GASTRORETENTIVE DRUG DELIVERY SYSTEM

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ABSTRACT

Oral route is most common and preferred route from efficacy and safety point of view. Many advancement, research and development have been done in oral drug delivery system. Oral-rate controlled drug delivery systems have an important area among a novel drug delivery system. Oral sustained release drug delivery system have several limitation like short gastric emptying time/gastric residence time to overcome these limitation several approaches have been developed. In order to improve the bioavailability of drug this review compiles the recent literature with special focus on various approaches of gastric retention.

This review also summarizes thefactors that influencegastric retention, various approaches for gastric-retention, to evaluate the performance*in-vitro* and *in-vivo* studies and application of gastroretentive drug delivery.

KEY WORDS- Gastroretentive, Mucoadhesive, floating

INTRODUCTION

Drug delivery to systemic circulation through oral route is more convenient and preferred because of improved therapeutic advantage, low cost of drug, patient compliance and adjustment in formulation according to need.[1] Among the novel drug delivery system, sustained oral drug delivery system has an important area.[2] The main disadvantage of oral drug delivery if drug is rapidly absorbed, gastric acid/enzyme degradation, first pass metabolism and short half-lives due to this drug eliminated quickly from systemic circulation. Therefore frequent dosing is required to achieve desired therapeutic window of drug. Now a day's pharmaceutical companies moving towards an oral sustained-controlled release drug delivery system to overcome problem of frequent dosing ; is required to achieve desired therapeutic effect by developing once a day formulation[3,4].

Drug with narrow absorption window in the upper part of GIT is not suitable for oral sustained-controlled release drug delivery system due to brief gastric emptying time .[5]Dosage forms which have absorption window in stomach and small intestine their bioavailability is generally limited because of short residence time thus drug release in stomach is often short. This problem can be overcome by prolonging the residence time of drug in the stomach. [6]

The medications with narrow absorption window are compounded in unique pharmaceutical dosage form with gastroretentive property.Themost important approaches for achieving a prolonged release of drug in the GI tract is

control the gastric residence time (GRT) by preventing its elimination from the GIT. Dosage forms with aincreased gastric residence time (GRT) is known as Gastroretentive dosage forms (GRDFs), this will provide new and important therapeutic options. GRDF play very important role in local treatment of diseases of the upper GI tract e.g. Peptic ulcer.[7]

Davis, 1968 firstly described the concept of floating drug delivery system after experiencing choking in some persons, while swallowing pills. The researcher removed such difficulty by providing the pills having density less than 1.0gm/ml, so that pills will float on water surface. Since then several approaches have been proposed for ideal floating delivery device.[8]

Table 1: Benefit characteristic of oral-controlled-release drug delivery system.[9]

Benefit	**Reason**
Therapeutic	Reduction in fluctuations of drug plasma level; maintenance of a steady plasma level of the drug over a prolonged time period, ideally simulating an intravenous infusion of a drug
Reduction in adverse side effects and improvement in tolerability	Drug plasma levels are maintained within a narrow window and with AUC of plasma concentration versus time curve comparable with total AUC from multiple dosing with immediate release dosage forms. This greatly reduces the possibility of side effects as the scale of side effects increase as we approach the MSC.
Patient comfort	Reduction in dosing frequency enhances patient compliance.
Reduce healthcare cost	The total cost of controlled release product used in therapy could be lower than the immediate-release product so overall expense in disease management also would be reduced.

GASTROINTESTINAL TRACT-

The GIT is a muscular tube like structure which is expend from mouth to anus. It takes nutrients in and eliminates waste by secretion, absorption, motility, digestion, and excretion, which are known as physiological processes. The gastrointestinal tract is divided into three main parts according to their structure-

- Stomach
- Small intestine
- Large intestine

Anatomy of stomach-

Stomach is looks like English alphabet J so it is also called J-shaped organ and it divided in to 4 regions-: cardia, fundus, body and pylorus (antrum). The main function of stomach is mixing of food with gastric secretion before emptying through pyrolic sphincter and storage of food before its digestion. In stomach; body acts as a reservoir and its main function is to store undigested material, whereas the cardia is the mainsite for mixing of food with each other and with gastric secretion. Pylorus act as a pump which help in gastric emptying by propelling actions.[10]

The basic arrangement of walls of the GIT is same from stomach to large intestine.The different layers present from outside to inside comprise serosa, intermuscular plane, longitudinal muscle, submucosa, circular muscle, lamina propria, muscularis mucosae, and epithelium.

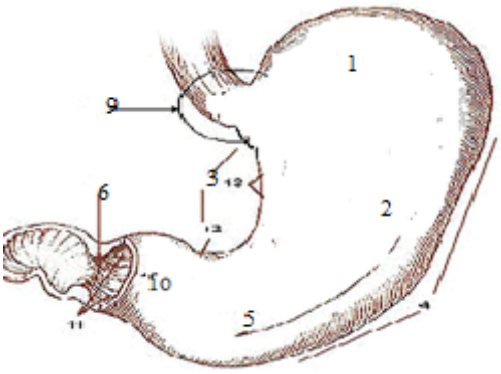

Figure 1: Anatomy of gastrointestinal tract[11], (1)fundus(2) body of stomach(3)lesser curvature(4) greater curvature (5) anterior wall (6) pyloric sphincter (7) esophagus (8) duodenum (9)cardia (10) pyloric antrum (11) pyloric canal (12) angular notch (13) gastric canal (14) rugal folds

2.2 Pattern of motility-Gastric emptying is continous process and occurs in both fasting as well as fed state. But pattern of motility is different in both states. In fasting stateevery 2-3 hours an electrical event takes place which cycle through both stomach and intestine. This pattern of motility is known as Migrating Myoelectric Cycle (MMC).MMC is divided in to 4 phase as described by Wilson and Washington-

Table 2: Migrating Myoelectric Cycle[12]

Phase	Time	Comments
Phase I (basal phase)	last for 30-60 minutes	rare contractions
Phase II (pre burst pha	last for 20-40 minutes	intermediate contraction as phase progress intensity and frequency also increase gradually
Phase III (burst phase)	Last for 0-5 minutes	Intense and regular contraction occurs during this phase fo short period of time. Due to this undigested food swept out from stomach down to small intestine
Phase IV	Last for 10-20 Minutes	occurs between phase III and 1 and 2 consecutive cycles

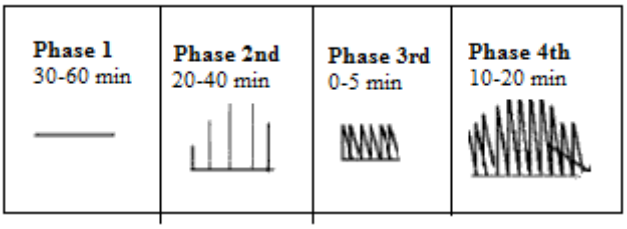

Figure 2: Migrating Myoelectric cycle [13]

Factors Controlling Gastric Retention of Dosage Forms-Anatomy and physiology of stomach plays important role in development of gastroretentive dosage form. Gastric retention time of oral dosage form controlled by following parameters[1, 3, 7, 13, 14]

- Density of dosage form
- Size and shape dosage form
- Food intake and nature of meal
- Physical activity and diseased state
- GIT pH

Density of dosage form- Densityof dosage form play is very important parameter in determination of gastric emptying time and location of the drug delivery system. If drug delivery system have density less than the gastric content it will float, while higher density system sediment. Low density drug delivery system and High density drug delivery both prevent dosage form exit from the pylorus. Density of stomach is 1.004 gm/cm^3 so to exhibit floating property density should be less than 1.0 gm/ cm[31].

Shape and size of the dosage form-Gastric residence time of non-floating dosage form greatly dependent on their size i.e. greater the size of dosage form larger will the gastric residence time because it would not pass quickly from pyloric antrum in to the intestine. Dosage forms having a diameter of more than 7.5mm show a better gastric residence time. Ring-shaped and tetrahedron-shaped devices show better gastric residence time as compared with other shapes[3].

Food intake-Food intake, volume of food,viscosity of food, caloric value and frequency of feeding may affect gastric retention of dosage forms. Presence and absence of food also have influenceon residence time of dosage form[13].

Nature of meal-Gastric motility pattern change by nature of meal such as fatty acid salt decrease the gastric emptying and increase the drug release. Gastric emptying for various food materials is in following order: carbohydrate > proteins > fats. Fats promote secretion of bile which too has an inhibitory effect on gastric emptying.[14]

Feeding and fasting state-During fasting state GI motility occurs every 1.5-2 hours. In fed state migrating myoelectric complex is delayed and gastric residence time is considerably longer.[13, 14]

Contaminant drug administration—after administration of anticholinergic drug like atropine and propantheline decrease the gastric motility and increase the gastric residence time.

Gastrointestinal pH-gastric emptying is retard at low stomach pH and promote at higher pH.

HCl > acetic acid > lactic acid >tartric acid > citric acid

Electrolytes and osmotic pressure-water, isotonic solution and solution of low concentration empty the stomach rapidly where as higher electrolyte concentration decreases gastric emptying rate.[7, 14]

Disease states-Diseases like gastroenteritis, gastric ulcer, pyloric stenosis, diabetes and hypothyroidism retard gastric emptying. Partial and total gastrectomy, duodenal ulcer and hyperthyroidism promote gastric emptying rate.[14]

Table 3: factor affecting gastric residence

Factor	Effect on residence time
Smaller size of dosage form	Smaller the gastric residence time
Presence of food in GIT	improve gastric residence time
Increase acidity and caloric value	Slow down gastric residence time
Stress and anxiety	Promote gastric emptying

NEED FOR GASTROINTESTINAL RETENTION-

- Drugs which are less soluble or that degrade at the alkaline pH.
- Drugs which are absorbed from proximal part of the stomach.
- Sustain delivery of drugs to stomach and proximal small intestine.
- For treatment of the peptic ulcer caused by H.pylori.[15]

Table 4: Potential drug candidates for Gastroretentive drug delivery systems

Drug candidates suitable for Gastroretentive drug deliveries		**Drug candidates not suitable for Gastrorete drug deliveries**	
Drug	**Example**	**Drug**	**Example**
Drug which disturb normal colonic microbe's	Antibiotics against Helicob pylori	Drugs those are instable in gastric environment	Erythromycin
Drug with low solubility	Diazepam, Chlordiazepo Verapamil	Drugs that show less acid solubility	Phenytoin
Drugs with narrow absorption window in gastrointestinal tract	DOPA, p-aminoben-zoic acid, Furosemide, Riboflavin	Drug substance that Under goes first pass metabolism	Nifidipine

Drugs those are unstable in the intestinal or colonic environment	Captopril, Ranitidine HCl, Metronidazole	Drugs which may cause irritation at gastric mucosa	-
Drugs those are active in the Stomach	Misroprostol, Antacids		

APPROACHES OF GASTRORETENTIVE FORMULATION

Dosage form developed for gastric retention should be able to stand up against gastric force caused by peristaltic movement in stomach, constant churning and grinding. Gastroretentive dosage form resists the gastric empting and once the aim of dosage form achieve it should be eliminate from stomach. Gastroretentive dosage forms need wide efforts in both academic and industry towards development. These effort results in gastroretentive drug delivery formulations based on following approaches-

- Mucoadhesive drug delivery system
- Low density drug delivery system
- Effervescent system
- Non-effervescent system
- High density drug delivery system
- Expandable drug delivery system
- Ion exchange resins [5, 9, 16, 17, 1]

6.1 Muco-adhesive system-This approach involve use of muco-adhesive polymer which adhere over mucous layer secreted by the goblet cells of the stomach.Mucus is translucent and viscid secretion, which forms gel like continuous, thin blanket over mucosal epithelial surface.

Table 5: composition of mucus[15]

S. no.	Components	% Amount
1	Water	95
2	Glycoprotein and lipids	0.5-5.0
3	Minerals salts	1
4	Free proteins	0.5-1.0

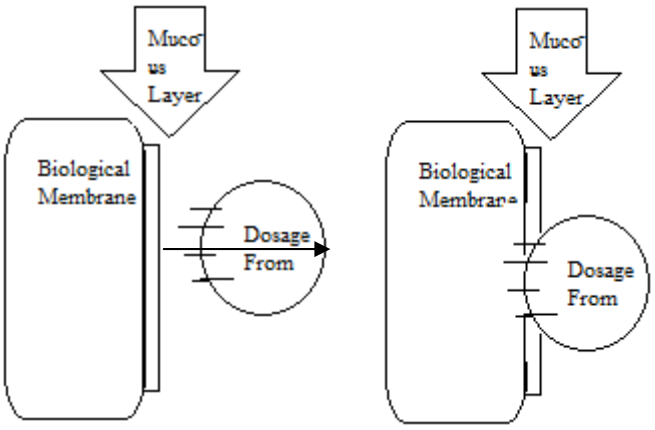

Figure 3: Mucoadhesive System[15]

Some excipients that have been used commonly in these systems includelectins,polycarbophil, chitosan gliadinandcarbopol etc. There are various theories which involve in adhesion are-

Table 3: muco-adhesive theories[19]

Theories	Description
Electronic theory	This theory involve transfer of electron from an adhesive polymer to a glycoprotein netwo
Absorption theory	Chemical bond formed it may be, hydrogen, covalent bond, Vander Wals forces, electrostatic forceand hydrophobic bonds
Wetting theory	They have ability to spread over a biological system
Diffusion theory	The polymer chains and the mucus mix to a sufficient depth to form a semi-permanent adhesive bond
Fracture theory	Analyses the maximum tensile stress developed during detachment of the BDDS from the mucosal surfaces.

6.2 Low density system-low density systems have density less than gastric contentso system remain buoyant in the stomach rate for a prolonged period of time without affecting gastric emptying. Low density system also known as **floating drug delivery system** (FDDS).[31-34]

FDDS can be divided in to **Effervescent and Non-effervescent drug delivery system**.

- **Effervescent drug delivery system**-This system prepared by swellable polymer like chitosan and effervescent substance like sodium bicarbonate, citric acid and tartaric acid. When system come in contact with gastric fluid it release carbon dioxide, causing the formulation remain floats in stomach.[32]

Effervescent drug delivery system further classified in to two types-

- Gas generating systems
- Volatile Liquid/Vacuum Systems.

Gas generating low density system – This system formed by mixing CO_2 generating agent carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) and drug within tablet matrix. Carbon dioxide generating agent present in the formulation produce carbon dioxide (CO_2) gas, thus reducing the density of system and making it float on the gastric fluid.[32, 33]

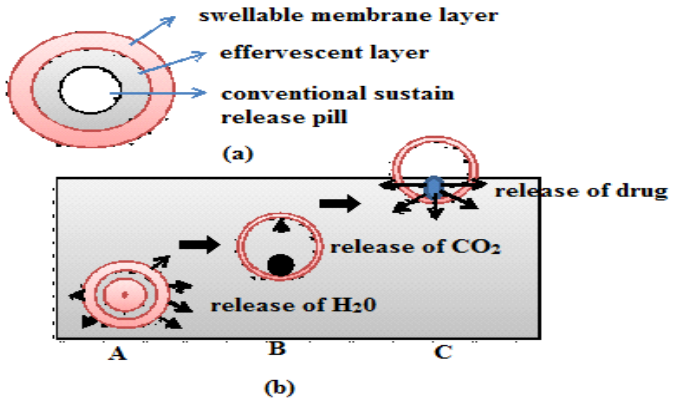

Figure 3: Gas generating low density system[3] (a)-Multiple unit oral floating drug delivery systems (b)-working principle of effervescent floating delivery system

Volatile liquid/vacuum system-This type system have a floating chamber which is filled with inert gas or volatile liquid and drug reservoir. Drug reservoir is encapsulated inside a microporous compartment. [35]

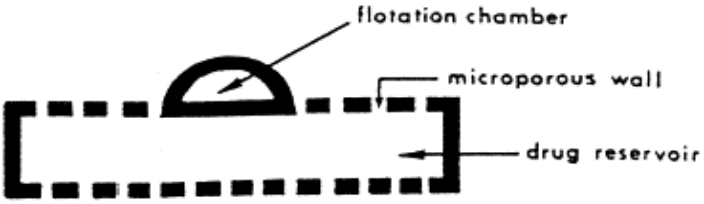

Figure 4: Intragastric floating drug delivery device[3, 8]

- **Non effervescent system-** This system based on mechanism of swelling of polymer. Most commonly used excipient in non-effervescent system are highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate,polyacrylate, polymethacrylate.[1, 3, 8, 36-38]

Various type of non-effervescent system are-

- **Single layered floating tablet**-Formed by mixing the drug with gel forming hydrocolloids or low-density enteric materials such as HPMC, which swell on contact with gastric fluid and maintaining density less than gastric content.

- **Bi-layer floating tablet-**Bi-layer tablet contain two layers, one for immideate release which release initial dose and another for sustained release which form gel barrier on its surface and maintain density less than gastric content (1.004 gm/cm^3).
- **Alginate beads-** Prepared by dropping the sodium alginate solution into the aqueous solution of the calcium chloride, causing the precipitation of calcium alginate leading to formation of the porous system.[37, 38]
- **Hollow microspheres –** Hollow microsphere also known as microballoons. It prepared by emulsion-solvent diffusion method. Hollow microspheres remain float over dissolution media containing surfactant for 12 hrs.[36]

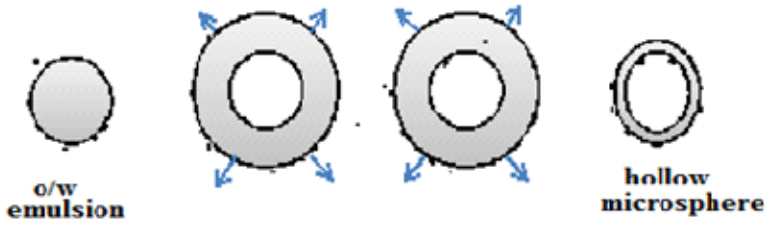

Figure 4: formation of microballoon[1]

6.3 High density drug delivery system-High density drug delivery systems have density more than the gastric content (> 1.004 g/cm3) due to this system sediment at the bottom of the stomach and retainedin the rugae or folds of the stomach body near the pyloric region. Commonly used excipients which increase the density of the system 1.5- 2.5g/cm3 are barium sulphate, zinc oxide, titaniumdioxide and iron powder, etc.

6.4 Expandable/swellable drug delivery system-This type of dosage form have size larger than the pyloric sphincter due to this they retain in stomach for longer time.In swellable system, swelling is usually results from osmotic absorption of water and dosage form should be small enough to be swallowed by the gastric fluid.[5, 11]

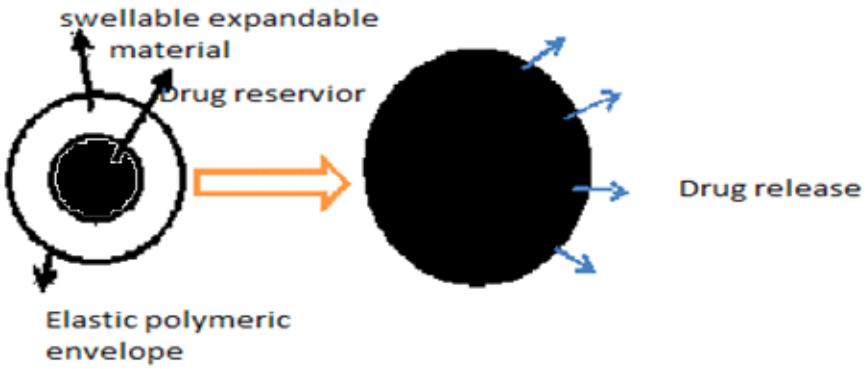

Figure 5: Drug release from swellable system[11]

6.5 Ion Exchange Resins- Ion exchange resins is a novel floating system investigated by Atyabi et al, 1994 based on exchange of ions. The system contain resin bead loaded with gas generating agent (bicarbonate) and negative charged drug tagged to the resin. The beads were further encapsulated in semipermeable membrane to prevent

rapid escape of CO_2.In acidic environment bicarbonate ion exchanged with chloride ion of HCl.As a result of this reaction carbon dioxide was released and trapped in the membrane and carrying beads towards the top of gastric content.[42]

Work on Gastroretentive drug delivery system- Previous literature reported on the GDDS include tablets (single layer and double layer), floating capsule, balloon tablets, multiparticulate systems, hollow microspheres and floating beads. The reports that are available are briefly reviewed as follows.

Literature review on Gastroretentive drug delivery system-

Name	Dosage Form	Technique	Result
Mucoadhesive Gastroretentive Drug Delivery System			
Patel et al.,(2005)[20]	Mucoadhesive micro-spheres of glipizide	Simple emulsificationphase separation techniqueusing glutaraldehyde as a cross-linking agent	Best batch exhibited a high drug entrapment efficiency of 75% and a swelling index of 1.42; % mucoadhesion after 1 hour was 78%. The drug release was also sustained for more than 12 hours.
Jain et al., [21](2008)	Mucoadhesive gastroretentive microspheres of acyclovir using Chitosan, thiolated chitosan, Carbopol 71G and Methocel K15M as mucoadhesive polymers	emulsion-chemical crosslinking technique	Release of drug was prolonged to 12 h (78.8 ± 3.9) when incorporated into mucoadhesive microspheres. The microspheres prepared from thiolated chitosan showed the highest mucoadhesiveness.
Yellanki et [22](2010)	Mucoadhesive microspheres of amoxicillin trihydrate for treatment of *Helicobacter pylori* induced peptic and duodenal ulcers	Emulsification phase separation technique	Microsphere contains ethyl cellulose as a matrix and carbopol 934P as a mucoadhesive polymer. Batch which contained less amount of ethyl cellulose showed more mucoadhesive property.

Dalvadi et al.,[23](2	Mucoadhesive tablets of Captopril using guar gum, xanthan gum, hydroxyl propyl methyl cellulose K4M and K15M as mucoadhesive polymers.	Emulsification p separation technique	Formulation containing HPMC K15M and xanthan gum (1:1) exhibited maximum bioadhesive strength of 31.59±0.05 gm and in vitro drug release was found to be 91.85 % at the end of 12 h with non-fickian diffusion mechanism.
Kumar et al.,[24](2011)	Mucoadhesive microcapsules of Metformin Hcl	Ionotropic Gelation process and Emulsification Ionotropic Gelation process employing Gum Karaya as the polymer.	Microencapsulation efficiency was in the range of 73% to 86% with various formulations. Metformin Hcl release from the microcapsules was slow, spread over extended period of time and depended on the composition.
Yadav et al., [25](2011)	Mucoadhesive microspheres of repaglinide	emulsion solvent evaporation technique consisting of chitosan mucoadhesive, repaglinide, an oral hypoglycemic agent and Eudragit RS-100 as polymer	The drug release was also found to be slow and extended for 24 h. The hypoglycemic effect obtained by mucoadhesive microspheres was for more than 16 h whereas repaglinide produced an antidiabetic effect for only 10 h suggesting that mucoadhesive microspheres are a valuable system for the long term delivery of repaglinide.
Ahmed et al.,[26](2010)	Gastro-retentive beads of captopril	Orifice ionic gelation method Alginate along with mucoadhesive polymers viz; hydroxy	The *in vitro* release studies were carried out in 0.1 N HCl and the release was found to be more sustained with alginate-chitosan

		propyl methyl cellulose, carbopol 934P, chitosan and cellulose acetate phthalate used in 1:1 and 1:9.	beads (9:1) than alginate-carbopol 934P (1:1) beads.
Arya et al.,[27](2010)	Mucoadhesive microspheres of Famotidine	w/o emulsification solvent evaporation method using mucoadhesive polymers sodium carboxy methyl cellulose and a release controlling polymer sodium alginate.	Microspheres exhibited prolonged drug release approximately 8 h
Nagda et al.,[28](2008)	Bioadhesive microspheres of aceclofenac employing carbopol	Solvent evaporation method	Drug to polymer ratio was increased from 1:1 to 1:6. The drug loaded microspheres in a ratio of 1:5 showed 47% of drug entrapment; percentage mucoadhesion was 81% and drug released in 10 h.
Low Density Drug Delivery System **a) Effervescent Drug Delivery System**			
Ali et al. [31]	Hydrodynemically balanced system for metformin as a single unit-floating capsule		Effect of various release modifiers was studied to ensure the delivery of drug from the HBS capsules over a prolonged period. Capsules prepared with HPMC K4M and ethyl cellulose gave the best in vitro percentage release and was taken as the optimized formulation
Rao et al. [32]	Floating tablet of cephalexin	Direct compression method incorporating	The diffusion exponent of krosmeyerpeppas for optimized

		HPMCK4M, xanthan gum, guar gum, sodium bicarbonate and tartaric acid as gas generating agent.	formulation was found to be 0.635 which significantly indicated the mechanism of drug release.
Ozdemir et al., [33] (2000)	Floating bilayer tablets of furosemide	Compression	Radiographic studies on 6 healthy male volunteers revealed that floating tablets were retained in stomach for 6 h and further blood analysis studies showed that bioavailability of these tablets was 1.8 times that of the conventional tablets
b) Non-Effervescent Drug Delivery System			
Sato et al., [36](2003)	Floatable hollow microspheres	Solvent diffusion method	The optimum loading amount of riboflavin in the microballoon the microballoon was found to impart ideal floatable properties to the microballons. Little entrapment was observed for aspirin due to the low distribution coefficient.
Murata et al.,[37](2000)	Floating alginate beads incorporating amoxycillin	Beads were produced by dropwise addition of alginate into calcium chloride solution followed by removal of gel beads and freeze-drying	Beads containing the dissolved drug remained buoyant for 20 h and high drug-loading levels were achieved.
Expandable Drug Delivery System			

ThauSheu et al.,[39](2008)	Expandable systems by using different types of swellable polymers HEC 250 examined (H,HX, HHX and M), Lower molecular weight PEO (mw 100-900) and addition of an ionic complex of polyelectrolytes	-	Swelling index obtained from the formulation with 10% to 50% of chitosan showed a good swelling index in the pH 1.2 media
Groning et al.,[40](2007)	Tablets which expand after contact with gastrointestinal fluids within a few minutes to a length of 4-6 cm	Direct Compression	Investigations showed that the ribo was released from the collagen ta over 12 h.
Klausner et al.,[41](2003)	Unfolding polymeric membranes, that combines extended dimensions with high rigidity.	-	Successful controlled release- ga retentive dosage form maint therapeutic Levodopa concentratio 500 mg ml $^{-1}$) over 9 h.

Advantage of gastroretentive drug delivery system-

Gastroretentive drug delivery system (FDDS) offered several applications for drugs having poor bioavailability because of narrow absorption window in the upper part of GIT. It retained the dosage form at the site of absorption and enhanced the bioavailability.[3, 9]

Enhanced bioavailability-Gastroretentive formulation enhanced the bioavailability of drug due to long retention time.**El-Kamal et al** prepared floating oral delivery system of ketoprofen. And found ketoprofen CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations.[43]

Sustained drug delivery-Sustained drug absorption from conventional oral controlled release dosage forms is limited due to short gastric retention time. However prolongation in the GRT may sustain the drug release behaviour.**Hejazi et al., (2002)** prepared chitosan microspheres for stomach-specific drug delivery system to increase the efficiency of tetracycline against *Helicobacter pylori*. Drug release from microspheres was found to degrade at pH 1.2 in 12 h. [44]

Targeted therapy for local ailments in the upper GIT-Sustained and prolong gastric retention time of the drug from gastroretentive drug delivery system to stomach may be beneficial for local treatment for e.g. peptic ulcer in stomach due to H.pylori and small intestine.[44]

Reduced fluctuations of drug concentration-Drug release from controlled release/sustained release GDS is in controlled/sustained manner over a prolonged period of time due to this blood drug concentration within narrow range. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented.

Minimize adverse activity at the colon- Long retention time of the drug at stomach minimizes the amount of drug reaches at colon. Thus, prevent the undesirable effect of drug in colon.

Site specific drug delivery- Site specific delivery of drug reduced side effect by preventing drug delivery at non-targeted site. Floating drug delivery is a feasible approach for drugs have limited absorption sites in upper small intestine. [1-5, 9, 13,]

Table 4: Comparative insight into GRTs of floating and non-floating delivery system[8]

Drug	Dosage form	GRT		References
		NFDS	FDS	
Diazepam	Capsule	1.0-1.5	4-10	Lissner-Muller et al,1981[45]
Ethmozine	Tablet	1-1.5	>6	Regmi et al.,1996[46]
Metoprolol tartrate	Tablets	1-1.5	5-6	Li et al.,1989[47]
Gentamycin sulfate	Tablets	1-2	>4	Xu et al.,1991[48]

Evaluations of gastroretentive dosage form-Various parameters need to be considered for the formulation of gastroretentive dosage form.

1. *In-vitro* evaluation[21,36]

- **Floating system-**

Floating time-It is the time taken by the dosage form to remain float on the surface of the dissolution media. It is performed in USP dissolution apparatus containing 900 ml stimulated gastric fluid or 0.1N HCl at 37°C.It is expressed in minute or second.[49]

Buoyancy Lag Time-It is time taken by dosage form to float on dissolution media after it place in media.[15]

Density-Density can be determined by displacement method by using benzene as a displacement medium.

1. **Swelling system**-

Swelling index- The swelling behaviour of dosage form measured by studying the weight in grams. First dosage form placed in basket of dissolution apparatus which is filled with dissolution media (stimulated gastric fluid or 0.1N HCl at 37 ± 0.5°C) after 0.5,1,2,3,4,5 and 6 hours dissolution basket containing dosage form remove and blotted with tissue paper to remove excess ofwater and weighted on analytical balance. Swelling index calculated by following formula-

$$\textbf{Swelling Index (S.I.)} = (W_t - W_o)/W_o$$

Where, S.I. = Swelling index

W_t = Weight of tablet at time t

W_o = Weight of tablet before placing in the beaker[15]

Water uptake-It is indirect measurement of swelling property of dosage form. Here swelling matrix placed in dissolution media and remove at regular interval and weight change determine with respect to time.[15, 49]

$$\textbf{Water uptake} = WU = (W_t - W_o) * 100 / W_o$$

Where, W_t = weight of dosage form at time t

W_o = initial weight of dosage form

1. **Mucoadhesive system**-

In vitro mucoadhesivity-*In-vitro***Wash off test** use to test mucoadhesivity. In this test pieces of intestinal mucosa (3cm×2cm) mount onto glass slides using cyanoacrylate glue. About 200 mg of dosage form (microspheres) spread onto each wet rinse tissue specimen and immediately thereafter the support is hung onto the arm of USP disintegration apparatus. In disintegration apparatus tissue specimen undergoes up and down movement in 0.1 N HCl (pH 6.8 at 37°C) in a 1 litre vessel. At the end of 30 minutes, 1 hour and then at hourly intervals apparatus is stopped and the tissue specimen is removed. The amount of dosage form (microsphere) which still adheres to tissue is removed by centrifugation, dried and weight.[50]

***In-vitro* dissolution-** Standard USP dissolution apparatus have been used to study in vitro release profile. Sample is withdrawn at different intervals and replace with the same volume of fresh medium to maintain constant level of dissolution medium. The withdrawn sample is analysed for drug contents. Medium used for release rate study was 900ml 0.1 N HCl during the course of study whole assembly was maintained at 37±0.5 °C.[8]

2-*In-vivo* evaluation

Radiology-Radio opaque marker such as barium sulphate is use to examine internal body system.$BaSO_4$ incorporate inside dosage form and X-ray is taken at regular interval to view gastric retention.

Scintigraphy-X-ray emitting material is used to fill inside dosage form and image is taken by scintigraphy. Gastroscopy, Magnetic Marker Monitoring, Ultrasonography, 13C Octanoic Acid Breath Test are used to evaluate the *in-vivo* gastric retention.[2, 15]

Conclusion- Gastroretentive dosage form one of the feasible approaches for achiving prolonged and control release of drug that will provide a new therapeutic options especially Particulate systems and Chronopharmacokinetic systems show high promise and acceptability. Particulate systems such as microparticle and nanoparticle approach that involves biodegradable polymers and is aimed at the uptake of intact drug-loaded particles via the Peyer's patches in the small intestine could be useful for delivery of peptide drugs that cannot, in general, be given orally**.** Oral controlled drug delivery with a pulsatile release regimen could effectively deliver drug where need exists to counter naturally occurring processes such as bacterial/parasitical growth patterns (e.g., the once-daily oral pulsys system introduced by Advancis Pharmaceutical Corp., which could potentially inhibit the emergence of resistant strains of microorganisms). Oral controlled drug delivery that targets regions in the GI tract and releases drugs only upon reaching that site could offer effective treatment for certain disease states (e.g. colon-targeted delivery of antineoplastics in the treatment of colon cancer). Mucoadhesion is a promising technique for drug delivery, which can offer rapid onset of action and superior bioavailability compared with simple oral delivery because it bypasses first-pass metabolism in the liver.

References

1. Nayak AK, Maji R, Das B. Gastroretentive drug delivery systems: a review, Asian Journal of Pharmaceutical and Clinical Research. 2010; 3(1):1-9.

2. Patil JM, Hirlekar RS, Gide PS and Kadam VJ. Trends in floating drug delivery system, journal of scientific and industrial research. 2006; 65:11-21.

3. Singh S, Joshi V and Barpete PK. Gastroretentive Drug Delivery System: Current Approaches,Journal of Pharmacy Research. 2009; 2(5):881-886.

4. Dahiya A, Rohilla A, Rohilla S, Khan MU. Gastroretentive Dosage Forms: An Approach to Oral Controlled Drug Delivery Systems, International Journal of Pharmaceutical & Biological. 2011; 2(2): 615-620.

5. Hoffman A, Klausner EA, Friedman M, Lavy E. Expandable gastroretentive dosage forms, Journal of Controlled Release. 2003; 90:143–162.

6. Singh B, Sharma V, Chuhan D. Gastroretentive floating sterculia–alginate beads for use in antiulcer drug delivery, chemical engineering research and design. 2010; 88:997–1012.

7. Garg R, Gupta GD. Progress in controlled gastroretentive delivery systems, Tropical Journal of Pharmaceutical Research. 2008; 7 (3):1055-1066.

8. Vyas S.P. and Khar R.K. Controlled drug delivery: concept and advances.7th ed. Noida: CBS Publication, 2008.

9. Das NG, Das SK. Controlled-Release of Oral Dosage Forms, Formulation, Fill & Finish. 2003; 10-16.

10. Kumar A, Verma R, Purohit S, Bhandari A. Overview of gastro-retentive drug delivery system, Journal of NaturaConscientia. 2011; 2(3):423- 436.

11. Prakash V, Jogpal V, Sharma V, Yadav D, Yadav SK. A review on gastroretentive drug delivery system, International Journal of Pharmacy & Life Sciences. 2011; 2(5):773-781.

12. Kumar D, Sethi S, Seth N, Khullar R, Sharma R**.** Approaches, techniques and evaluation of gastroretentive drug delivery system: an overview, International journal of research in ayurveda and pharmacy. 2011; 2(3):767-774.

13. Wilson CG, Washington N, The stomach: its role in oral drug delivery. In: Rubinstein MH, ed. Physiological Pharmaceutical: Biological Barriers to Drug Absorption, Chichester, UK; Ellis Horwood. 1989; 47-70.

14. Arora S, Ali J, Ahuja A, Khar RK and Baboota S. Floating Drug Delivery Systems: A Review, American Association of Pharmaceutical Scientists. 2006; 6(3):E372-E390.

15. Soni RV, Patel AV, Patel RB, Dr. Patel MR, Dr. Patel KR, Dr. Patel NM. Gastroretentive drug delivery systems: a review, International Journal of Pharma World Research. 2011; 2(1):1-24.

16. Jain A, Jain SK, Jain R, Soni A, Singhai P and Gurnany E. Gastro retentive drug delivery system- a review, Journal of Pharmacy Research. 2011; 4(6):1899-1908.

17. Surana AS, Kotecha RK. An overview on various approaches to oral controlled drug delivery system via gastroretention, International Journal of Pharmaceutical Sciences Review and Research. 2010; 2(2):68-72.

18. BanjiD,Vasa S. Approaches for gastrotentive drug delivery systems, International Journal of Applied Biology and Pharmaceutical Technology. 2010; 1(2):589-561.

19. Singh MK, Sharma PK, Sharma N. Gastroretentive Drug Delivery System Based On Natural Mucoadhesive Polymers: A Brief Review, Journal of Pharmacy Research. 2011; 4(2):519-521.

20. Patel JK, Patel RP, Amin AF, Patel MM. Formulation and evaluation of mucoadhesive glipizide microspheres, American Association of Pharmaceutical Scientists.2005; 06(01): E49-E55.
21. Yellanki SK, Singh J, Syed JA, Bigala R, Goranti S, Nerella NK. Design and characterization of amoxicillin trihydrate mucoadhesive microspheres for prolonged gastric retention. International Journal of Pharmaceutical Sciences and Drug Research. 2010; 2(2): 112-114.
22. Dhaliwal S, Jain S, Singh HP, Tiwary AK. Mucoadhesive microspheres for gastroretentive delivery of acyclovir: *In Vitro* and *In Vivo* evaluation, American Association of Pharmaceutical Scientists. 2008; 10(2): 322-330.
23. Dalvadi HP, Patel JK, Rajput GC, Muruganantham V and Jayakar B .Development and characterization of controlled release mucoadhesive tablets of captopril**,**ArsPharmaceutica 2011; 52(2): 31-37.
24. Kumar AA, Balakrishna T, Jash R, Murthy TEGK and Kumar AA**.** Formulation and evaluation of mucoadhesive microcapsules of metformin HCL with gum karaya, International Journal of Pharmacy and Pharmaceutical Sciences. 2011; 3(3): 150-155.
25. Yadav VK, Kumar B, Prajapati SK, Shafaat K. Design and evaluation of mucoadhesive microspheres of repaglinide for oral controlled release, International Journal of Drug Delivery. 2011; 3: 357-370.
26. Ahmed MG.Formulation and evaluation of gastric mucoadhesive drug delivery systems of captopril, Journal of Current Pharmaceutical Research. 2010; 2(1): 26-32.
27. Arya RKK, Singh R and Juyal V.Mucoadhesive microspheres of famotidine: preparation characterization and *in vitro* Evaluation, International Journal of Engineering Science and Technology. 2010; 2(6): 1575-1580.
28. Nagda CD, Chotai NP, Patel SB, Soni TJ, Patel UL. Preparation and *in vitro* evaluation of bioadhesivemicroparticulate system, International Journal of Pharmaceutical Sciences and Nanotechnology. 2008; 1(3): 257-266.
29. Srinivas M, Reddy MS, Kushtagi P, Achutha NU, Parambil A, Averineni KR and Udupa N. Chitosan and enteric polymer based once daily sustained release tabletsof aceclofenac: *In Vitro and In Vivo* Studies, American Association of Pharmaceutical Scientists. 2008; 9(2): 651-659.
30. Chavanpatil MD, Jain P, Chaudhari S, Shear R, Vavia PR. Novel sustained release, swellable and bioadhesive gastro-retentive drug delivery system for Ofloxacin, International Journal of Pharmaceutics. 2006; 316: 86-92.
31. Ali J, Arora S, Ahuja A, Babbar AK, Sharma RK, Khar RK, et al. Formulation and development of hydrodynemically balanced system for metformin: In vitro and in vivo evaluation. European Journal of Pharmaceutics Biopharm. 2007; 67:196-201.

32. Rao BP, Kottan NA, Snehith VS, Ramesh C. Development of Gastro retentive drug delivery system of cephalexin by using factorial design, ARS Pharmaceutica. 2009; 50:8-24.
33. Ozdemir N, Ordu S, Ozkan Y. Studies of floating dosage forms of furosemide: *in vitro* and *in vivo* evaluation of bilayer tablet formulation, Drug Dev. Ind. Pharm. 2000; 26:857-866.
34. Baumgartner S, Kristel J, Vreer F, Vodopivec P, Zorko B.Optimisation of floating matrix tablets and evaluation of their gastric residence time. International Journal of Pharmaceutics. 2000; 195:125-135.
35. Boltan S, Desai S. Floating control release drug delivery system: in vitro-in vivo evaluation, Pharma Res. 1993; 10:1321-1325.
36. Sato Y, Kawashima Y, Takeuchi H, Yamamoto H. Physicochemical properties to determine the buoyancy of hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method, European Journal of Pharmaceutics and Biopharmaceutics. 2003; 55: 297-304.
37. Murata Y, Sasaki N, Miyamoto E, Kawashima S. Use of floating alginate gel beads for stomach-specific drug delivery, European Journal of Pharmaceutics and Biopharmaceutics 2000; 50: 221-226.
38. Badve SS, Sher P, Korde A, Pawar AP. Development of hollow/porous calcium pectinate beads for floating-pulsatile drug delivery, European Journal of Pharmaceutics and Biopharmaceutics 2007; 65:85-93.
39. Yi Lina S, Siow WS, O Ho H, Sheu MT.Development and characterization of swellable/expandable systems for their potential application as a gastroretentive delivery (GRD) device, Asian Journal of Pharmaceutical Sciences 2008; 3 (1): 1-11.
40. Groning R, Cloer C, Georgarakis M and Muller R.S. Compressed collagen sponges as gastroretentive dosage forms: *In vitro* and *in vivo* studies. European Journal of Pharmaceutics Sciences 2007; 30: 1-6.
41. Klausner EA, Eyal S, Lavy E, Friedman M, Hoffman A. Novel Levodopa gastroretentive dosage form: *in vivo* evaluation in dogs, Journal of controlled release 2003; 88: 117-126.
42. Atyabi F, sharma HL, Mohammad HAH and Fell JT.Ion exchange resin, Journal of Control Release 1996;42:105
43. El-Kamel AH, Sokar MS, Al Gamal SS, Naggar VF. Preparation and Evaluation of Ketoprofen Floating Oral Delivery System. International Journal of Pharmaceutics 2001; 220:13-21.
44. Hejazi R, Amiji M. Stomach-specific anti-*H.pylori* therapy: Preparation and characterization of tetracycline-loaded chitosan microspheres, International Journal of Pharmaceutic 2002; 235: 87-94.
45. Muller-Lissner SA, Blum AL. Preparation and evaluation of floating drug delivery system of Diazepam, New English Journal of medicine. 1981; 304:1365.

46. Regmi BM, Lui JP, Tu XD. Floating drug delivery system of Ethmozine, Yao HsuchPao. 1996; 31:54.
47. Li S, Tu XD, Mao FF. Floating drug delivery system of Metoprolol tartrate, Yao HsuchPao. 1989; 24:31.
48. Xu WL, Tu XD, Lu ZD. Floating drug delivery system on Gentamycin sulphate, Yao HsuchPao. 1991; 26:541.
49. Burns SJ, Corness D, Hay G. Development and validation of an in vitro dissolution method for a floating dosage form with biphasic release characteristics. International Journal of Pharmaceutics. 1995; 121: 37-34.
50. Rajput GC, Dr.Majmudar FD, Dr.Patel JK, Thakor RS, Patel BP and Rajgor NB. Stomach Specific Mucoadhesive Tablets As Controlled Drug Delivery System – A Review Work, International Journal on Pharmaceutical and Biological Research. 2010; 1(1):30-41.