Features and Facts of Gastro-retentive Drug Delivery System: A Review

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Abstract

Gastro-retentive Drug Delivery System (GRDDS) is one of the achievable and appreciable approaches in controlled release drug delivery systems.These systems overcome several limitations regarding the oral drug delivery system. Various limitations which vary from patient to patient or may also vary from drug to drug. However, the therapeutic efficacy and bioavailability of therapeutic agents are laid on the retention time of within the targeted site.Hence, GRDDS enhances bioavailability by increasing residence time in the stomach along with showing targeted action within stomach as well as in the upper small intestinal window without affecting gastric emptying time. Bioavailability can be enhanced, especially for those drug candidates which have narrow absorption windows, shorter half-life, areunstable at alkaline pH, etc. Thus, GRDDS comprises of different classes of systems which actthrough different ways of action including Effervescent systems.Floating systems. Raft forming systems. Ion exchangeable resins. High density systems etc. Today, GRDDS has earned a wide range of opportunities and scope inthe marketcomparatively conventional dosage forms.

Keywords: -Gastro- retentive Drug Delivery system,Bioavailability,Gastric Retention time, Various Approaches.

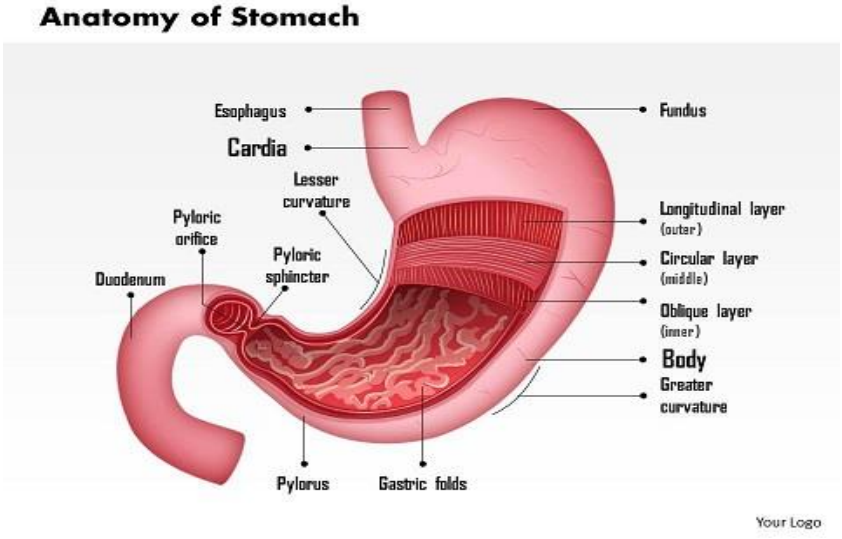
Introduction

Oral Route of drug administration is the most compliable, easy, preferred and convenient way of drug administration. oral drug delivery is most acceptable due to several merits including ease of administration, cost-effectiveness, patient compliance, non-invasive in nature, flexibility in formulation, ease to store and transport[1].There are some limitations of some drugs such as short half-life, frequent dosing to achieve adequate therapeutic range, quickly eliminated from Gastro-intestinal tract;some drugs are unstable at gastric pH and may cause irritation to mucosal linings; some are less soluble at elevated pH, etc. There are many drugs are prone to degradation due to a high pH range (e.g.,captopril, ranitidine, metronidazole etc.)[2],[3].

Therefore, to overcome these limitations, the development of oral sustained controlled release formulations is an attempt to increase gastric residence time and thereby release the drug slowly and locally in the GI tract[4].One of the novelapproachesto avoid these adversities is GRDDS. The dosage forms that can be retained in the stomach for a prolonged time and releases the drug at desired rate and time are called as Gastro- retentive drug delivery system [GRDDS] or gastro- retentive dosage forms[5].

GRDDS is a promising approach for the treatment of not only systemic diseases but also local diseases.Local diseases like peptic ulcers associated with H. pyloriinfection, Zollinger-Ellison syndrome, Reflux esophagitis, etc. By using various antibiotics GRDDS is used for the eradication of deeply buried H. Pyloribacteria[6],[7],[8],[9]. GRDDS are preferable to conventional dosage forms by increasing solubility, improving bioavailability,increasing therapeutic efficacy by enhancing drug absorption and targeted action of the drug at the gastro-retentive tract[10]. This Review tells us about the anatomy and physiology of the stomach, factors that impact on GRT, various GRDDS that have been developed to date, merits and demerits of GRDDS in comparison to conventional dosage forms.

Diagram Of Stomach: -



Anatomy And Physiology of stomach: -

In The Development of GRDDS, the stomach plays a vital role. The stomach volume is about 1.5L. There are two parts of the stomach one is proximal and another is the distal stomach. There are three basic anatomical regions of the stomach are[11].

A) Fundus
B) Body
C) Antrum(pylorus)

The Proximal Stomach comprises of fundus and body whereas,the distal stomach comprises of antrum(pylorus). The Fundus and body store the undigested food while the distal part(antrum) provides a site for grinding and mixing of food. The antrum also plays a key role in gastric emptying by propelling action through the pylorus to the duodenum. Propelling action of stomach occurs during fed state and empty state of stomach[12],[13].

The Motility Pattern occurs throughout the stomach and intestine every 2 to 3 hours. This event is called Migrating Myoelectric Complex (MMC)[14]. Each cycle of MMC consists of 4 phases.The hormone motilin in the blood regulates the mechanism and span of the phase cycle.

1) Phase 1(Basal Phase): -This basal phase lasts for 30-60 minutes with very less or with no contractions.
2) Phase 2(Pre-Burst Phase): - This phase of MMC continues up to 20-40 minutes with the intermittent contractions, which increase gradually.
3) Phase 3 (Burst Phase): -The contractions in this phase last upto 10-20 minutes, which are regular and intense for short time. These contractor waves are also called "House Keeper Waves "or burst waves. It helps to propel food from the stomach to the small intestine.
4) Phase 4: - It lasts for 0-5 minutes, and is a transition period between 1 and phase 3.

Factors Affecting on Gastric Retention[15]: -

- **Density**: -The system can easily float on gastric content;therefore, the density of systems must be less than gastric content (1.004g/ml)
- **Size**: - The dosage forms which have diameter greater than7.5mm have a significant GRT than those having diameter of 9.9mm.
- **Shape of Dosage Form**: - The multiple unit formulations show significant amount of bioavailability than single unit dosage forms. Tetrahedron shape dosage forms stay in stomach for longer duration than other of similar size.
- **Fed or unfed state: -**In an unfed or fasting state, the rate of MMC wave is high, which promotes more gastric motility that maylead to short gastric retention. Strong motor activity that lasts for 1.5-2 hours. while in a fast, state the MMC is delayed and the GRT is longer.
- **Nature of Meal: -** In fed state, the presence of fatty acids or indigestible polymers can decrease gastric emptying rate and prolong the GRT.
- **Caloric Content ofMeal:** -Caloric content in meal increases GRT by 4-10 folds.
- **Gender**: -The GRT in males is less (3.4 hours) as compared to females (4.6 hours) regardless of height, weight, and body surface area.
- **Age: -** People with age more than 70 have longer GRT.

Table 1. Commonly used drug in formulation of gastro retentive dosage forms[16],[17]

Sr.no	Dosage forms	Drugs
1.	**Floating Tablets**	Aspirin, Amoxicillin trihydrate, Atenolol, Acetaminophen, Captopril, Cinnarizine, Ciprofloxacin, Diltiazem, Isosorbide mononitrate, p-Amino benzoic acid (PABA), Prednisolone, Nimodipine, Sotalol, theophylline, Verapamil
2.	**Floating Capsules**	Chlordiazepoxide HCL, diazepam, furosemide, L-DOPA and Benserazide, Nicardipine, Misoprostol, Propranolol, Pepstatin.
3.	**Floating Microspheres**	Aspirin, Griseofulvin, p-nitro aniline, ibuprofen, Terfenadine, Tranilast.
4.	**Floating Granules**	Diclofenac sodium, Indomethacin, Prednisolone

Table 2. Gastro retentive products available in market[18]

Brand Name	Active Ingredients

Cifran OD®	Ciprofloxacin
Madopar®	L-DOPA and Benserazide
Valrelease®	Diazepam
Topalkan®	Aluminium-magnesium antacid
AmalgateFlat Coat®	Aluminium-magnesium antacid
Liquid Gavison®	Aluminium hydroxide
Conviron®	Ferrous sulfate
Cytotec®	Misoprostol

There are different approaches have been developed to ensureadequate gastric retention and release of dru

1] FLOATING SYSTEM: -

A) Effervescent

B) Non-effervescent

2] NON- FLOATING SYSTEM

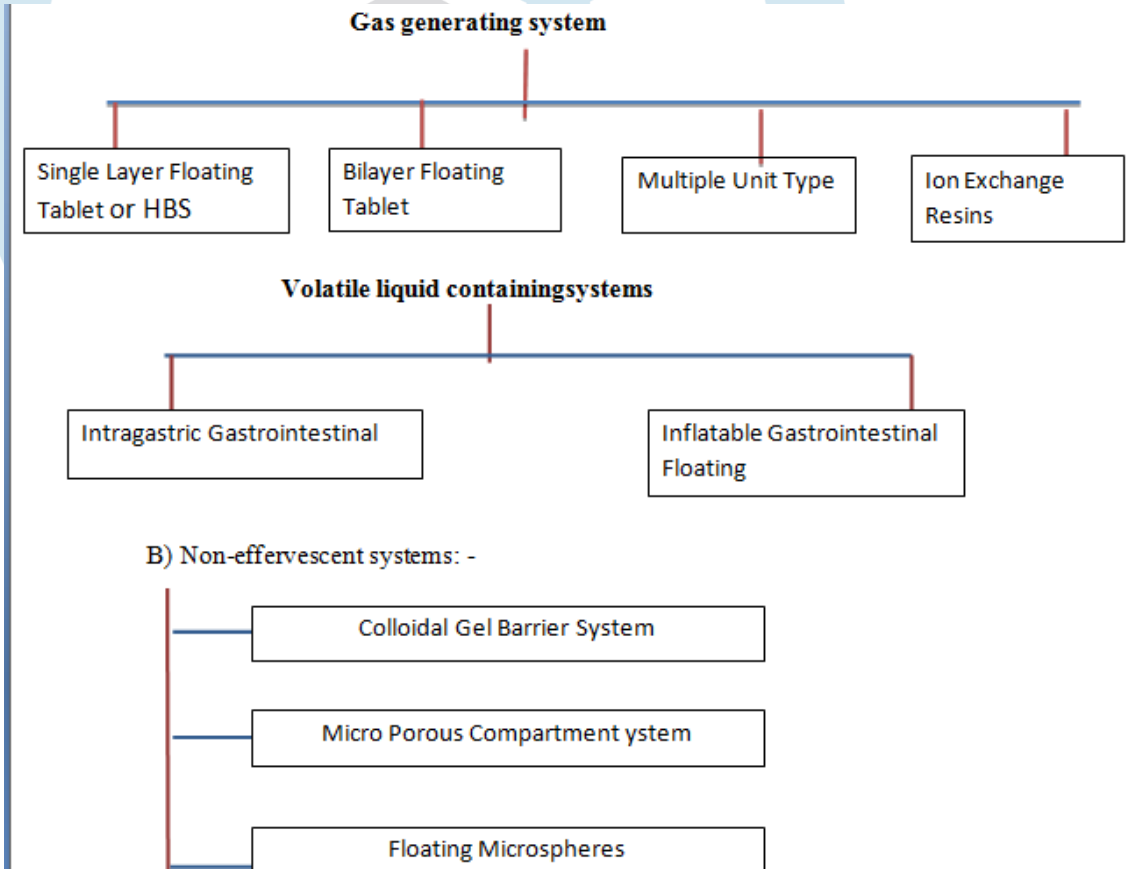
1]Floating System:

A) Effervescent systems: -

a) Gas generating systems

b) Volatile liquid containing systems

Gas generating system



2] Non –Floating System: -

Volatile liquid containing systems

EFFERVESCENT SYSTEMS:

The Effervescent system is a buoyant system composed of polymers such as polysaccharidese.g. Chitosan. It swells when it is exposed to gastric fluid. Some polymers are used as release retardant polymers like ethyl cellulose, eudragitL100,polyethylene oxide N12K,xanthumgum[19].

Along with swellable polymers, some effervescent agents like sodium bicarbonate, citric acid and tartaric acid are also incorporated that effervesce at body temperature. for the generation of CO2, the optimum ratio of citric acid and sodium

bicarbonate should be 0.76:1[20].By the gas- generating reactions carbon dioxide is liberated and entrapped in gel hydrocolloid;because of these reactions taking place, the system becomes buoyant enough to float over gastric fluid[21]. Effervescent systems are further classified into 2 types as follows-

1] Gas Generating Systems

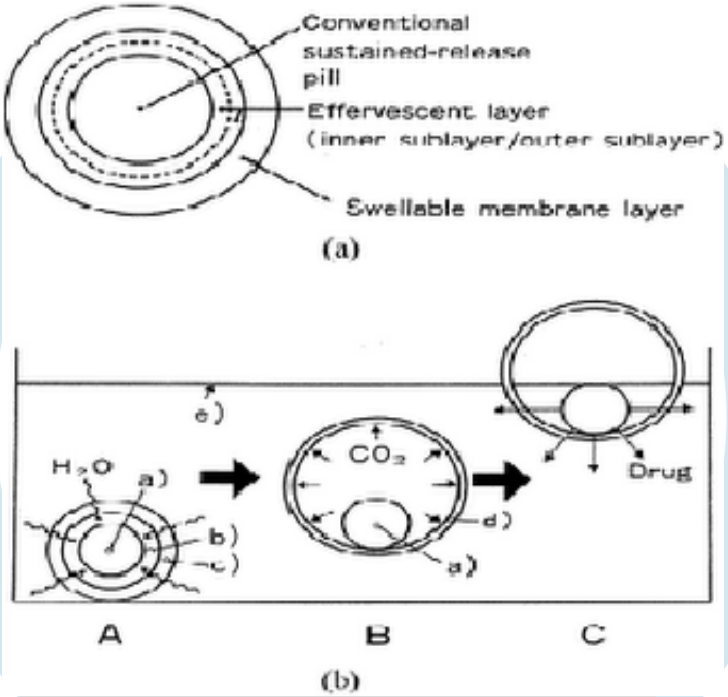
2] Volatile Liquid-Containing System

1] Gas Generating System: -

a) Single Layer Floating Tablet/ Hydro DynamicallyBalanced System: -

This system consists of the gas (CO_2) generating agents i.e., sodium bicarbonate and organic acids like citric or tartaric acids and drugs to be mixed in the matrix tablet. Therefore,this system can float on the gastric fluid for a longer period. The drug is slowly released from the system in a controlled and predetermined manner. This facilitates its constant therapeutic level over longer duration. This mechanism of action leads to anincrease in gastric retention time without fluctuation in the plasma concentration of the drug. The residual system is expelled from the stomach after a complete release of drug[22].

Fig: -



b) Bilayer Floating Tablet: -

Bilayer Tablet consists of two layers, one half of the tablet contains an immediate release layer and another contains a sustained release layer. The Initial dose is released by the immediate release layer and the sustained release layer absorbs the gastric fluid that creates a colloidal gel barrier on its surface. This maintains the floatability of the system for an extended period of time.

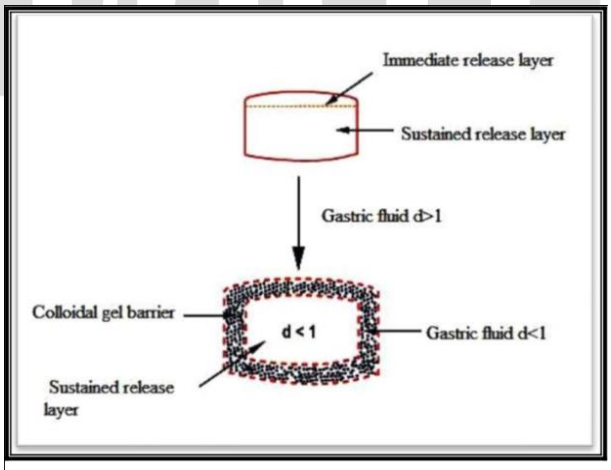


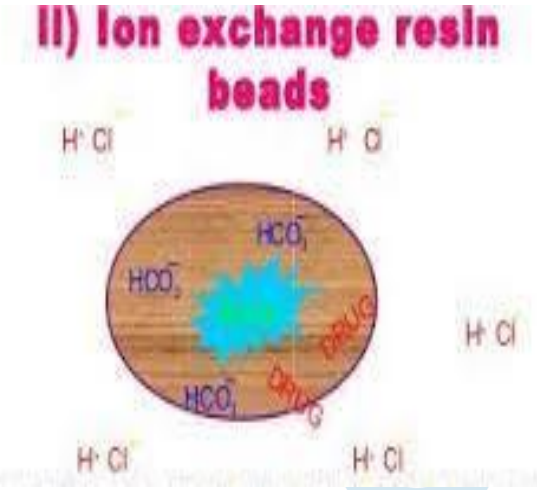
Figure 1.14: Bilayer floating tablet

c) Multiple Unit Type/ Floating Pills: -

These are multiple unit floating systems as pills or seeds which are encapsulated by a double layer. The inner layer consists of effervescent components and the outer layer is made up of swellable polymer.When it comes in contact with GI fluid, initially it sinks into it, but when carbon dioxide is liberated then its bulk density lowers and floats over the gastric fluid. The pills are seeming like swollen balloons[23].

d) Ion Exchange Resins: -

Ion exchange resins are multiple unit type drug delivery systems loaded with bicarbonate ions and the negatively charged drug condensed on the resin. Then these beads are then covered with a semi-permeable membrane to avoid rapid loss of carbon dioxide. Upon administration, these beads come in contact with the acidic fluid of thegastrointestinal tract which results in an exchange of chloride and bicarbonate ions. Due to this reaction, CO2 is generated and trapped in membrane; this leads to floatation of beads on top of gastric content[24].

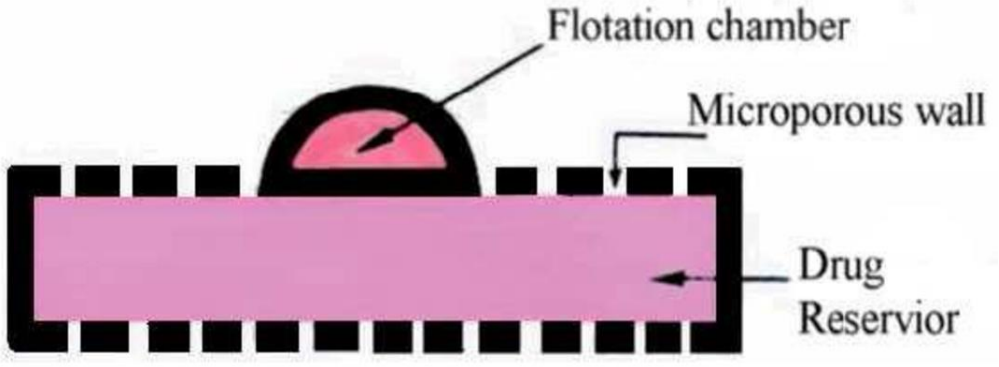


2]Volatile liquid containing systems: -

The inflatable chamber is a vital part of the volatile liquid containing system. The inflatable chamber contains volatile liquids,e.g., ether and cyclopentane that gasify at body temperature to inflate the chamber in the stomach. The system also consists of a bio-erodible plug made up of polyvinyl alcohol, polyethylene that slowly dissolves in GI fluid. After the dissolution it causes the inflatable chamber to inflate, release gas and collapse after the desired time leads to ejection of the inflatable system from the stomach[25].

a) Intra-Gastric Floating Gastrointestinal Drug Delivery System: -

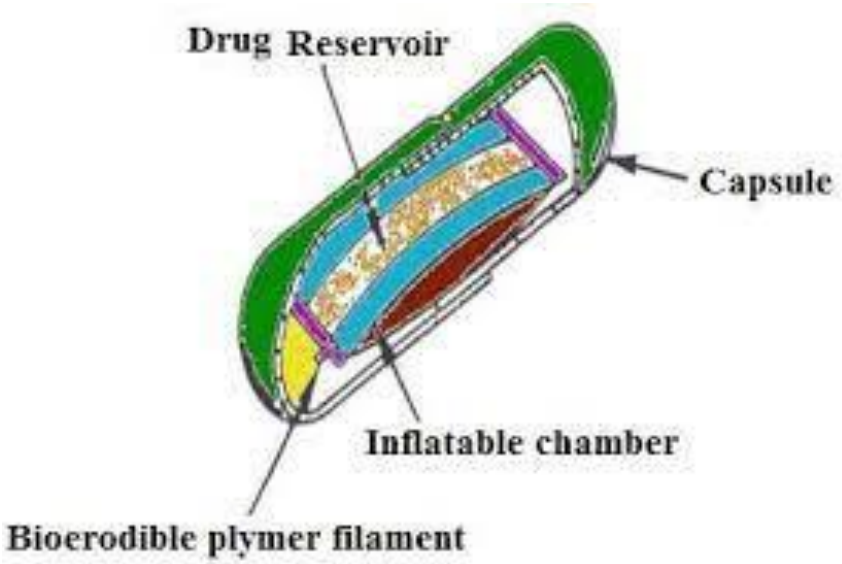
A Floatation Chamber inside the system makes it float in the stomach and the drug reservoir is enclosed in a micro porous compartment system. There are two apertures present at the top and bottom walls that permit the inflow of gastric fluid and dissolve the drug. Thefloatation chamber may be vacuum sealed, filled with air, or filled with a harmless gas.[26],[27].



b) Inflatable Gastrointestinal Delivery System: -

This system utilizes an inflatable chamber that is filled with ether that gasifies at body temperature in order to inflate in the stomach. Typically, a drug reservoir is placed in the inflatable chamber which is loaded with a polymer matrix and this is covered in a gelatin capsule.

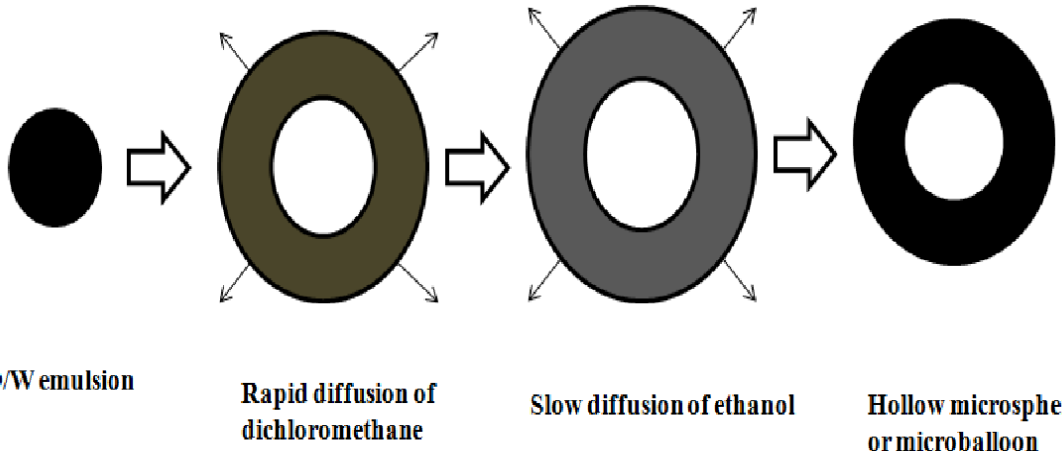
Upon oral administration, as the capsule dissolves in the GIT the drug reservoir along with the inflatable chamber is released into the gastric fluid.After release, the chamber inflates and the drug reservoir is released into the stomach[28].



B] Non- Effervescent Systems: -

It is one of the approaches, that involves use of gel-forming, highly swellable, polysaccharides and matrix forming polymers like polyacrylates, polymethacrylates, polycarbonates and polystyrene. The uniform mixing of drug with gel-forming hydrocolloids forms the systems which in contact with gastric fluid entraps the air and get swells. It confers the shape and buoyancy of these dosage forms. These systems are based on the mechanism of swelling or adhesiveness of polymers used. The various types of approaches of this system are as follows[29]:

1) Colloidal Gel Barrier System: -Such a system contains drugs with the hydrocolloid gel formingagents that remain buoyant in the stomach. This system consists of high amounts of gel forming agents which are highly soluble e.g., Hydroxy propyl methyl cellulose, polysaccharide, hydroxyl-ethyl cellulose. Etc. Upon administration the hydrocolloid in the system comes into contact with gastric fluid;it hydrates and creates a gel like barrier around its surface[30].
2) Micro PorousCompartment System: - These Techniques involve the drug reservoir being enclosed inside a micro porous compartment that has apertures on the top and bottom walls. This system utilizes a floatation chamber that enables the delivery system to float over the GI fluid. The drug reservoir is enclosed within the chamber. When the fluid enters through apertures of the compartment and dissolves the drug. Allowing it to be transported to the intestine and absorbedcompletely[31].
3) Floating Microspheres: -Floating microspheres use non-effervescent approach to retain in the stomach. Microspheres are tiny, hollow, spherical and free-flowing made up of proteins or polymers, ideally having a size range of less than 200micro meter. Thefloating time of microspheres depends on the type and number of polymers. A novel emulsion solvent diffusion method is used to prepare hollow microspheres loaded with drug. To prepare a solution, ethanol/DCM solution of drug and enteric acrylic polymer were gently poured into a thermally controlled solution of PVA (40◦C).
Dichloromethane was evaporated, this led to the generation of gas in dispersed polymer droplets. The micro balloons float continuously over the gastric content containing surfactants for more than 12hours.The active constituents are released at a specified rate at the targeted site of the stomach. Microspheres are multiple floating units.Hence, having exclusive advantages over others[32],[33],[34],[35].



4) Alginate Floating Beads: -

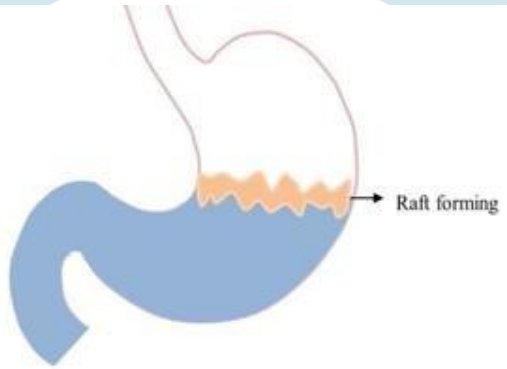
These buoyant systems are also promising multiple-unit floating systems developed by the calcium alginate complex. They were made by using Ca+ and low methoxylated pectin (anionic polysaccharide) or Ca+ low methoxylated pectin and sodium

alginate. These are spherical beads of approximately size range 2.5mm. The precipitate of calcium alginate is obtained by dropping the sodium alginate solution into an aqueous solution of calcium chloride. These beads are separated and freeze-dried at -40◦C for 24 hours, leading to the formulation of a porous system, which can maintain a floating force for over 12 hours[36],[37].

5) Raft-Forming Systems: -

The raft forming system is a foremost approach that involves the formation of a continuous layer called a raft. Raft is a viscous cohesive gel in contact with gastric fluid[38],[39]. Due to the generation of CO2 within the system, the layer of gel tends to float on gastric fluid without affecting the gastric emptying time for a prolonged period of time[40].

Usually, the system includes the combination of gel-forming agents like sodium alginate and gas- generating or alkaline agents like bicarbonates and carbonates that are responsible for generation of CO2 gas. Due to generation of gas within the system, the layer of gel tends to float over gastric fluid. The active constituent releases slowly at desired rate and the residual system is expelled from the stomach, this ultimately leads to increased GRT and sustained release of drug at a predetermined rate[41]. Raft forming systems are usually used to treat diseases like hyperacidity, reflux esophagitis therefore, formulations contain antacids like aluminum hydroxide or calcium carbonate[42],[43],[44],[45].



2] Non – Floating Systems: -

a) High Density Systems: -

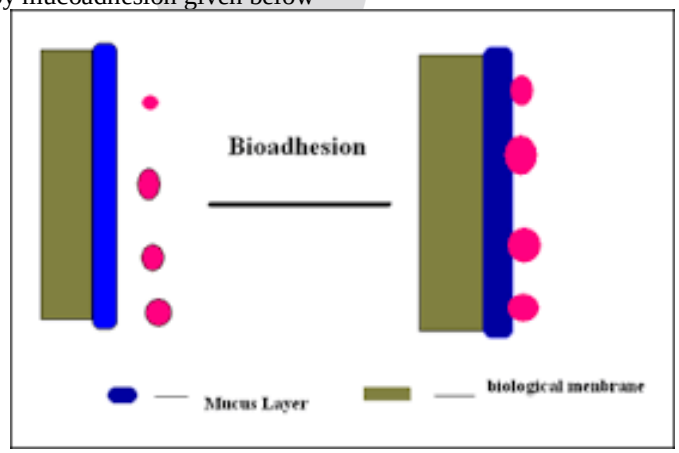
These formulations should be heavy enough to remain intact in GIT for a longer duration. These are developed in such a way that their density must be greater than the density of normal gastric content (1.004g/cm3)[46].The drug is coated over heavy core and mixed with other excipients which are barium sulfate, zinc oxide, ferrous oxide, titanium dioxide[47].These materials increase density by about 1.5-2.4g/cm3.For significant gastric retention time and sedimentation in gastric fluid, the density of the system should be about 2gm/cm3 and are capable to withstand during peristaltic movements[48].Therefore,these systems are also called sinking or non- floating systems. These systems experienced less patient compliance because of the high amount of drugs required to maintain a high density of systems.

b) Bio Adhesive or Mucoadhesive Systems: -

The mucoadhesive system was first introduced by Park and Robinson in 1984[49].By increasing the adherence of system to gastric epithelial cell surface, can obtain a longer GRT of drug [50],[51]. Mucoadhesive materials are an integral part of system that may be synthetic or natural polymers. Adhesion of the system to gastric mucosa occurs through various chemical bonding like ionic bonds, covalent bonds, H- Bonding, van der Waals,etc[52].

Therefore,the presence of chemical groups on molecules impacts on nature of the adhesion of molecules. Mucoadhesive polymers commonly used are Carbopol, chitosan, sodium alginate, HPMC, PEG etc[53].Mucoadhesion involves 2 steps contact step and consolidation. In the contact step there is simply contact, swelling and, wetting occur. While in the consolidation step there is bond formation takes place to assist prolonged adherence of system to mucosa[54].

There are various theories followed, by mucoadhesion given below[55]-



c) Expandable Systems: -

Wetting Theory	An intimate contact occurs between a bio-adhesive polymer and a mucus membrane.
Diffusion Theory	There is a physical interweaving or entanglement of mucin and polymer.
Electronic Theory	Due to electrostatic force of contraction between glycoprotein mucin network and mucoadhesive.
Adsorption Theory	Adherence is due to primary forces (ionic, covalent), secondary forces (Vander-Waal, H-bonding, hydrophobic forces) between surfaces.
Fracture Theory	Force requires to detach the polymer from the mucus is known as a fracture.

Expandable systemsareanother type of GRDDS, as these establish longer GRT increases in their volume and shape. The complete mechanism of action of this system involves 3 configurations. Small size for easy oral administration, expanded form of system to remain intact in the stomach and to avoid an exit from pyloric sphincter, size reduction for expulsion and evacuation from the stomach after complete drug release[56],[57].These systems canbe obstructed at pylorus; therefore, these are named "plug-type systems".12-18mm expanded state should be needed to remain as logged at pyloric sphincter for many hours even in the fed state. The rate and duration of swelling of the system are based on the degree of cross-linking between the polymeric chains. If a high degree of cross-linking, then there is the less swelling capacity of the polymeric chain.

d) Magnetic Systems:

These systems are based on the application of magnetic fields, a small internal magnet and a magnet placed externally on the abdomen over the position of the stomach[58].The movement of gastro-retentive formulation with a small internal magnet is controlled by the position of external magnet and by this mechanism the GRT can be enhanced. But this system compromises patient compliance because of the external magnet placed over the stomach with a degree of precision through which the internal magnet along with formulation can work properly. Ito et al, used the bio-adhesive granules, which consist of ultra-fine ferrite. They carry them to the esophagus with the external magnet, initially for 2 min and almost all the ferrite granules were able to stay in the region after 2hours[59].

Merits and Demerits of Gastro-retentive Drug Delivery System: -

Approach	Merits	Demerits	reference
High density system	1) It can sink in GI fluid for a longer duration. 2) Targeted therapy at stomach or upper small intestine window is possible.	1) Technically it is difficult to formulate a formulation with a density of about 2.8-3gm/cm3. 2) It is not useful in human beings and till date not available in the market.	[60],[61]
Low Density system	1) Reduced dose frequency. 2) Reliable to treat local diseases of the GI tract e.g., peptic ulcers. 3) Enhance the bioavailability of drug by increasing in retention time of system. 4) No risk of dose dumping. 5) Improves patient acceptance.	1) FDDS requires high gastric fluid requirement to float. 2) Single-unit low density system may stick and which may produce chances of mucosal irritation. 3) Single-unit dosage forms are comparatively less reliable than multi-unit systems.	[62],[63],[64]

Bio-adhesive systems	1) Very reliable for targeted local drug delivery. 2) No risk of dose dumping. 3) Reduced dose frequency. 4) Increase in bioavailability by increase in adherence time of system to mucosa.	1) Because of continuous secretion of mucin in GIT bio-adhesion of the system to GI mucosa is difficult. 2) There may be a high risk of adhesion to the esophagus which may lead to collateral lesions.	[65],[66],[67],[68]
Magnetic system	1) Magnetic systems can extend the GRT of a system by means of applied magnetic field.	1) Low patient acceptance. 2) It is not widely used. 3) Performance of formulation is depending on the precision of position of external magnet on the stomach; it might be critical.	[69],[70],[71],[72]
Ion exchange resin	1) upon arrival of system in gastric environment CO_2 is released by an exchange of chloride and bicarbonate ions leading to system becomes more buoyant.	2) Time-consuming manufacturing process. 3) Not most widely used.	[73]

In-vitro assessment:

In-vitro assessment for GRDDS is an essential part to predict the various parameters which are comparatively related to the in-vivo parameters like gastric transit time, gastric retention time, swelling and bio-adhesiveness[74].

a) Buoyancy Lag Time: -

The time taken by the system to come onto the surface or to float is known as buoyancy lag time. It is predicted by using USP dissolution apparatus containing 900ml of 0.1N HCL as a dissolution medium which is kept at a temperature of 37°C[75].

b) Floating Time: -

It can be also determined by using USP dissolution apparatus containing 900ml of dissolution medium maintained at 37°C. By observing visually, the time required to remain float for the system can be determined[76].

c) Specific Gravity/Density: -

The determination of the specific density of formulation is a foremost part that impacts the floating behavior, which is estimated by using the Displacement method.

d) Water Uptake: -

The water uptake capacity of the system is directly related to the swelling capacity. it is estimated by periodical removal of the system from the dissolution medium and calculating of weight change[77].

Water Uptake (WU)= $(W_t-W_i)*100/W_i$

Where,

W_i= Initial weight

W_t= weight at time t

e) Weight Variation: -

The individual weight and then the average weight of random 20 tablets is calculated and then compare the individual weight of tablet with the average weight. From this data weight variation is calculated.

f) Hardness and Friability: -

There are various types of testers are used for hardness testing like Pfizer tester, Monsanto tester, Strong cob tester, etc. Roche friabilator is used to determine the friability of tablets[78],[79].

In-Vivo assessment: -

a. Radiology: -

The barium sulfate is used as a radio-opaque agent along with a gastro retentive system to determine its position in GIT concerning time using an X-ray. To record the precision of position of dosage form, X-ray at different intervals is taken[80],[81].

b. Scintigraphy: -

In Scintigraphy rather than X-ray, 99mTc pertechnetate is used as a emitting material to record the image of system. Same as Radiology Scintigraphy is used to record the precision of dosage forms in the body[82],[83].

c. Gastroscopy: -

This is a widely used technique for imagingdeep inside body parts like the stomach, duodenum, esophagus and small intestine. In this technique, different types of endoscopes are used such as optical, tubular, slender, etc[84],[85].

d. MagneticMarkerMonitoring: -

This technique is radiation less hence, it is non-hazardous. In this, the dosage form is incorporated with traces of ferromagnetic particles and it acts as a magnetic dipole forrecording the magnetic dipole field by an apparatus responsive to bio-magnetic measurement. Gastrointestinal motility and dissolution behavior of dosage form can be recorded by this technique[86].

e. Ultrasonography: -

In this technique ultrasounds are used to view deep inside the body structures. The demerit of this technique isit's non-detect ability at entrails[87].

Conclusion: -

The ultimate aim of the Gastro-retentive Drug Delivery System is to enhance the gastric retention time period of formulations through which targeted drug delivery of a therapeutic amount of drug and maintenance of desired plasma drug concentration can be achieved. The incomplete release of drugs has a great impact on the bioavailability of drug. Some drugs get emptied promptly from stomach to intestine; hence these are not able to provide desired therapeutic efficacy. Since there are various promising approaches of GRDDS have been developed like FDDS, ionic exchange resins, raft forming systems, expandable systems, magnetic systems, etc. which act through different mechanisms of action. Drugs thathave a narrow therapeutic index, which is unstable at acidic pH,and instability at alkaline pH GRDDS have the potential to improve the therapeutic efficacy of these drug candidates. Local GI disorders became easy to treat with the use of GRDDS such as Peptic ulcer, reflux esophagitis, hyperacidity, Zollinger-Ellison disease, etc.

REFRENCE

1. [1]Lopes CM, Bettencourt C, Rossi A, Buttini F, Barata P. Overview on gastroretentive drug delivery systems for improving drug bioavailability. International journal of pharmaceutics. 2016 Aug 20;510(1):144-58.
2. [2]Nayak AK, Malakar J, Sen KK. Gastroretentive drug delivery technologies: Current approaches and future potential. Journal of Pharmaceutical Education and Research. 2010 Dec 1;1(2):1.
3. [3]Kesarla RS, Vora PA, Sridhar BK, Patel G, Omri A. Formulation and evaluation of floating tablet of H2-receptor antagonist. Drug development and industrial pharmacy. 2015 Sep 2;41(9):1499-511.
4. [4]Amit Kumar N, Ruma M, Biswarup D. Gastroretentive drug delivery system: a review. Asian Journal of Pharmaceutical and Clinical Research. 2010 Jan;3(1):1-0.
5. [5]Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. Journal of Controlled release. 2000 Feb 3;63(3):235-59.
6. [6]Prinderre P, Sauzet C, Fuxen C. Advances in gastro retentive drug-delivery systems. Expert opinion on drug delivery. 2011 Sep 1;8(9):1189-203.
7. [7]Aoki H, Iwao Y, Mizoguchi M, Noguchi S, Itai S. Clarithromycin highly-loaded gastro-floating fine granules prepared by high-shear melt granulation can enhance the efficacy of Helicobacter pylori eradication. European journal of pharmaceutics and biopharmaceutics. 2015 May 1;92:22-7.
8. [8]Adebisi AO, Laity PR, Conway BR. Formulation and evaluation of floating mucoadhesive alginate beads for targeting H elicobacter pylori. Journal of Pharmacy and Pharmacology. 2015 Apr;67(4):511-24.

9. [9]Kim JY, Bae HJ, Choi J, Lim JR, Kim SW, Lee SH, Park ES. Efficacy of gastro-retentive forms of ecabet sodium in the treatment of gastric ulcer in rats. Archives of pharmacal research. 2014 Aug;37(8):1053-62.
10. [10]Tripathi J, Thapa P, Maharjan R, Jeong SH. Current state and future perspectives on gastroretentive drug delivery systems. Pharmaceutics. 2019 Apr 20;11(4):193.
11. [11]Pant S, Badola A, Kothiyal P. A review on gastroretentive drug delivery system. Indian Journal of Pharmaceutical and Biological Research. 2016 Apr 1;4(2):1.
12. [12]Vantrappen GR, Peeters TL, Janssens J. The secretory component of the interdigestive migrating motor complex in man. Scandinavian journal of gastroenterology. 1979 Sep 1;14(6):663-7.
13. [13]Wilson CG, Washington N. The stomach: its role in oral drug delivery. In physiological pharmaceutical: Biological barriers to drug absorption, Edited rubinstein MH.
14. [14]Jassal M, Nautiyal U, Kundlas J, Singh D. A review: Gastroretentive drug delivery system (grdds). Indian journal of pharmaceutical and biological research. 2015 Jan 1;3(1):82.
15. [15]Rathod HJ, Mehta DP, Yadav JS. A review on Gastroretentive Drug Delivery Systems. PharmaTutor. 2016 Jul 1;4(7):29-40.
16. [16]Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: a review. Aaps PharmSciTech. 2005 Sep;6(3):E372-90.
17. [17]Vyas SP, Khar RK. Gastroretentive systems. Controlled drug Delivery. Vallabh Prakashan, Delhi, India. 2006:197-217.
18. [18]BAVISIA KD. FORMULATION AND EVALUAT.
19. [19]Meka VS, Li CE, Sheshala R. Design and statistical optimization of effervescent floating drug delivery system of theophylline using response surface methodology. Acta Pharmaceutica. 2016 Mar 31;66(1):35-51.
20. [20]Sanjay S, Vaibhav J, Kumar BP. Gastro retentive drug delivery systems. InNational Institute of Pharmaceutical Education and Research (NIPER), Pharmatech 2003.
21. [21]Satinderkakar RS. Gastroretentive drug delivery systems: A review. African Journal of Pharmacy and Pharmacology. 2015 Mar 29;9(12):405-17.
22. [22]Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. Journal of Controlled release. 2000 Feb 3;63(3):235-59.
23. [23]Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage forms. Journal of controlled release. 2003 Jun 24;90(2):143-62.
24. [24]Kouchak M, Atyabi F. Ion-exchange, an approach to prepare an oral floating drug delivery system for diclofenac. Iranian Journal of Pharmaceutical Research. 2022 May 20;3(2):93-7.
25. [25]Mayavanshi AV, Gajjar SS. Floating drug delivery systems to increase gastric retention of drugs: A Review. Research Journal of Pharmacy and Technology. 2008 Oct;1(4):345-8.
26. [26]Atyabi F, Sharma HL, Mohammad HA, Fell JT. Controlled drug release from coated floating ion exchange resin beads. Journal of controlled release. 1996 Oct 1;42(1):25-8.
27. [27]Shah SH, Patel JK, Patel NV. Stomach specific floating drug delivery system: A review. Int J Pharm Tech Res. 2009 Jul;1(3):623-33.
28. [28]Bhardwaj V, Nirmala HS. Floating drug delivery system: A review. Pharmacophore. 2013 Jan 1;4(1):26-38.
29. [29]Sanjay S, Joshi V, Barpete PK. Gastroretentive drug delivery system: Current approaches. J. Pharm. Res. 2009 May;2(5):881-6.
30. [30]Gupta R, Tripathi P, Bhardwaj P, Mahor A. Recent advances in gastro retentive drug delivery systems and its application on treatment of H. Pylori infections. Journal of Analytical & Pharmaceutical Research. 2018;7(4):404-10.
31. [31]Chandiran S, Kumar BP, Narayan V. Formulation and in vitro evaluation of floating drug delivery system for salbutamol sulphate. International Journal of Pharma Biomed Sciences. 2010 Jun;1(1):12-5.
32. [32]Jain NK. Progress in controlled and novel drug delivery systems. CBSS. Gopalakrishnan et al. Journal of Pharmaceutical Science and Technology. Publishers and Distributors, New Delhi, Bangalore. 2004;3(2):84-5.
33. [33]Goyal M, Prajapati R, Purohit KK, Mehta SC. Floating drug delivery system. Journal of current pharmaceutical research. 2011;5(1):7-18.
34. [34]Khan PD, Vinchurkar K. Features & Facts of Gastroretentive Drug Delivery System–A Review Gastroretentive İlaç Dağıtım Sisteminin Özellikleri ve Gerçekleri-Bir İnceleme.
35. [35]Satinderkakar RS. Gastroretentive drug delivery systems: A review. African Journal of Pharmacy and Pharmacology. 2015 Mar 29;9(12):405-17.
36. [36]Nayak AK, Malakar J, Sen KK. Gastroretentive drug delivery technologies: Current approaches and future potential. Journal of Pharmaceutical Education and Research. 2010 Dec 1;1(2):1.
37. [37]Gupta R, Tripathi P, Bhardwaj P, Mahor A. Recent advances in gastro retentive drug delivery systems and its application on treatment of H. Pylori infections. Journal of Analytical & Pharmaceutical Research. 2018;7(4):404-10.
38. [38]Vinod KR, Vasa S, Anbuazaghan S, Banji D, Padmasri A, Sandhya S. Approaches for gastrotentive drug delivery systems.

39. [39]Sawicki W. Pharmacokinetics of verapamil and norverapamil from controlled release floating pellets in humans. European journal of pharmaceutics and biopharmaceutics. 2002 Jan 1;53(1):29-35.
40. [40]Pandey A, Kumar G, Kothiyal P, Barshiliya Y. A review on current approaches in gastro retentive drug delivery system. Asian Journal of Pharmacy and Medical Science. 2012;2(4):60-77.
41. [41]Ibrahim HK. A novel liquid effervescent floating delivery system for sustained drug delivery. Drug discoveries & therapeutics. 2009 Aug 1;3(4).
42. [42]Washington N. Investigation into the barrier action of an alginate gastric reflux suppressant, liquid Gaviscon®. Drug Investigation. 1990 Mar;2(1):23-30.
43. [43]Kapadia CJ, Mane VB. Raft-forming agents: antireflux formulations. Drug development and industrial pharmacy. 2007 Jan 1;33(12):1350-61.
44. [44]Fabregas JL, Claramunt J, Cucala J, Pous R, Siles A. "In-Vitro" testing of an antacid formulation with prolonged gastric residence time (almagate flot-coat®). Drug development and industrial pharmacy. 1994 Jan 1;20(7):1199-212.
45. [45]Havelund T, Aalykke C, Rasmussen L. Efficacy of a pectin-based anti-reflux agent on acid reflux and recurrence of symptoms and oesophagitis in gastro-oesophageal reflux disease. European journal of gastroenterology & hepatology. 1997 May 1;9(5):509-14.
46. [46]Kotreka U, Adeyeye MC. Gastroretentive floating drug-delivery systems: a critical review. Critical Reviews™ in Therapeutic Drug Carrier Systems. 2011;28(1).
47. [47]Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. Journal of Controlled release. 2000 Feb 3;63(3):235-59.
48. [48]Clarke GM, Newton JM, Short MB. Comparative gastrointestinal transit of pellet systems of varying density. International journal of pharmaceutics. 1995 Jan 31;114(1):1-1.
49. [49]Park K, Robinson JR. Bioadhesive polymers as platforms for oral-controlled drug delivery: method to study bioadhesion. International journal of pharmaceutics. 1984 Apr 1;19(2):107-27.
50. [50]Sarparanta MP, Bimbo LM, Mäkilä EM, Salonen JJ, Laaksonen PH, Helariutta AK, Linder MB, Hirvonen JT, Laaksonen TJ, Santos HA, Airaksinen AJ. The mucoadhesive and gastroretentive properties of hydrophobin-coated porous silicon nanoparticle oral drug delivery systems. Biomaterials. 2012 Apr 1;33(11):3353-62.
51. [51]Prajapati VD, Jani GK, Khutliwala TA, Zala BS. Raft forming system—An upcoming approach of gastroretentive drug delivery system. Journal of controlled release. 2013 Jun 10;168(2):151-65.
52. [52]Liu JL, Eisenberg B. Poisson-Fermi modeling of ion activities in aqueous single and mixed electrolyte solutions at variable temperature. The Journal of chemical physics. 2018 Feb 7;148(5):054501.
53. [53]Bardonnet PL, Faivre V, Pugh WJ, Piffaretti JC, Falson F. Gastroretentive dosage forms: Overview and special case of Helicobacter pylori. Journal of controlled release. 2006 Mar 10;111(1-2):1-8.
54. [54]Smart JD. The basics and underlying mechanisms of mucoadhesion. Advanced drug delivery reviews. 2005 Nov 3;57(11):1556-68.
55. [55]Andrews GP, Laverty TP, Jones DS. Mucoadhesive polymeric platforms for controlled drug delivery. European journal of pharmaceutics and biopharmaceutics. 2009 Mar 1;71(3):505-18.
56. [56]Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage forms. Journal of controlled release. 2003 Jun 24;90(2):143-62.
57. [57]Bardonnet PL, Faivre V, Pugh WJ, Piffaretti JC, Falson F. Gastroretentive dosage forms: Overview and special case of Helicobacter pylori. Journal of controlled release. 2006 Mar 10;111(1-2):1-8.
58. [58]Shinde S, Tadwee I, Shahi S. Gastro retentive drug delivery system: A review. Int. J. Pharm. Res. & All. Sci. 2012;1(1):01-13.
59. [59]Ito R, Machida Y, Sannan T, Nagai T. Magnetic granules: a novel system for specific drug delivery to esophageal mucosa in oral administration. International Journal of Pharmaceutics. 1990 Jun 11;61(1-2):109-17.
60. [60]Bardonnet PL, Faivre V, Pugh WJ, Piffaretti JC, Falson F. Gastroretentive dosage forms: Overview and special case of Helicobacter pylori. Journal of controlled release. 2006 Mar 10;111(1-2):1-8.
61. [61]Moes AJ. Gastric retention systems for oral drug delivery. Business Briefing: Pharmatech. 2003:157-59.
62. [62]Hwang SJ, Park H, Park K. Gastric retentive drug-delivery systems. Critical Reviews™ in Therapeutic Drug Carrier Systems. 1998;15(3).
63. [63]Sarojini S, Manavalanb R. An overview on various approaches to gastroretentive dosage forms. International journal of drug development and research. 2012;4(1):0-.
64. [64]Vinod KR, Vasa S, Anbuazaghan S, Banji D, Padmasri A, Sandhya S. Approaches for gastrotentive drug delivery systems.
65. [65]Badoni A, Ojha A, Gnanarajan G, Kothiyal P. Review on gastro retentive drug delivery system. The pharma innovation. 2012 Oct 1;1(8, Part A):32.
66. [66]Sarojini S, Manavalanb R. An overview on various approaches to gastroretentive dosage forms. International journal of drug development and research. 2012;4(1):0-.
67. [67]S.S. Davis, A.F. Stockwell, M.J. Taylor, J.G. Hardy, D.R. Whelley, C.G. Wilson, H. Bechgaard, F.N. Christensen, The effect on density on the gastric emptying of single and multiple-unit dosage forms, Pharm. Res. 3 (1986) 208–213.
68. [68]Chawla G, Bansal A. A means to address regional variability in intestinal drug absorption. Pharm tech. 2003 Jul;27(2):50-68.

69. [69]A. Badoni, A. Ojha, G. Gnanarajan, P. Kothiyal, Review on gastro retentive drug delivery system, Pharma Innov. 1 (8) (2012) 32–42
70. [70]Groning R, Berntgen M. Estimation of the gastric residence time of magnetic dosage forms using the Heidelberg capsule. Die Pharmazie. 1996 May 1;51(5):328-31.
71. [71]Gröning R, Berntgen M, Georgarakis M. Acyclovir serum concentrations following peroral administration of magnetic depot tablets and the influence of extracorporal magnets to control gastrointestinal transit. European journal of pharmaceutics and biopharmaceutics. 1998 Nov 1;46(3):285-91.
72. [72]Vinod KR, Vasa S, Anbuazaghan S, Banji D, Padmasri A, Sandhya S. Approaches for gastrotentive drug delivery systems.
73. [73]Nayak AK, Das B, Maji R. Gastroretentive hydrodynamically balanced systems of ofloxacin: In vitro evaluation. Saudi Pharmaceutical Journal. 2013 Jan 1;21(1):113-7.
74. [74]Khan PD, Vinchurkar K. Features & Facts of Gastroretentive Drug Delivery System–A Review Gastroretentive İlaç Dağıtım Sisteminin Özellikleri ve Gerçekleri-Bir İnceleme.
75. [75]Hilton AK, Deasy PB. In vitro and in vivo evaluation of an oral sustained-release floating dosage form of amoxycillin trihydrate. International Journal of pharmaceutics. 1992 Oct 10;86(1):79-88.
76. [76]Sangekar S, Vadino WA, Chaudry I, Parr A, Beihn R, Digenis G. Evaluation of the effect of food and specific gravity of tablets on gastric retention time. International Journal of Pharmaceutics. 1987 Mar 1;35(3):187-91.
77. [77]Patel N, Nagesh C, Chandrashekhar S, Jinal P, Devdatt J. Floating drug delivery system: an innovative acceptable approach in gastro retentive drug delivery. Asian J. Pharm. Res. 2012 Jan;2(1):07-18.
78. [78]Cargill R, Caldwell LJ, Engle K, Fix JA, Porter PA, Gardner CR. Controlled gastric emptying. 1. Effects of physical properties on gastric residence times of nondisintegrating geometric shapes in beagle dogs. Pharmaceutical research. 1988 Aug;5(8):533-6.
79. [79]Shivakumar HG, Gowda DV, Kumar TM. Floating controlled drug delivery systems for prolonged gastric residence: a review. Ind. J. Pharm. 2004;38(45):172-78.
80. [80]Timmermans J, Moës AJ. Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: new data for reconsidering the controversy. Journal of pharmaceutical sciences. 1994 Jan;83(1):18-24.
81. [81]Hendee WR, Ritenour ER. Medical imaging physics. John Wiley & Sons; 2003 Apr 14.
82. [82]Darunde D, Katiyar S. FLOATING INSITU GELLING SYSTEM: A REVIEW.
83. [83]Vyas SP, Khar RK. Gastroretentive systems. Controlled drug Delivery. Vallabh Prakashan, Delhi, India. 2006:197-217.
84. [84]Fatema K, Shahi S, Shaikh T, Zaheer Z. Gastroretentive drug delivery system: an overview. Asian Pacific J. Health Sci. 2016;3:131-44.
85. [85]Sharma D, Sharma A. Gastroretentive drug delivery system-a mini review. Asian Pacific Journal of Health Sciences. 2014;1(2):80-9.
86. [86]Biller S, Baumgarten D, Haueisen J. Magnetic marker monitoring: a novel approach for magnetic marker design. InXII Mediterranean Conference on Medical and Biological Engineering and Computing 2010 2010 (pp. 260-263). Springer, Berlin, Heidelberg.
87. [87]Schneider F, Koziolek M, Weitschies W. In vitro and in vivo test methods for the evaluation of gastroretentive dosage forms. Pharmaceutics. 2019 Aug 16;11(8):416.