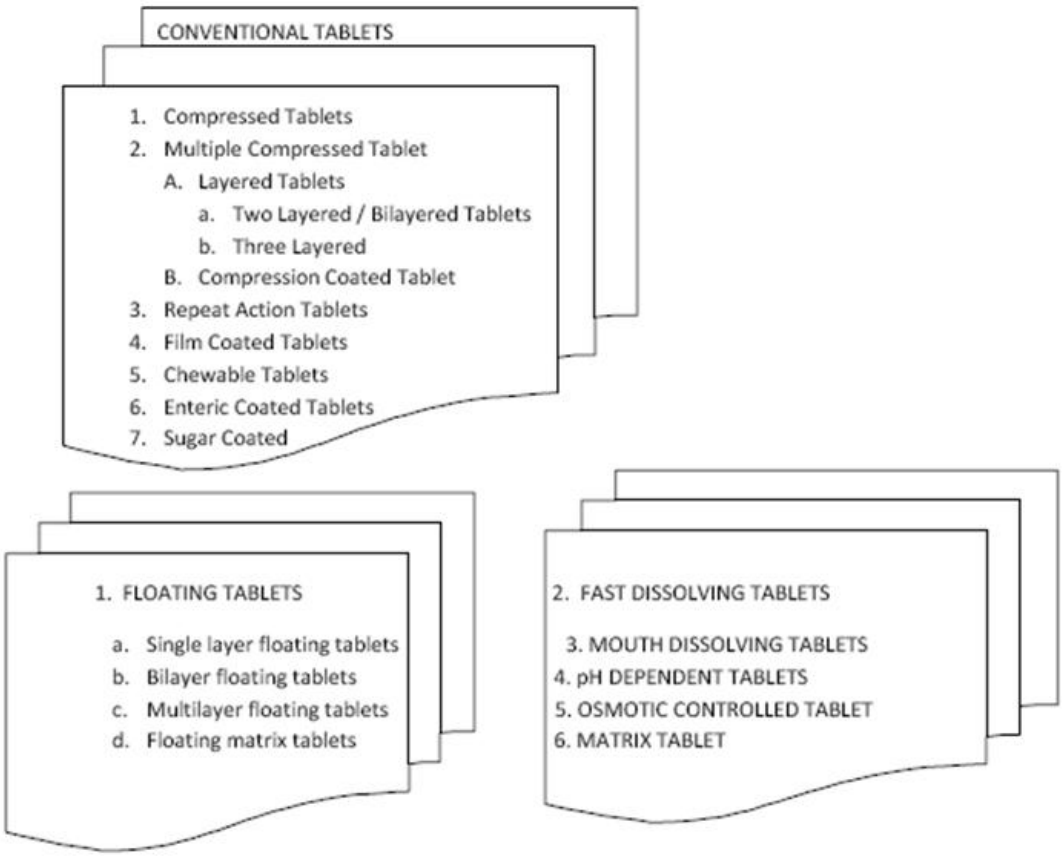
The main purpose of sustain drug delivery is to increase safety of drug to prolong its duration of action. Floating drug delivery systems (FDDS) are aimed to retain the drug in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids.[3] According to British Pharmacopoeia tablets are defined as convex or flat faces which are circular and are formed by compression of active pharmaceutical ingredient and other excipients.[5] Tablets can be produced by two method granulation and direct compression. Granulation can be dry granulation and wet granulation. But now a day's direct compression method is commonly used because novel excipients are commonly used. Oral Controlled release drug delivery systems (OCRDDS) that can be retained in the stomach for a long time have many advantages over sustained release formulations.[2] Controlled drug delivery system release the drug in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption site in the upper gastrointestinal tract.[2] Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined , predictable, and controlled rate.[6] Controlled-release drug delivery system is capable of achieving the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproducible release rates for extended time period; enhancement of activity of duration for short half-life drugs; elimination of side effects; reducing frequency of dosing and wastage of drugs; optimized therapy and better patient compliances.[7,8] The successful development of oral controlled drug delivery systems requires an understanding of the three aspects of the system, namely.

1. The physiochemical characteristics of the drug
2. Anatomy and physiology of GIT and Characteristics of Dosage forms. [9]

Corresponding author: Richa Joshi*
Grd (PG) Institute of Management And Technology, Department Of Pharmacy,
Rajpur Road, Dehradun- 248001, Uttrakhand, India.
E-mail: rchjoshi1991@gmail.com



However the developmental process is precluded by several physiological difficulties such as inability to restrain & locate the CDDS within the desired regions of GIT due to various gastric emptying & motility. The gastric emptying process can vary from a few minutes to 12 hrs.[11] This mainly lead to unpredictable time for peak plasma levels & bioavailability, therefore CRDFs not suitable for various important drugs and is characterized by a narrow absorption window in the upper part of GIT which is a relatively short transit time of DFs in this anatomical segments in period of less than 6 hrs.[11] Such drugs leave the upper part of GIT and reaches non-absorbing distal segment.[11] Furthermore, the relative gastric emptying time (GET) which is normally 2 to 3 hrs.[11] Through the major absorption zone (stomach or upper part of intestine), and can result in incomplete drug released from the DDS leading to diminished efficacy of the administered dose.[11] Therefore placing of DDS in specific region of the GIT offers numerous advantages, specially the drugs having narrow absorption window in GIT, primary absorption in the stomach, stability problem in the intestine, poor solubility at alkaline pH, local activity in stomach, and property to degrade in colon.[12] The gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms that reside in the stomach for a longer period of time than conventional dosage forms.[13]



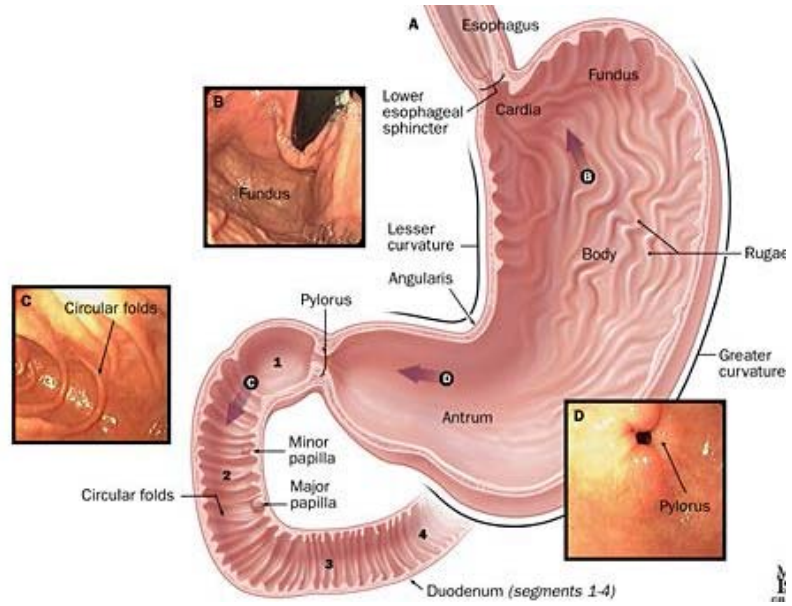
Floating drug delivery systems (FDDS) are aimed to retain the drug in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids[3] & maintain a constant level of drug in the blood plasma inspire of the fact that the drug dose not undergoes disintegration. Floating was first described in year 1968 by Davis.[4] The system

remains buoyant in stomach for a prolonged period of time because they have density lower than the gastric content.[4] Main principle is to make the dosage form less dense than the gastric fluids so that it can float on them. The density of the system can be reduced by incorporating a number of low density fillers into the systems such as hydroxyl cellulose, lactates or micro crystalline cellulose.[3] Main factor which effect floating system is presence of food and fluid in the stomach.

Basic Gastrointestinal Tract Physiology

The main function of the stomach is to process and transport food. It serves as a short-term storage reservoir, allowing a rather large meal to be consumed quickly.[6]Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.[17]

Stomach Physiology: The stomach is an expanded section of the digestive tube between the oesophagus and small intestine.[2] The wall of the stomach is structurally similar to the other parts of the digestive tube, with the exception that stomach has an extra, oblique layer of smooth muscle inside the circular layer, which aids in the performance of complex grinding motions.[2] In the empty state, the stomach is contracted and its mucosa and sub mucosa are thrown up into distinct folds called rugae (Fig.)[18]



Physiology of stomach

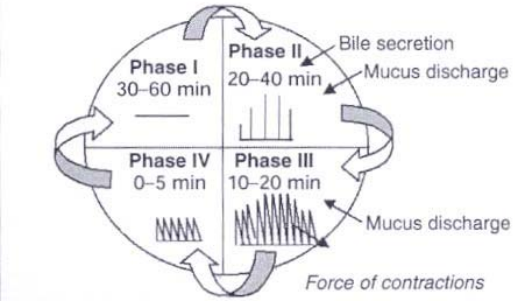
There are images to four major types of secretary epithelial cells that cover the surface of the stomach and extend down into gastric pits and glands:

- **Mucous cells**: secrete alkaline mucus that protects the epithelium against shear stress and acid.
- **Parietal cells**: secrete hydrochloric acid.
- **Chief cells**: secrete pepsin, a proteolytic enzyme.
- **G cells**: secrete the hormone gastrin. The contraction of gastric smooth muscle serves two basic functions:
  - Ingested food is crushed, ground, mixed and liquefying to form Chyme.
  - Chyme is forced through the pyloric canal into the small intestine, a process called gastric emptying.[2]

Gastric empty rate

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours.[15]This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington. [16]

1. Phase I (Basal phase) lasts from 30 to 60 minutes with rare contractions.
2. Phase II (Preburst phase) lasts for 20 to 40 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 10 to 20 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 2 consecutive cycles.[6]



FACTORS AFFECTING THE GASTRORETENTIVE SYSTEM [13, 14]

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include use of floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric emptying delaying devices and co-administration of gastric-emptying delaying drugs. Most of these approaches are influenced by a number of factors that affect their bioavailability and efficacy of the gastro retentive system.

- **Density** – Gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density.
- **Size** – Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.
- **Shape of dosage form** – Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes**.**
- **Single or multiple unit formulation** –Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.
- **Fed or unfed state** – Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.
- **Nature of meal** – Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.
- **Caloric content** – GRT can be increased by 4 to10 hours with a meal that is high in proteins and fats. **Frequency of feed** – The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
- **Gender** – Mean ambulatory GRT in males (3.4±0.6 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.
- **Age** – Elderly people, especially those over 70, have a significantly longer GRT.
- **Posture** – GRT can vary between supine and upright ambulatory states of the patient.
- **Concomitant drug administration** – Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride can affect floating time.
- **Biological factors** – Diabetes and Crohn's disease, etc.

Approaches to Gastric Retention

Various approaches have been pursued to increase the retention of an oral dosage form in the stomach. These systems include:

A. Floating systems
   1. Non effervescent system:
      - Colloidal gel barrier systems
      - Micro porous compartment systems
      - Multiparticulate system: Floating Beads
      - Microballoons
   2. Effervescent system:
      - Volatile liquid containing systems
      - Gas generating systems

B. Bioadhesive systems
C. Swelling and expanding systems
D. High density systems and
E. Modified systems

A. Floating systems

Floating drug delivery system is also called the hydro dynamically balanced system (HBS). Floating drug delivery systems (FDDS) have 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.[6] 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.[19]This results in an increased GRT and a better control of the fluctuations in plasma drug concentration.[2]

1. **Non effervescent system**

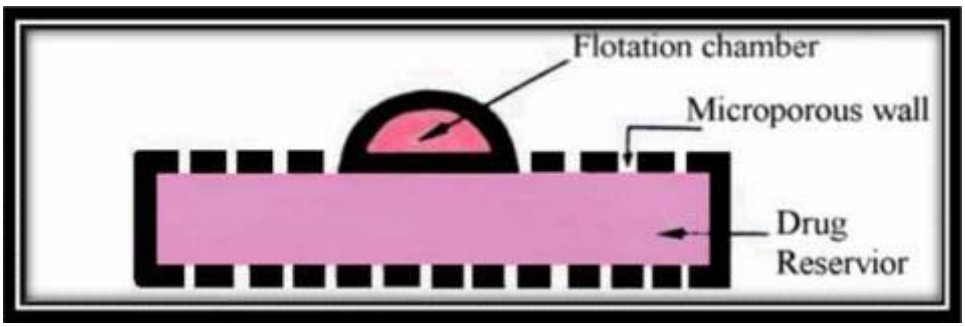
In this system commonly used excipients are gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene.[3]

- **Colloidal gel barrier systems[20]**

Hydrodynamically balanced system (HBS), which contains drugs with gel forming hydrocolloids, was first designed by Sheth and Tossounian in 1975. These systems incorporate a high level (20-75%w/w) of one or more gel forming, highly swellable, cellulose type hydrocolloids, polysaccharides and matrix forming polymers. On coming in contact with gastric fluid, the hydrocolloids in the system hydrate and form a colloidal gel barrier around its surface. This gel barrier controls the rate of fluid penetration into the device and consequent release of the drug.

- **Microporous Compartment System [21]**

In this inside the microporous compartment which has pores in the top and bottom walls contains encapsulated drug reservoir. In drug reservoir peripheral walls are completely sealed due to this sealing direct contact of undissolved drug with gastric surface is prevented. Entrapped air in the floating chamber stimulates the system to float over gastric content. Through an aperture the gastric fluid enters which dissolves the drug for absorption across intestine.



- **Multiparticulate system: Floating Beads [2]**

Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00mm. Thus multi particulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet.

- **Microballoons**[2]

There are various approaches in delivering substances to the target site in a controlled release fashion. One such approach is using polymeric microballoons as carrier for drugs. Hollow microspheres are known as the microballoons. Microballoons were floatable in vitro for 12 hrs, when immersed in aqueous media. Radio graphical studies proved that microballoons orally administered to human were dispersed in the upper part of stomach and retained there for three hr against peristaltic movements.

2. Effervescent systems[6]

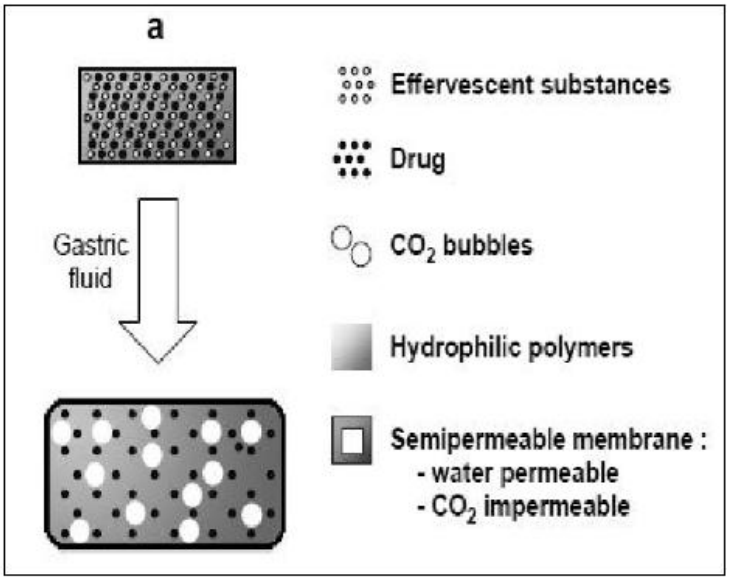
A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas.[10] These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to them dosage forms. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1.

- **Volatile liquid containing systems** [22]

Inflatable chamber with a liquid can be incorporated which provide sustained gastric retention of drug delivery system. Liquids in this system include cyclopentane, ether that gasifies at body temperature which causes inflatation of the chamber in the stomach. 18 They contain hollow deformable unit which are osmotically controlled floating systems. System is divided into two compartment first compartment contains drug and there is volatile liquid in the second compartment.

- **Gas generating systems** [2,20]

These buoyant delivery systems utilizes effervescent reaction between Carbonate/ bicarbonate salts and citric/tartaric acid to liberate CO2, which gets entrapped in the jellified hydrocolloid layer of the system, thus decreasing its specific gravity and making it float over chime. These are formulated by intimately mixing the CO2 generating agents and the drug within 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.



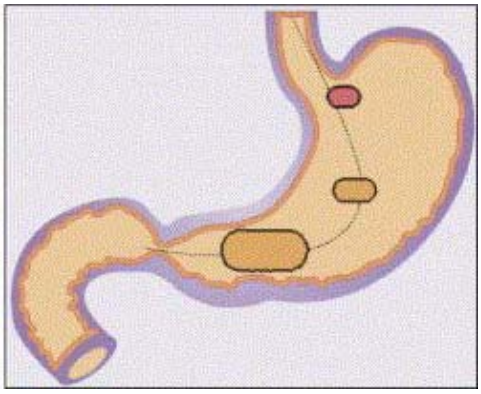
Gas generating system: schematic monolayer drug delivery system

B. Mucoadhesive & bioadhesive systems [23,24]

Bioadhesive drug delivery systems are used to localize a delivery device within the lumen to enhance the 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. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, CMC and gliadin, etc.

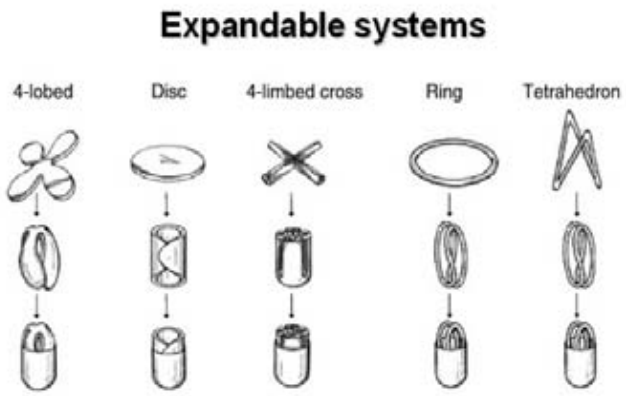
C. Swelling and expanding systems[25, 26]

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.



Swellable tablet in stomach

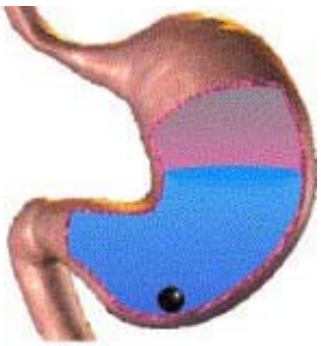
By selection of polymer with the proper molecular weight and swelling properties controlled and sustained drug release can be achieved. Upon coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is a result of the presence of physical-chemical cross links in the hydrophilic polymer network. These cross link prevents the dissolution of polymer and thus maintain 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.



Different geometric forms of unfoldable systems

D. High density systems [29]

These systems, which have a density of ~3g/cm3, are retained in the rugae of stomach and capable of withstanding its peristaltic movements[27, 28]. 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 2.4-2.8g/cm^3. Diluents such as barium sulphate (density= 4.9), zinc oxide, titanium oxide, and iron powder must be used to manufacture such high-density formulation.



High density systems

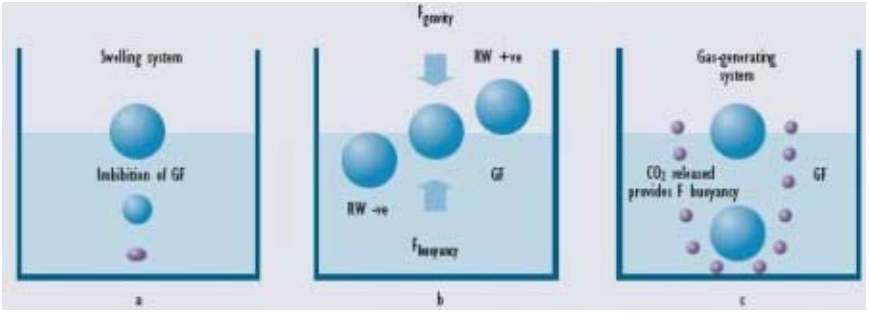
E. Modified systems [30]

Systems with non disintegrating geometric shape molded from silastic elastomers or extruded from polyethylene blends, which extend the GRT depending on size, shape and flexural modules of drug delivery device.

Mechanism of floating systems

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time.[3] 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.[3] While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system.[3] After release of drug, the residual system is emptied from the stomach.[3] This results in an increased GRT and a better control of the fluctuations in plasma drug concentration[31]. However, besides a minimal gastric content needed to allow the proper achievement of the 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.[3] To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature[32]. 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[33].

F = F buoyancy - F gravity = (Df - Ds) gv Where, F= total vertical force; Df = fluid density; Ds = object density; v = volume and g = acceleration due to gravity.



The mechanism of floating systems

Selection of Polymers [34, 35, 36]

A. Gas generating agent

Alkalinizing agents and acidulent

Sodium bicarbonate, Calcium carbonates, Citric acid, Tartaric acid, Adipic acid

Rational behind the selection

Effervescent compound generally use for this purpose. Sodium bicarbonate, calcium carbonate with citric acid and tartaric acid. When these compounds come in contact with the acidic gastric contents, carbon dioxide is liberated and gets entrapped in swelled hydrocolloids, which provide buoyancy to the dosage forms. Sodium bicarbonate induced CO2 generation in the presence of dissolution medium (0.1 N HCL). The gas generated trapped and protected with in the gel, formed by the hydration of polymer, thus decreasing the density of the tablet as the density of the tablet falls below 1, the tablet become buoyant.

Acidulent is used; since the pH of the stomach is elevated under fed condition (~3.5). Acidulent (Citric acid, Tartaric acid, Adipic acid) was incorporate in the formulation to provide an acidic medium for sodium bicarbonate.

B. Viscolyzing agent

Sodium alginate, Carbopol 934

Rational behind the selection

They used to increase the viscosity in the system. Carbopol is being used in the controlled release solid dosage formulations since last four decades. The numbers of manufacturers commercializing controlled release tablets using carbomers are increasing considerably in recent period of development. Tablet formulations using Carbopol polymers have demonstrated zero-order and near zero-order release kinetics. These polymers are effective at low concentrations (less than 10%). Still they show extremely rapid and efficient swelling characteristics in both simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). The Carbopol polymers produce tablets of excellent hardness and low friability. These polymers can be successfully formulated into a variety of different tablet forms, including the traditional swallowable tablets, chewable tablets, buccal tablets, sublingual tablets, effervescent tablets, and suppositories; providing controlled-release properties as well as good binding characteristics. Carbomers show larger dissolution times at lower concentrations than other excipients. Because of these factors Carbopol polymers have greater extent in formulating dosage forms. Because Carbopol polymers swell rapidly in water and absorb great quantities, to avoid the use of flammable solvents, roller compaction is being used as the method to prepare a new form of Carbopol polymer 71G NF. Carbopol polymer 71G NF is a useful and versatile controlled-release additive for tablet formulations in direct compression.

Drug Dissolution Mechanism from Carbopol Polymers

In the dry state, the drug is trapped in a glassy core. As the external surface of the tablet is hydrated, it also forms a gelatinous layer upon hydration; however, this gel layer is significantly different structurally from the traditional matrix tablet. The hydrogel are not entangled chains of polymer, but discrete microgels made up of many polymer particles, in which the drug is dispersed. The crosslink network enables the entrapment of drugs in the hydrogel domains. Since these hydrogels are not water soluble, they do not dissolve, and erosion in the manner of linear polymers does not occur. Rather, when the hydrogel is fully hydrated, osmotic pressure from within works to break up the structure, essentially by sloughing off discrete pieces of the hydrogel. It is postulated that as the concentration of the drug becomes high within the gel matrix and its thermodynamic activity or chemical potential increases, the gel layer around the tablet core actually acts almost like a rate controlling membrane, resulting in linear release of the drug. Because of this structure, drug dissolution rates are affected by subtle differences in rates of hydration and swelling of the individual polymer hydrogels, which are dependent on the molecular structure of the polymers, including crosslink density, chain entanglement, and crystallinity of the polymer matrix. The magnitude and rate of swelling is also dependent on the pH of the dissolution medium. The channels which form between the polymer hydrogels are

influenced by the concentration of the polymer, as well as the degree of swelling. Increasing the amount of polymer will decrease the size of the channels, as does an increase in swelling degree. All of these factors must be taken into account to describe the mechanism for release control in tablets formulated with carbopol polymers.

C. Swelling agent/Gel forming polymer

Hydroxy propyl methyl cellulose (HPMC)

Rational behind the selection

Hypermellose powder is stable material, although it is hygroscopic after drying. Solution is stable at pH 3-11. Increasing temperature reduces the viscosity of solutions. Hypermellose undergoes a reversible sol-gel transformation upon heating and cooling, respectively. The gel point 50-90°C, depending upon grade and concentration of material. Grades which are generally used in floating tablet are which are highly viscous in nature like HPMC K 100, HPMC K 4, and HPMC K 15.

D. Disintegrating agent

Povidone, Polyplasdone XL and XL-10

Rational behind the selection

PVP belongs to a class of compounds known as superdisintegrantes. When they comes in contact with the fluid media they provide the swelling properties to the system they used as highly active explosive agent and as an accelerating agent for disintegration of solid medications. In tabletting, povidone solutions are used as binder in the wet granulation processes.

Sustained release polymers	HPMC K100M , HPMCK15M , HPMC E LV , Polycarbonate , Polyethylene glycol , Sodium alginate , Carbopol , Eudragit
Effervescent generating system	Citric acid , Tartaric acid , Sodium bicarbonate , Citroglycine
Polymers which increase buoyancy	Ethylcellulose
Polymers which decrease release	Talc , Magnesium stearate , Dicalcium phosphate
Polymers which increase release	Mannitol , Lactose
Inert polymer	Long chain fatty polymer ,Fatty acid , Beeswax
Polymer with low density	Foam powder of polypropylene. [4]

Suitable drug candidates for FDDS [3,6]

Delivery of the Drugs in continuous and controlled manner have a lower level of side effects and provide their effects without the need for repeated dosing or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, from where absorption occurs and contact time is limited. Appropriate candidates for controlled release gastroretentive dosage forms are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT.

- Drugs with narrow absorption window in GIT, e.g., Riboflavin and Levodopa
- Drugs that primarily absorbed from stomach and upper part of GIT, e.g., Calcium supplements, chlordiazepoxide and cinnarazine.
- Drugs that act locally in the stomach, e.g., Antacids and Misoprostol.
- Drugs that degrade in the colon, e.g. Ranitidine Hcl and Metronidazole.
- Drugs that disturb normal colonic bacteria, e.g., Amoxicillin Trihydrate.

Methods for preparing Floating Dosage forms [37-39]

Following approaches can be used for preparing floating dosage forms:

- Using gel-forming hydrocolloids such as hydrophilic gums, gelatin, alginates, cellulose derivatives, etc.
- Using low-density enteric materials such as methacrylic polymer, cellulose acetate phthalate.
- By reducing particle size and filling it in a capsule.
- By forming carbon dioxide gas and subsequent entrapment of it in the gel network.
- By preparing hollow micro-balloons of drug using acrylic polymer and filled in capsules.
- By incorporation of inflatable chamber, which contained in a liquid e.g. solvent that gasifies at body temperature to cause the chambers to inflate in the stomach?

Advantages of FDDS [2,3,4,10,40]

FDDS is highly advantageous in the treatment of the disorders related to the stomach. As the prime objective of such systems is to produce a gastro retentive product or a product which has an enhanced retention time in the stomach.

1. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
2. Controlled delivery of drugs.
3. Delivery of drugs for local action in the stomach.
4. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
5. Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
6. Simple and conventional equipment for manufacture.
7. Ease of administration and better patient compliance.
8. Site-specific drug delivery.
9. Drugs with considerably short half life can be administered in this manner to get an appreciable therapeutic activity.
10. Enhancement of the bioavailability for drugs which can metabolized in the upper GIT.
11. They also have an advantage over the conventional system as it can be used to overcome the adversities of gastric retention time as well as the gastric emptying time.
12. The duration of treatment through a single dose, which releases the an active ingredient over an extended period of time
13. The active entity is delivered specifically to the site of action, thus minimizing or eliminating the side effects.
14. Over all other oral routes these are microbiologically and chemically stable.
15. Better suited for large scale production.
16. Masking of bitter taste and bad odour by coating.
17. Swallowing of tablets is easy.
18. Lesser cost compared to other oral dosage forms.
19. Enhanced bioavailability.

Disadvantages of FDDS [3, 41, 42]

1. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
2. Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
3. High variability in gastric emptying time due to its all or non-emptying process.
4. Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diameter and size. Therefore patients should not be dosed with floating forms just before going to bed.
5. The major disadvantage of floating system is requirement of a sufficient high level of fluids in the stomach for the drug delivery to float. However this limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the mucosal lining of the stomach.
6. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
7. Patients should not be dosed with floating forms just before going to bed.
8. The dosage form should be administered with a minimum of glass full of water (200-250 ml).
9. The drugs, which are absorbed throughout GIT, which under go first-pass metabolism (Nifedipine, Propranolol etc.), are not desirable candidate.

Evaluation Techniques

In vitro evaluation of floating tablets

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

1. Pre-compression parameters

a) Angle of Repose (Ɵ)

The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

The granules were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$$\tan \Theta = h/r$$

$$\Theta = \tan^{-1} (h/r)$$

Where, **Ɵ** = angle of repose **h** = height of the heap **r** = radius of the heap [43]

The relationship between Angle of repose and powder flow is as follows in table.

Table: Relationship between angle of repose and powder flow

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

b) Compressibility Index

The flowability of powder can be evaluated by comparing the bulk density (ρo) and tapped density (ρt) of powder and the rate at which it packed down. Compressibility index was calculated by –

Compressibility index (%) = ρt – ρo/ ρt x 100

Where **ρo** = Bulk density g/ml002E

ρt = Tapped density g/ml.

2. Post-compression parameters

a) Shape of Tablets

Compressed tablets were examined under the magnifying lens for the shape of the tablet.

b) Tablet Dimensions

Thickness and diameter were measured using a calibrated varniear caliper. Three tablets of each formulation were picked randomly and thickness was measured individually.

c) Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It was expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.[44]

d) Friability test

The friability of tablets was determined by using Roche Friabilator. It was expressed in percentage (%). Ten tablets were initially weighed (W initial) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (Wfinal). The % friability was then calculated by **$\%F = 100\ (1-W_0/W)$**

% Friability of tablets less than 1% was considered acceptable.[43]

e) Tablet Density

Tablet density was an important parameter for floating tablets. The tablet would floats only when its density was less than that of gastric fluid (1.004). The density was determined using following relationship.[45]

$V = \pi r^2 h$

d = m/v

v = volume of tablet (cc)

r = radius of tablet (cm)

h = crown thickness of tablet (g/cc)

m = mass of tablet

f) Weight Variation Test

Ten tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation was allowed in the weight of a tablet by U.S. Pharmacopoeia. [43]The following percentage deviation in weight variation was allowed show in table.

Average weight of a tablet	Percent deviation
130 mg or less	10
>130 mg and <324 mg	7.5
324 mg or more	5

Percentage deviation in weight variation

g) Buoyancy / Floating Test

The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

h) Swelling Study

The swelling behavior of a dosage form was measured by studying its weight gain or water uptake. The dimensional changes could be measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake was measured in terms of percent weight gain, as given by the equation.

WU = (W1 – W0)/ W0 x 100

Wt = Weight of dosage form at time t.

W0 = Initial weight of dosage form.

i) In vitro drug release studies [2,33,31,44,45,46]

The test for buoyancy and in vitro drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 37°C. In practice, floating time is determined by using the USP dissolution apparatus containing 900ml of 0.1 Hcl as a testing medium maintained at 37°C. The time required to float the HBS dosage form is noted as floating (or floatation) time. Dissolution tests are performed using the USP dissolution apparatus. Samples are withdrawn periodically from the dissolution medium, replenished with the same volume of fresh medium each time, and then analyzed for their drug contents after an appropriate dilution. Recent methodology as described in USP XXIII states that the dosage unit is allowed to sink to the bottom of the vessel before rotation of blade is started. A small, loose piece of non reactive material such as not more than a few turns of wire helix may be attached to the dosage units that would otherwise float. However, standard dissolution methods based on the USP or British Pharmacopoeia (BP) have been shown to be poor predictors of *in vitro* performance for floating dosage forms. Illay and Fassihi investigated the application of the helical a wire sinker to the swellable floating systems containing theophylline (a sparingly water soluble drug). They observed that the procedure tends to inhibit the three dimensional swelling process of the dosage form and consequently drug release from the formulation was suppressed. Based on their observations, the authors proposed an alternative method in which the floatable delivery system was fully submerged under a ring/mesh assembly. The results showed a significant increase in drug release (>20%). In addition, the proposed method was found to provide reproducible hydrodynamic conditions and consistent release profiles. However, in the case of swellable floating systems, which contain diltiazim (a highly water soluble drug) the authors did not find any difference in release between the proposed method and the USP method.[2] These finding led to the conclusion that drug release from swellable floating systems depends on full surface exposure, unhindered swelling and the drug solubility in water. Another method to modify official dissolution methods were made by Burns et al.26 who developed and validated an in vitro dissolution method for a floating dosage form which had both rapid release and SR properties.[2] The method, although based on the standard BP (1993)/ USP (1990) apparatus 2 method, was modified such that paddle blades were positioned at the surface of the dissolution medium. The results obtained with this modified paddle method showed reproducible biphasic release profiles when paddle speeds were increased from 70 to 100 rpm and the dissolution medium pH was varied from 6.0 to 8.0. The dissolution profile was also unaltered when the bile acid concentration in the dissolution medium was increased from 7 to 14mM. In contrast, the standard paddle or basket method, as described in the BP (1993) was unable to provide either sufficient mixing of the dissolution medium to disperse oily rapid release material or sufficient mechanical erosion of the SR component of the formulation.[2] In additional studies, the authors modified a standard dissolution vessel for more reliable assessment of the performance of the floating dosage forms, particularly those which rely on an erosion mechanism for drug release. The result showed a more reproducible dissolution profile while eliminating the need for the positioning of the paddle blades at the surface of the dissolution medium, thereby simplifying sampling procedures and preventing the adhesion of dosage forms to the paddle blades. Nevertheless, the method retained its ability to differentiate between acceptable and unacceptable dissolution performance. Further, the optimization of floating formulations should be realized in terms of stability and durability of the floating capability that might occur during in vivo studies. The method involves the use of a specially designed apparatus for measuring the total force acting vertically on an object immersed in a liquid. The technical details of the apparatus for measuring the total force acting vertically on an object immersed in a liquid have been described elsewhere. The in vivo gastric receptivity of floating dosage forms are usually determined by γ- scintigraphy54. Studies are done both on fasted and fed conditions using floating and non floating dosage forms.

Limitations of Floating Drug Delivery Systems [6 , 10]

1) A high level of fluid in the stomach is required for drug delivery to float and work efficiently.
2) Drugs which have stability and solubility problems in GIT are not suitable candidates for these types of systems.
3) Drugs such as nifedipine, which under goes first pass metabolism may not be desirable for the preparation of these types of systems.
4) Drugs which are irritant to Gastric mucosa are also not desirable.
5) The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
6) The dosage form should be administered with a full glass of water (200-250 ml).

Application of floating drug delivery systems [3, 50]

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

1) **Sustained drug delivery**

FDDS can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be

overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited. E.g. Sustained release floating capsules of Nicardipine Hydrochloride

2) **Site-specific drug delivery**
These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine. E.g. Riboflavin and Furosemide

3) **Absorption enhancement:**
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. E.g. A significantly increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric coated LASIX-long product (29.5%).

RECENT ADVANCEMENT IN FDDS

1. **Osmotic Regulated systems** [20]
It is comprised of osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside from a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to be inflates the bag. The osmotic controlled drug delivery device consists of two components – drug reservoir compartment and osmotic ally active compartment.

2. **PVA-PVP Spray Dried Tablets** [50]
These tablets shows immediate floating with almost no lag time, floating for 24 hr and do not sink. No swelling and erosion takes place in the GIT, so the release does not depend upon osmolarity of the medium. Buoyancy in such system is due to high porosity in the tablet. The exceptionally good compressibility of spray dried PVA-PVP combination makes it possible to produce mechanically stable oral DF, even with extremely low pressure.

3. **Ion exchange resins Beads** [51]
A coated ion exchange resin bead formulation has been shown to have gastric retention properties which were loaded with bicarbonates. Ion exchange resins were loaded with bicarbonate and a negatively charged drug is bound to the resin. The resulted beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of stomach, an exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to uncoated beads, which will sink quickly.

4. **Micro particles** [52]
This approach is based on low-density foam powder. This system is advantageous because of its zero to negligible lag time before starting of floatation. These floating microcapsules prepared by emulsion solvent evaporation technique, contain polypropylene foam powder, polymers and model drug. Drug release increases rate significantly increases with different types of polymers.

5. **Lipid based sustained release matrix systems** [53,54]
Floating glycerol monooleate single-unit lipid matrix containing high drug: excipients ratio achieved sustained drug release. Hydrophobic lipid, gelucire 43/01 can be considered as an effective carrier for design of multiple –unit FDDS of highly water-soluble drugs.

6. **Chitosan granules/Microcapsules** [55]
These are prepared by de-acidification process. When added to acidic and neutral media these granules were immediately buoyant and provide a controlled release of the drug. Laminated preparations can be prepared by coating with chitosan granule layer with chitosan membrane. These preparations buoyant and provide sustained release.

7. **Floating Rafts** [56, 57]
Floating Rafts are used in the treatment of gastric oesophageal reflux. This raft formulation based on an alginate biopolymer. On ingestion, this formulation reacts with gastric acid to form floating raft structure, which impedes the reflux of acid and food by acting as a physical barrier. The raft has a pH value higher than that of the stomach.

CONCLUSION

Controlled release floating drug delivery system is a promising delivery system that is absorbed primarily in the upper part of GI tract, i.e., the stomach, duodenum, and jejunum. It is a challenge for FDDS to remain in stomach for sufficient time i.e. why now a day many approaches and techniques are widely used. It may be a best way to cure disease related to upper part of GI tract like stomach.

REFERENCE

1. Patil J.M., Hirlekar R.S., Gide P.S., Kadam V.J. Trends in floating drug delivery systems, Bharti vidyapeeth's college of pharmacy , sector 8, C B D Belapur , Navi Mumbai 400 614.
2. Agarwal Dilip , Gupta M.K. , Khinchi Mahaveer Pr., Natasha Sharma, A comprehensive review on floating drug delivery system, Department of pharmaceutics, Kota College of Pharmacy, Kota, Rajasthan, India.
3. Geetha.A , Kumar J. Rajendra, Mohan CH. Krishna, Raju P N, & Sateesh V., A review on floating drug delivery systems ,St. John College of Pharmacy, Yellapur, Hasanparthy, Warangal, AP, India 2KLR College of Pharmacy, Paloncha, Khammam, AP, India.
4. Arora Sandeep, Dhiman Sonia, Kaur Parmjit, Floating bilayer tablet technology: A Review, Chitkara College of Pharmacy, Chitkara University, Chandigarh-Patiala National Highway (NH-64) – 140401, Punjab, India.
5. Jain N.K., Gastro retentive Drug Delivery System. In: Progress in Controlled and Novel Drug Delivery System, Vol. CBS Publishers , 2008, 76-97.
6. Narang Neha, An updated review on: Floating drug delivery systems(FDDS), Shri Baba Mastnath Institute of Pharmaceutical Sciences and Research, Asthal Bohar, Rohtak, (Haryana), Pin Code124001.*Received: 30 July2010, Revised and Accepted: 05 Oct 2010.*
7. Chien YW., Rate-control drug delivery systems: controlled release Vs. sustained release. Med Prog Techn. 1989, 15, 21-46.
8. Chien YW, Oral drug delivery and delivery system in novel drug delivery Systems, ed,50, Marcel Dekker publication, New York, 1992.
9. Patel GM., Floating drug delivery system: An innovative approach to prolong gastric retention. www.pharmainfo.net, 2007.
10. Chikhalikar S.S., Wakade R.B., Floating drug delivery system – An approach to oral controlled drug delivery, Department of pharmaceutics sudhakarrao naik institute oF pharmacy, Pusad-445204 Dist: Yavatmal (M.H.), India.
11. Garg R., Gupta G.D., Progress in Controlled GastroretentiveDeliverySystems, Trop J Pharm Res. September 2008; 7(3), 1055-1066.
12. Arora Sonia, Chandel Abhishek, Chauhan Kapil, Kumar Hitesh, Parashar Bharat., Floating drug delivery systems: A better approach; Department of Pharmacy, Manav Bharti University, Solan -173229, Himachal Pradesh, India.
13. A. Padmasri, Banji David, R.Vinod K., S. Anbuazaghan., S .Sandhya, Vasa Santhosh, Approaches for gastrotentive drug delivery systems. International Journal of Applied Biology and Pharmaceutical Technology, 589-601.
14. DasBiswarup., MajiRuma, Nayak Amit Kumar, Gastroretentive drug delivery systems: a review. Asian Journal of Pharmaceutical and Clinical Research, Vol.3 Issue 1, January- March 2010, 2-10.
15. Lisbeth I., Stanley SD, Drug delivery systems for challenging molecules. Int. J. Pharm. 1998, 176 , 1-8.
16. Khar RK., Vyas SP, Controlled drug delivery: Concepts and advances, Vallabh Prakashan Delhi, 2002, 1 ,123-231.
17. Desai S., A novel floating controlled release drug delivery system based on a dried gel matrix network, Jamaica, NY, St John's University, 1984.
18. Banker GS, Rhodes CT. Modern Pharmaceutics. Marcel Dekker, New York 1996; 3 : 125-128.
19. Gajjar SS., Mayavanshi AV., Floating drug delivery systems to increase gastric retention of drugs: A review, J Pharm Tech 2008; 1(14): 345-348.
20. Kim Kwon H., Singh Brahma N., Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention, Journal of Controlled Release 63 (2000) 235– 259.
21. C. Mayur A, HH Gangurde, K. Senthilkumaran, S. Tamizharasi., Floating Drug Delivery System: A versatile approach for gastric retention, International Journal of Pharmaceutical Frontier Research 1, 2011, 96-112.
22. Patel AV. , Patel KR., Patel MR., Patel NM., Patel RB., Soni RP, Gastroretentive drug delivery systems: A Review International Journal of Pharma World Research 2, 2011.
23. Patel R., Recent development in floating drug delivery system for gastric retention of drugs: an overview. 2007.
24. Asane GS. Mucoadhesive gastrointestinal drug delivery system: An overview. 2007.
25. Bolton S and Desai S, 1989, US 4,814,179.
26. Garg S., Gupta P., Virmani K; Hydrogels: From controlled release to pH responsive drug delivery. Drug Discovery Today 2002; 7(10): 569-579.

27. Singh BN, Kim KH. Floating drug delivery system: An approach to the controlled drug delivery via gastric retention. J Control Release 2000; 63: 235-259.
28. Devereux JE, Newton JM, Short MB,The influence of density on the gastrointestinal transit of pellets. J Pharm Pharmacol 1990; 42(7): 500-501.
29. Chawla G, Bansal AK, Gupta P, Koradia V,. Gastroretention: A Means to address regional variability in intestinal drug absorption. Pharm Tech 2003; 27: 250-268.
30. Etienne A, Hoffman M, Kedzierewicz F, Lemut J, Maincent P, Thaivenot P., Evaluation for peroral silicon dosage forms in human by gamma-scintigraphy. J Control Release 1999; 58: 195-205.
31. Deshpande A.A., Malick W., Rhodes C.T, Shah N.H.; Development of a novel controlled-release system for gastric retention. Pharm Res. 1997; 4: 815-819.
32. Bechgaard H, Ladefoged K., Distribution of pellets in gastrointestinal tract., The influence on transit time exerted by the density or diameter of pellets. J Pharm Pharmacol. 1978; 30: 690-692.
33. Bhavana V, Jain N.K., Jain W.D, Khopade A.J, Shelly., Targeted Oral Drug Delivery, Indian drugs., 1996, 33: 365-373.
34. Cargil,R; Engle,K; Fix,J.A, Gastric residence time of a non-disintegrating geometric shape in human volunteers, Pharm. Res. 1995, 12(3), 397-405.
35. Bolton.S; Desai,S, A floating controlled – release drug delivery system; In vitro /invivo Evaluation, Pharm. Res, 1993, 10, 1321-1325.
36. Franz,M; Oth,M; Timmermans,J, The bilayer floating capsule : A stomach – dried drug delivery system for misoprostal, Pharm. Res, 1992, 9, 298-302.
37. The American Society for Gastrointestinal Endoscopy: a history Gastrointestinal Endoscopy, Volume 37, Supplement 2, March 1991, Pages S1-S26.
38. Hardenia Shiv Shankar et al., Asian Journal of Pharmacy and Life Science, Vol. 1 (3), July-Sept 2011:284-293.
39. A Alka, A Javed, A Shweta, B Sanjula, K Roop K., Floating drug delivery systems: a review, AAPS Pharm Sci tech. 2005, 6(3)47, E372- E390.
40. Khar Roop K., Controlled Drug Delivery, Gastroretentive system 4th edn., 202-203.
41. KRW, Waugh A., Anatomy and Physiology in Health and Illness. 9th ed. London, Churchill Livingstone, 1996.
42. Dehghan H.G.,Khan F.N, Int J Health Res 2009; 2(1), 23.
43. Cargil, R.C, Gardner. C.R, Waldwell. L.J, US Patent 4,735,804, 1988.
44. Moes AJ., Timmermans J, Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: New data for reconsidering the controversy. J. Pharm. Sci. 1994, 83, 18.
45. Clarke GM, Newton JM, Short MD. Comparative gastrointestinal transit of pellet systems of varying density. Int. J. Pharm., 1995, 114, 1-11.
46. Moes AJ, Timmermans J., The cut off size for gastric emptying of dosage forms. J. Pharm. Sci. 1993, 82 , 854.
47. Afifi NH, Ghorab DM, Moursy NM, El-Saharty Y. Pharmazie 2003; 58: 38-43.
48. Shayeda. Nadigoti Jagadeeshand, Floating Drug Delivery Systems. International Journal of Pharmaceutical Sciences and NanotechnologyVolume 2 Issue 3, October - December 2009, 595-604.
49. AtyabibFatemeh, KouchakaMaryam., Ionexchange An Approach to Prepare an Oral Floating Drug DeliverySystem for Diclofenac .Iranian Journal of Pharmaceutical Research (2004) 2, 93-97.
50. Bodmeier R.., Siepmann J., Streubel A., Floating matrix tablet based on low density foam powder. Effects of formulation and processing parameter on drug release. Eur Journal of Pharm sci,18(2003), 37-45.
51. Kumar K et al., Effects of drug solubility and different excipients on floating behavior and release from glyceryl mono-oleate matrices, Int J Pharm,272 (2004), 151-160.
52. BandariSuresh, Jukanti Rajuand Veerareddy Prabhakar Reddy, SiripuramPraneeth Kumar, Formulation and Characterization of Floating Gelucire Matrices of Metoprolol Succinate., Dissolution Technologies AUG 2010, 34-39.
53. Gaffar. Abdel, M El GibalyI Meki A., Novel B melatonin loaded chitosan microcapsule: In vitro characterization and antipoptosis efficacy for aflatoxin B1 induced apoptosis in rat liver, Int J Pharm,260(2003), 5-22.
54. Eccelston G M, Paterson R S O'mahnoy B, Stevens H N E., An assessment of floating raft formation in man using MRI, J Pharm Pharmacology, 8(2000) S2.
55. Mathur Pooja, Saroha Kamal, Syan Navneet, Verma Surender, Nanda Sanju., An overview on recent advancements and developments ingastroretentive buoyant drug delivery system., Pelagia Research LibraryDer Pharmacia Sinica, 2011, 2 (1),161-169.

Source of support: Nil, Conflict of interest: None Declared