Review Article

FLOATING DRUG DELIVERY SYSTEM - AN APPROACH FOR GASTRORETENTIVE DRUG DELIVERY

Shravya*, Shabaraya AR and Narasimharaj A

Srinivas College of Pharmacy, Valachil, Mangalore, Karnataka, India.

ABSTRACT

Floating drug delivery system (FDDS) provides local delivery of the drug to specific region of stomach and proximal part of small intestine and also shows a better bioavailability and improved therapeutic efficacy and hence a significant benefits to the patients. Oral sustained release gastro-retentive dosage forms offer many advantages for drugs with the absorption from upper parts of the gastro intestinal tract. Gastric emptying is a complex process and it is highly variable. The floating drug delivery systems are useful methods to avoid this variability which increases the retention time of the drug delivery systems for more than 12 hours. Effervescent and non effervescent are two class of floating drug delivery system.[1]

Keywords: Floating drug delivery system, Buoyancy, Gastric residence time.

INTRODUCTION

Oral drug delivery is the most preferable form of drug delivery, i.e. having the highest degree of patient compliance. Current pharmaceutical methods focus on the development of sustained drug delivery systems to achieve required therapeutic concentration with less amount of dose. Oral delivery tends to be the most popular route of administration due to its versatility, administered easily and most probably important patient compliance. Oral controlled release drug delivery has gained increasing interest in pharmaceutical field to achieve improved therapeutically benefits, such as easily administered dose, patient compliance and formulation flexibility. Drugs which have short half-lives and drugs that are easily absorbed from gastrointestinal tract (GIT) are eliminated immedeately from the systemic circulation. For these types of drugs formulation of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration for a long time in the systemic circulation. After oral administration of this type of drug delivery they will remain in the stomach and release the drug in a controlled and systemic manner. To formulate a site-specific orally administered controlled release dosage form, it is necessary to achieve prolong gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, enhances the duration of drug release and reduces drug waste, prolonged gastric retention time (GRT) in the stomach which could be beneficial for local action in the upper part of the small intestine e.g. treatment of peptic ulcer, etc.[1,2]

Physiology of the stomach

Stomach is a J- shaped enlargement of the GI tract. It is a saclike organ located in between the oesophagus & the small intestine. The cell lining of the stomach secretes 3 important substances: Mucus, HCl, Pepsinogen (precursor of pepsin).

1. Mucus: - Protects gastric cells from injury.
2. HCl: **-** Provide acidic medium to kill pathogens as well as to promote the protein breakdown by the pepsin.
3. Pepsin: **-** Protein digesting enzyme.

The stomach has 4 main areas.

a) Cardia b) Fundus c) Body d) Pylorus

- The right margin of oesophagus is continuous with lesser curvature of the stomach, while the left margin joins the greater curvature at an acute angle termed as cardinal.
- The rounded portion superior to & to the left of the cardia is the fundus.
- Inferior to the fundus is the large central portion of the stomach called the body.
- The region of the stomach that connects to the duodenum is the pylorus (Pyle = gate, ouros = guard). [3]

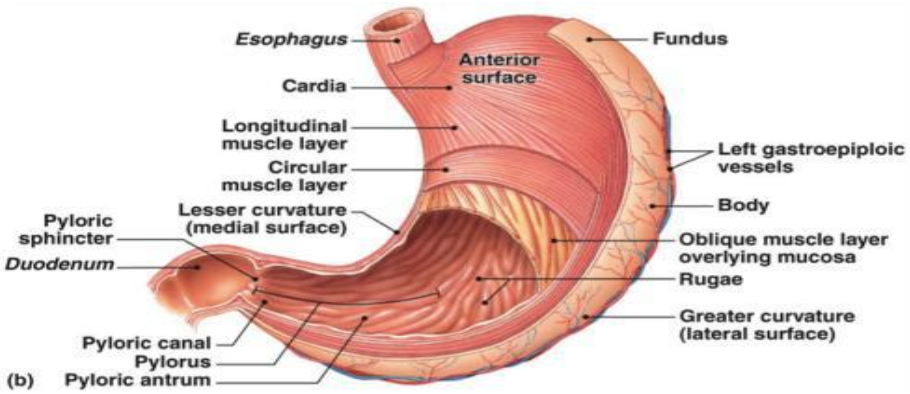

Fig. 1: Physiology of stomach

Gastric Emptying: It occurs during fasting as well as in fed states. The two modes of state of continuous motility comprising in GI tract are; Inter-digestive motility pattern & Digestive motility pattern.

In the fasted states, it is known by an interdigestive series of electrical events, which cycle both through stomach and intestine for every 2 to 3 hours. It is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following four phases.

Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions. It is characterized by lack of any secretary, electrical activity and contractile motions.

Phase II (preburst phase) lasts for 20 to 40 minutes with intermittent action potential and contractions. Bile enters the duodenum during this phase, while the gastric mucous discharge occurs during the later part of phase I and throughout the phase III.

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”.

Phase IV (transition period) lasts for 0 to 5 minutes and occurs between phase III and phase I.[3]

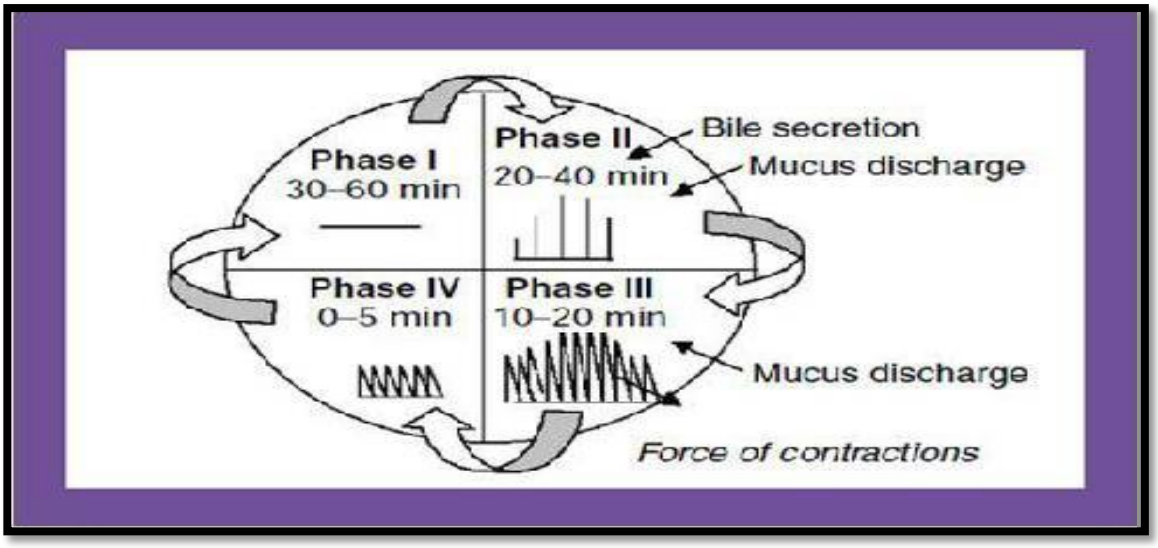

Fig. 2: Phase of gastric cycle

Factors effecting gastric residence time

Density of dosage forms

The density of a dosage form tends to affect the gastric emptying rate and determines the location of the system in the stomach. Dosage forms that have a density less than the gastric contents can float to the surface, while those having high density systems sink to bottom of the stomach. A density of < 1.0 gm/cm^3 is essential to exhibit floating property.

Shape of dosage form

Shape and size of the dosage forms are very important in formulating indigestible single unit solid dosage forms. The larger the dosage form the longer will be the gastric retention time (GRT) due to greater size of the dosage form. Mean gastric residence times of non-floating dosage forms are highly variable and are dependent on their size, which may be large, medium and small units.

Single or multiple unit formulation

Multiple unit formulations allows co- administration of units with different release profiles or those which contain incompatible substances and allow a larger margin of safety against dosage form failure when compared with single unit dosage forms.[4]

DRUGS REPORTED TO BE USED IN THE FORMULATION OF FLOATING DOSAGE FORMS ARE:

1. Floating microspheres (Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Terfinadine and Tranilast)
2. Floating granules (Diclofenac Sodium, Indomethacin and Prednisolone)
3. Films (Cinnarizine)
4. Floating capsules (Chlordiazepoxide hydrogen chloride, Diazepam, Furosemide, Misoprostol, L-Dopa, Benserazide, Ursodeoxycholic acid and Pepstatin)
5. Floating tablets and pills (Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Diltiazem, Fluorouracil, Isosorbide mononitrate, Paraamino Benzoic acid, Piretamide, Theophylline and Verapimil hydrochloride, etc.). [5]

Some of the marketed formulations are listed as follows

• Valrelease® – floating capsule of Diazepam.
• Madopar® – Benserazide and L-Dopa combination formulation
• Liquid Gaviscon® – floating liquid alginate preparations
• Topalkan® – aluminium – magnesium antacid preparation
• Almagate Flot-Coat® – antacid preparation.[5]

Advantages of floating drug delivery system

- **Sustained drug delivery:** A floating drug delivery system can retain in the stomach for several hours and the assumed to have prolongation in the gastric retention is thought to cause sustained drug release behaviour.
- **Site-specific drug delivery:** Targeting of drug to stomach appears to be useful for all substances which are meant to produce a lasting local action on the gastro duodenal wall.
- **Reduced counter-activity of the body:** Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.
- **Minimized adverse activity at the colon:** Retention of the drug in the gastroretentive dosage form at the stomach reduces the amount of drug that reaches the colon. Thus, unwanted activities of the drug in colon may be prevented.
- **Pharmacokinetic advantage:** Along with the total gastrointestinal transit duration is increased, a higher amount of drug may be delivered and thus the bioavailability will be consequently increased.
- **Enhanced bioavailability:** The bioavailability of riboflavin controlled release GRDF [CRGRDF] is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations.[5]

Disadvantages of floating drug delivery system

- Floating system is not appropriate for those drugs that have solubility or stability problem in G.I. tract.
- These systems need a higher level of fluid in the stomach for drug delivery to float and work efficiently.
- The drugs that are absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
- Some drugs present in the floating system tend to cause irritation to gastric mucosa.[5]

Floating Drug Delivery Systems (FDDS)

- Floating systems was first described by Davis in 1968. FDDS is an efficient technology to increase the gastric residence time in order to improve the bioavailability of the drug. FDDS are low-density systems that have appropriate buoyancy to float over the gastric contents and remain in the

stomach for a prolonged period. While the system tends to floats over the gastric contents, the drug is released slowly at the desired rate which results in increased GRT and reduces fluctuation in plasma drug concentration.[6]

Types of Floating Drug Delivery System[6]

They are of 2 types: 1. Effervescent system
2. Non- Effervescent system

Effervescent System

These buoyant delivery systems utilize matrices prepared with swellable polymers such as Methocel or polysaccharides, e.g., Chitosan, and effervescent components, e.g., Sodium bicarbonate and Citric or Tartaric acid or matrices containing chambers of liquid that gasify at body temperature24^{0}C-26^{0}C. Flotation of a drug delivery system in the stomach can be attained by incorporating a floating chamber filled with vacuum, air, or an inert gas. Gas can be introduced into the floating chamber by the volatilization of an organic solvent (e.g., Ether or Cyclopentane) or by the CO_2 produced as a result of an effervescent reaction between organic acids and carbonate–bicarbonate salt. The matrices are formulated in such a way that upon entry into the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloid. This forms an upward motion of the dosage form and maintains its buoyancy. A decrease in specific gravity causes the dosage form to float on the chime.[6]

They are further classified as: 1. Gas Generating System
2. Volatile Liquid/ Vaccum Containing Systems[4]

1. Gas Generating Systems

A. Tablets

Floating bilayer tablets with controlled release for drug can be developed by using this technique. The low solubility of the drug could be enhanced by using the kneading method, preparing a solid dispersion with β Cyclodextrin mixed in a 1:1 ratio. One layer contained the polymers HPMC K4M, HPMC K100M and CMC (for the control of the drug delivery) and the drug. The second layer contains the effervescent mixture of sodium bicarbonate and citric acid.[4]

B. Floating Capsules

Floating capsules are formulated by filling with a mixture of sodium alginate and sodium bicarbonate. The systems were shown to float as a result of the production of CO_2 that was trapped in the hydrating gel network on exposure to an acidic environment.[4]

C. Multiple Unit Type Floating Pills

The system consists of sustained release pills as ‘seeds’ surrounded by 2 layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is introduced in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This reduction in density is due to production and entrapment of CO_2 within the system.[4]

D. Floating System with Ion-Exchange Resins

A floating system using ion exchange resin that was prepared by mixing the beads with 1M sodium bicarbonate solution.

The loaded beads were then surrounded by a semi permeable membrane to avoid sudden loss of CO_2. Upon contact with gastric contents an exchange of chloride and bicarbonate ions took place that resulted in CO_2 generation thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads. [4]

2. Volatile Liquid / Vacuum Containing Systems

A. Intra-Gastric Floating Gastrointestinal Drug Delivery System

These systems are 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.[4]

B. Inflatable Gastrointestinal Delivery Systems

In these systems an inflatable chamber is introduced, which has liquid ether that gasifies at body temperature to cause the inflatation of the chamber in the stomach. These systems are formulated by

loading the inflatable chamber with a drug reservoir, which can be a drug along with polymeric matrix, encapsulated in a gelatin capsule. After administration through oral route, the capsule tends to dissolve to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and the drug reservoir compartment remains in the stomach. The drug is then continuously released from the reservoir into the gastric fluid.[4]

C. Intragastric Osmotically Controlled Drug Delivery System

It comprises of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the 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 vapour and liquid and has a drug delivery orifice. The osmotically active compartment consists of 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. The osmotic pressure thus created acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate drug release through the delivery orifice. The floating support is also made to contain a bio erodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.[4]

Non-Effervescent Systems

Non-effervescent systems contain a greater level (20%–75% w/w) of one or more gel forming, highly swellable, cellulosic hydrocolloids (e.g., Hydroxy Ethyl Cellulose, Hydroxy Propyl Cellulose, Hydroxy Propyl Methyl Cellulose [HPMC], and Sodium Carboxy Methyl Cellulose), polysaccharides, or matrix-forming polymers (e.g., polycarbophil, polyacrylates, and polystyrene) into tablets or capsules. Upon contact with gastric fluid, these gel formers, polysaccharides, and polymers hydrate and form a colloidal gel barrier that regulates the rate of fluid penetration into the device and thus results in consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density of and confers buoyancy to the dosage form**.**

The various types of this system are as: A. Single Layer Floating Tablets
B. Bi- Layer Floating Tablets
C. Alginate Beads
D. Hollow Microspheres

A. Single Layer Floating Tablets

They are prepared by mixing the drug with a gel-forming hydrocolloid, which swells when comes in contact with gastric fluid and maintains bulk density of less than one. They are formulated by intimate mixing of drug with low-density enteric materials such as Cellulose Acetate Phthalate (CAP), Hydroxy Propyl Methyl Cellulose (HPMC).[4]

B. Bi-Layer Floating Tablets

A bi-layer tablet consists of two layers 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 tend to maintain a bulk density of less than one and thereby it can remain buoyant in the stomach.[4]

C. Alginate Beads

Dosage forms can be developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours.[4]

- **Naveen KB *et al.,*** have designed buoyant oil entrapped gastro retentive calcium pectinate gel beads of Cefixime by emulsion gelation method by employing pectin and sodium alginate as

sustained release polymers. Cefixime is considered as third generation cephalosporin antibacterial agent which results from inhibition of mucopeptide synthesis in the bacterial cell wall. Hence Cefixime beads were prepared by emulsion gelation method by employing pectin and sodium alginate as sustained release polymers in three different ratios and olive oil was used to enable floating property to gel beads. Based on drug entrapment efficiency, buoyancy, swelling and *in*-vitro release, F9 was further subjected to surface morphology by SEM [7]

D. Hollow Microspheres

Hollow microspheres (microballoons), loaded with drug are prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at 400ºC. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in microsphere of polymer with drug.[4]

Methods used for the preparation of floating gel beads are

Preparation of oil-entrapped beads

1. Ionotropic gelation method
2. Emulsion gelation method

1. Ionotropic gelation method

Ionotropic gelation is a method based on the ability of polyelectrolytes to cross link in the presence of counter ions to form hydrogel beads also called as gelispheres. Gelispheres are spherical crosslinked hydrophilic polymeric entity that has a ability of extensive gelation and swelling in simulated biological fluids and thus the release of drug through it is controlled by polymer relaxation. The hydrogel beads are prepared by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations. The cations tend to diffuse into the drug-loaded polymeric drops, resulting in the formation of a three dimensional lattice of ionically crosslinked moiety. Biomolecules can also be loaded into these gelispheres under mild conditions to retain their three dimensional structure.[8]

- **Ramteke KH *et al.,*** have formulated and evaluated Metformin hydrochloride beads by ionotropic gelation technique. Formulation was prepared using ionotropic external gelation method using Ca^{+2} and Al^{+3} ions. Ca^{+2} cross linked beads show sustained release while Al^{+3} cross linked beads shown sustained release of drug about 10 hrs. The entrapment efficiency was also lesser in Ca^{+2} cross linked beads. The Alginate beads swelled and eventually disintegrated in phosphate buffer (pH 6.8). The results revealed that aluminum is better cross linking agent than calcium indicating that valence affects cross linking.[9]

- **Payam K *et al.,*** he has formulated ibuprofen beads by ionotropic gelation. In this study the formulation of CA-alginate beads of ibuprofen, through ionotropic gelation has been investigated. For this purpose, different cross-linking agents including: Ca^{+3}, Ba^{+2}, Mn^{+2} and Pb^{+2} were used in the bead preparation. Next, characterization of beads, size distribution, encapsulation efficiency of ibuprofen within beads, bead swelling and the drug release kinetics were investigated. Results showed that only Ca ion is suitable for Ibuprofen beads.[10]

2. Emulsion gelation method

Polymer is dissolved in distilled demineralised water with stirring. Drug and different concentrations of oil are then added to the polymer solution. This resultant solution containing drug and oil is dropped through 21G needle in to 5% calcium chloride and left at room temperature for 2h. The resultant hydrogel beads are washed twice with distilled water and kept for drying at room temperature up to 12 hours.[9]

- **Kumari A *et al.,*** have designed buoyant oil entrapped calcium pectinate gel beads of Famotidine by emulsion gelation method. Oil entrapped pectinate gel beads was employed to increase gastric retention time of the drug. Results have shown that the obtained bead were capable for floating in gastric fluid and thus increases gastric retention time. Drug release was found to be uniform and maximum for 24hrs around 80%.[11]

Characterization of floating gel beads include

a) Percentage Yield

The prepared floating beads with given size range will be collected and weighed. The measured weight divided by total amount of non-volatile component which are used in the formulation gives percentage yield.[8]

$$\textbf{Percentage yield} = \frac{\textbf{Actual weight of the produt}}{\textbf{Total weight of drug and excipients}} \times \textbf{100}$$

b) Size analysis of floating gel beads

The mean diameter of dried beads was determined by digital vernier calliper by which the size of beads could be determined.

c) Drug Content and Drug Entrapment Efficiency

100mg equivalent drug loaded polymer beads will be dissolved in suitable solvent. It will be stirred using magnetic stirrer. The resulting solution will be then filtered and filtrate will be suitably diluted with suitable solvent.[16]

Drug content can determined spectrophotometrically. Drug content and entrapment efficiency determined using equation:

$$\textbf{Drug content} = \frac{\textbf{Concentration} \times \textbf{Dilution factor}}{\textbf{1000}} \times \textbf{100}$$

$$\textbf{Entrapment efficiency} = \frac{\textbf{Actual yield}}{\textbf{T heoretical yield}} \times \textbf{100}$$

Buoyancy Studies

The *in-vitro* floating study can be performed using a USP dissolution apparatus 2, having 900ml of buffer. The medium temperature was kept at 37± 0.5^0C. Selected 20 beads soaked in the dissolution medium and the medium agitated with a paddle at 50 rpm. After agitation, buoyancy (sink/float) was observed visually.[8,16]

$$\textbf{Percentage buoyancy} = \frac{\textbf{Weight of the floating beads}}{\textbf{Weight of floating beads} + \textbf{weight of the settled beads}} \times \textbf{100}$$

d) Scanning electron microscopy (SEM)

Morphological examination of the surface and internal structure of the dried beads can be performed by using a scanning electron microscope (SEM).[8,14,16]

e) *In-vitro* release study

In vitro release rate studies carried out using USP dissolution apparatus Type II. Suitable dissolution medium (900 ml) is used and maintained at 37± 0.5^0C. The paddle speed is controlled at 50 rpm. At regular interval predetermined sample is withdrawn & fresh medium is added to maintain the sink condition. %CDR from the formulation can be analysed by using UV spectrophotometer.[8,13,20]

f) Stability studies

As per ICH guidelines, the beads filled in hard gelatin capsule shells, stability studies are performed on the formulations as short time stability study at 40^0C±2^0C and 70±5% RH for 3 months to assess their stability. [8,12,24]

Future Potential

Floating dosage form offers various future potential as evident from several recent publications. The reduced fluctuations in the plasma level of drug results from delayed gastric emptying. Buoyant delivery system considered as a beneficiary strategy for the treatment of gastric and duodenal cancers. The floating concept can also be used in the development of various anti-reflux formulations and these are potential to treat the Parkinson's disease. Some of the unresolved critical matters related to the rational development of FDDS include, the quantitative efficiency of floating delivery systems in the fasted and fed states and the correlation between prolonged GRT and characteristics. However, we are as close as we have ever been to see a greater transition of gastric retention devices from developmental level to the manufacturing and commercial level.[13]

Polymers used in floating drug delivery system are

S. No.	Polymer	Source
1.	Guar gum	Endosperm of seed of cynopsis tetragonolobus.
2.	Chitosan	Shell of marine invertibrates.
3.	Xanthum gum	Fermentation of glucose by *Xanthomonas compestris.*
4.	Gellan gum	*Pseudomonas elodea.*
5.	Sodium alginate	*Laminaria hyperboria*

REFERENCES

1. Pritesh J, Vipul P, Himashu S, Girish J, Ushma K. A review article on pharmaceutical aspects of various floating drug delivery system. World J Pharm Pham Sci.2015; 4(4):569-89.
2. Amit KN, Ruma M, Biswarup D. A review on gastro retentive drug delivery system. Asian J Pharm Clin Res.2010; 3(1):2-10.
3. Ruhsar K, Anup O, Ritika A, Kumud U, Himanshu C. Recent trends in floating drug delivery systems-A review. 2017; 6(0):404-22.
4. Vinod KR, Santhosh V, Anbuazaghan S, David B, Padmasri A. Approches for gastroretentive drug delivery sytem. IJABPT. 2010; 1(2):589-601.
5. Kunal PN, Pratik U, Jayant D, Arohi RV, Nirav PC. A review on gastro retentive drug delivery systems and recent approaches. J Pharm Res opinion.2012; 2(1):1-8.
6. Anand S, Rakhee KK. An overview on various approaches to oral controlled drug delivery system via gastroretention. Int J of Pharm Sci review and Res. 2010; 2(2):68-72.
7. Naveen KB, Mounika B, Vasudeva MS. Design and development of buoyant oil entrapped gastro retentive multiparticulate Calcium pectinate gel beads of Cefixime. W J Pharm Pharm Sci.2014; 3(8):764-76.
8. Poonam P, Daksha C, Miland W. A review on ionotropic gelation method. Int J Pharm and Pharm Sci.2012; 4(4):28-32.
9. Ramteke KH, Vansola JB, Tailor DJ, Parmar JR. Formulation and evaluation of Metformin hydrochloride beads by ionotropic gelation technique. JPSI.2012; 1(1):75-78.
10. Payam K, Abbas P, Fereshteh H. Formultion of ibuprofen beads by ionotropic gelation method. Int J Pharm Res.2008;7(3):163-70.
11. Kumari A, Koland M, Jha G, Jha S, Charyulu N. Buoyant oil entrapped calcium pectinate gel beads of Famotidine. IRJP. 2012;3(4):240-50.
12. Sravanthi D, Anusha M, Madhavi S, Shaik F , Buchi NN. Simultaneous estimation of Levodopa and Carbidopa in bulk, pharmaceutical dosage forms and dissolution sample analysis by RP-HPLC-PDA method. JCPRC.2013; 5(11):442-528.
13. Varun KK, Srikanth CP, Ajaykumar B. Design and evaluation of stomach specific drug delivery of Domperidone using floating Pectin beds. IJDDR.2013; 5(1):219-28.
14. Gupta P, Gnanaranjan, Preethi K. Floating Drug Delivery System: A review. Int J Pharm Res and review. 2015; 4(8):37-44.
15. Kulkarni DP, Saboo SS. Polymers used in floating drug delivery system: A review. EJPMR. 2017; 4(8):611-16.
16. Satheeshbabu BK, Sarvaiya GL. A research paper on formulation and evaluation of oil entrapped Calcium pectinate gel beads of Famotidine. Ind J Pharm Sci.2016; 78(2):203-09.
17. Anand SS, Rakhee KK. An overview on various approaches to oral controlled drug delivery system via gastro retention. Int J Pharm Sci Rev Res.2010; 2(2):68-72.
18. Durga J, Arundhati B, Indranii KY, Hari PS, Dinesh C, Jain DA. Formulation and evaluation of oil entrapped floating alginate beads of Ranitidine hydrochloride. Int J Pharm Pharm Sci.2009; 1(1):128-40.
19. Satinder K, Sashi K, Bharat P. A review on sustained release drug delivery system. Int J Pharm and life sciences.2012; 2(3):356-76.
20. Syed I, Maria S, Lahoti S, Zahid Z, Sabina M, Furqan K. Formulation and evaluation of floating drug delivery system of Ramipril.JIPBS.2016; 3(1):85-95.
21. Dusane A, Gaikwad PD, Bankar VH, Pawar SP. A review on sustained release technology. Int J Res in ayurveda and pharmacy.2011; 2(6):1701-08.
22. Vinod KR, Santosh V, Anbuazghan S, David B, Padmasri A, Sandhya S. A review on gastroretentive approaches of drug delivery systems. IJABT.2010; 1(2):590-601.

23. Pradeep KN, Vidyasagar G. Preparation and evaluation of Calcium alginate beads of Clarithromycin. Der Pharmacla Sinca.2010; 1(1):29-35.
24. El-Kamel AH, Al- Gohary OMN, Honsy EA. Alginate-Diltiazem hydrochloride beads: Optimization of formulation factors, in-vitro and in-vivo availability. J Microencapsulation.2003; 20(2):211-25.