Current Research in Pharmaceutical Sciences
Available online at www.crpsonline.com

ISSN 2250 – 2688

Received: 20/08/2012
Revised: 15/09/2012
Accepted: 22/09/2012

H. K. Pathan
Radharaman College of Pharmacy, Ratibad, Bhopal (M.P.), India

Amit Dasani
Rajiv Gandhi institute of Pharmacy, Satana (M.P.), India

Ajay Saraf
Department of Pharmaceutical Sciences, Dr. Hari Singh Gour Vishwavidyalaya, Sagar (M.P.) India

Correspondence
Ajay Saraf
Department of Pharmaceutical Sciences, Dr. Hari Singh Gour Vishwavidyalaya, Sagar (M.P.) India
E mail : ajaysaaraf15@rediffmail.com

Stomach Specific Gastro retentive Drug Delivery System: A Review

H. K. Pathan, Amit Dasani and Ajay Saraf

ABSTRACT

The aim of this review on Stomach specific gastro retentive drug delivery system attempts to compile the present information with all the possible approaches like mucobioadhesive system, swelling system, expanding system and floating system and other contributing factors used to achieve gastric retention and current technology and literature used in the development of gastro retentive dosage forms. To avoid the physiological troubles such as short gastric residence times and unpredictable gastric emptying times and inability to restrain and localize the system within the desired region of the gastrointestinal tract makes the need of development of stomach specific gastro retentive drug delivery system. This approach is currently utilized to facilitate local drug delivery to the stomach and significantly prolong the gastric residence time of drugs and improve bioavailability of drug after oral administration. Gastroretention could also helps to administerd those drugs having narrow absorption window and shows the poor absorption in stomach therefore it could helps to provide availability of new products and consequently improved therapeutic activity and substantial benefits to patients.

Keywords: Gastric retention, Narrow absorption window, Gastro retentive approach, floating system

1. INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation, etc. From immediate release to site specific delivery, oral dosage forms have really progressed. However, it is a well-accepted fact that it is difficult to predict the real *in vivo* time of release with solid, oral controlled release dosage forms. Thus, drug absorption in the gastrointestinal (GI) tract may be very short and highly variable in certain circumstances. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time (GRT). Dosage forms with a prolonged GRT, i.e., Gastro retentive Dosage Forms (GRDFs), will provide us with new and important therapeutic options. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment and drugs with narrow absorption windows. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. Longer residence time in the stomach could be advantageous, for treatment of peptic ulcer disease [1,2,3].

Needs of Stomach Specific Drug Delivery System

Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous and controlled manner. Drugs delivered in this manner have a lower level of side effects and provide their therapeutic effects without the need for repeated dosages or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, which is where absorption occurs and contact time is limited. Stomach Specific FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentration. The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as 'hydro dynamically balanced systems' ('HBS') since they are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant (3- 4 hours) on the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents. Among the different hydrocolloids recommended for floating form formulations, cellulose ether polymers are most popular, especially HPMC. Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase buoyancy. Parallel to formulation studies, investigations have been undertaken in animals and humans to evaluate the intragastric retention performances of floating forms. These assessments were realized either indirectly through pharmacokinetic studies with a drug tracer, or directly by means of X-ray and gamma scintigraphic monitoring of the form transit in the GI tract [4].

2. PHYSIOLOGY OF STOMACH [5]

- The main function of stomach is to store food temporarily, grind it and then release it to duodenum. The end portion of stomach and starting of intestine means duodenum is joined by Pyloric sphincter, which a valve type unit and it can open maximum up to 12.8±7 mm. So dosage forms having higher size are retained more time in stomach.
- Gastric fluid volume in stomach is minimum of 25-50 ml at resting stage pH of gastric fluid is generally 1.5–2 in fasted state and may raised up to 2–6 in fed condition but it come back down soon by secretion of more gastric acid.
- Gastric Retention Time of any dosage form is generally 1-2.5 hours in fasted state but in fed condition GRT is increased, especially with fatty food. Food is passed out from stomach to intestine by gastric motility. There is specific motility pattern in fasted condition called as Migrating Myoelectric Complex (MMC) cycle. MMC is subdivided into four phases (figure1).

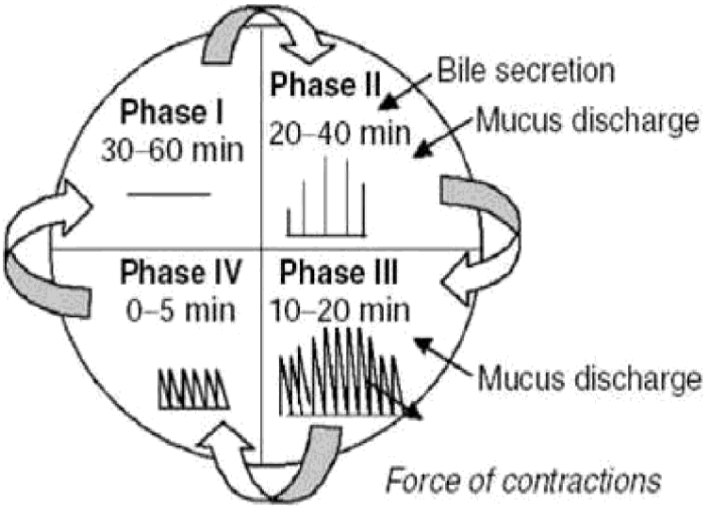

Figure 1. Phases of Migrating Myoelectric Complex (MMC) cycle

Phase I is basal phase, which is silent period of 30-60 minutes and characterized by lack of secretory, electrical and contractile activity and there is no contractions.

Phase II is pre-burst phase, which exhibit intermittent action for 20-40 minutes. Some bile secretion started and contractile motions increases frequency. Mucus discharge is started during later part of phase II.

Phase III is burst phase, which is characterized by intense and large regular contractions termed as "house keeper waves". These waves sweep off undigested food by maximizing the pyloric opening and lasts for 10-20 minutes. Thus, this phase enables efficient evacuation of the stomach contents.

Phase IV is transition period up to 5 minute, between phase III & I.

The whole MMC cycle is repeated every 2-3 hours. The motor activity in the fed condition is induced 5-10 min after the ingestion of the meal and persists as long as food remains in the stomach. The larger the amount of food ingested, the longer the period of fed activity, with usual time spans of 2-6 hrs and more typically 3-4 hrs. Its phasic contractions are similar to those seen during phase II of the MMC.

Suitable Drug Candidates For Gastroretention [15, 16]

In general, appropriate candidates for gastro retentive dosage forms are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT.

- Drugs acting locally in the stomach
  e.g. Antacids and drugs for H. Pylori viz., Misoprostol
- Drugs that are primarily absorbed in the stomach
  e.g. Amoxicillin
- Drugs that is poorly soluble at alkaline pH
  e.g. Furosemide, Diazepam, Verapamil, etc.
- Drugs with a narrow window of absorption
  e.g. Cyclosporine, Methotrexate, Levodopa, etc.
- Drugs which are absorbed rapidly from the GI tract.
  e.g. Metonidazole, Tetracycline.
- Drugs that degrade in the colon.
  e.g. Ranitidine, Metformin HCl.
- Drugs that disturb normal colonic microbes
  e.g. antibiotics against Helicobacter pylori.

3. FACTORS AFFECTING GASTRIC RETENTION TIME OF THE DOSAGE FORM [6, 7]

1. Density: gastric residence time (GRT) is a function of dosage form buoyancy that is dependent on the density. The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach. Both positions may isolate the dosage system from the pylorus. A density of < 1.0 gm/ cm3 is required to exhibit floating property.

2. Size & Shape of dosage form: Shape and size of the dosage forms are important in designing indigestible single unit solid dosage forms. The mean gastric residence times of non floating dosage forms are highly variable and greatly dependent on their size, which may be large, medium and small units. In most cases, the larger the dosage form the greater will be the gastric.

3. Single or multiple unit formulation: Multiple unit formulations show a more Predictable release profile and insignificant impairing of performance due to failure of units allow co- administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

4. Fed or unfed state: under fasting conditions: GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that ofthe MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

5. Nature of meal: feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastricemptying rate and prolonging drug release.

6. Caloric content: GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.

7. Frequency of feed: the GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC.

8. Gender: Male 3.4 ± 0.6 hr , Female 4.6±1.2 hrs.

9. Age: Elderly people, especially those over 70, have a significantly longer GRT.

10. Posture: GRT can vary between supine and upright ambulatory states of the patient.

11. Concomitant drug administration: Anticholinergic like atropine, propentheline-increase GRT.Metoclopramide and cisapride-decrease GRT.

12. Disease state: Gastric ulcer, diabetes, hypothyroidism increase GRT.

4. ADVANTAGES OF GASTRO RETENTIVE DELIVERY SYSTEMS [8, 9]

1. Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose e.g. Furosemide.
2. Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics. e.g. b-lactam antibiotics (penicillins and cephalosporins).

3. For drugs with relatively short half life, sustained release may result in a flip- flop pharmacokinetics and also enable reduced frequency of dosing with improved patient Compliance.

4. They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET).

5. As these systems are expected to remain buoyanton the gastric fluid without affecting the intrinsic rate of employing, because their bulk density is lower than that of the gastric fluids.

6. Gastro retentive drug delivery can produce prolongs and sustains release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.

7. The controlled, slow delivery of drug form gastro retentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable effects of side effects.

8. Gastro retentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented. This feature is of special importance for drug with a narrow therapeutic index.

9. Gastro retentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency.

10. Reduction of fluctuation in drug concentration makes it possible to obtain improved selectivity in receptor activation.

11. The sustained mode of drug release from Gastro retentive doses form enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes.

Limitations of the Techniques of Gastro retention

1. More predictable and reproducible floating properties should be achieved in all the extreme gastric conditions.

2. The floating systems in patients with achlorhydria can be questionable in case of swellable systems, faster swelling properties are required and complete swelling of the system should be achieved well before the gastric emptying time.

3. Bioadhesion in the acidic environment and high turnover of mucus may raise questions about the effectiveness of this technique. Similarly retention of high density systems in the antrum part under the migrating waves of the stomach is questionable.

4. Not suitable for drugs that may cause gastric lesions e.g. Non- steroidal anti inflammatory drugs. Drugs that are unstable in the strong acidic environment, these systems do not offer significant advantages over the conventional dosage forms for drugs, that are absorbed throughout the gastrointestinal tract.

5. The mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.

6. In all the above systems the physical integrity of the system is very important and Primary requirement for the success of these systems.

5. APPROACHES TO GASTRIC RETENTION

(A) Floating – A low density approach
- I. Single Unit Floating Dosage Systems
  - (a) Non-effervescent Systems
  - (b) Effervescent Systems (Gas-generating Systems)
- II. Multiple Unit Floating Dosage Systems
  - (a) Non-effervescent Systems
  - (b) Effervescent Systems (Gas-generating Systems)

(B) Expandable approach
- I. Swelling systems
- II. Unfolding systems

(C) High density approach

(D) Raft forming system

(E) Bioadhesive system

Floating – A Low Density Approach

Floating drug delivery systems (FDDS) or hydro-dynamically balanced systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the stomach. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the gastric retention time and a better control of fluctuations in the plasma drug concentration in some cases.

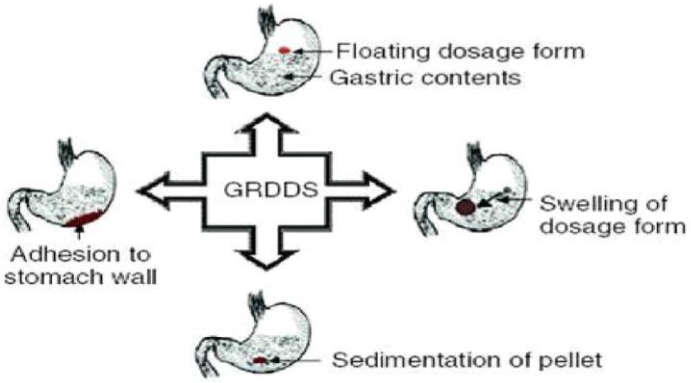

Figure 2. Recent GRDDS Technologies

Floating Drug Delivery system (FDDS)

The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as 'hydrodynamically balanced systems' ('HBS') since they are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant (3-4 hours) on the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents. Many results have demonstrated the validity of the concept of buoyancy in terms of prolonged GRT of the floating forms, improved bioavailability of drugs and improved clinical situations. These results also demonstrate that the presence of gastric content is needed to allow the proper achievement of the buoyancy retention principle. Among the different hydrocolloids recommended for floating form formulations, cellulose ether polymers are most popular, especially hydroxypropyl methylcelluloses. Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase buoyancy.[10, 11]

Parallel to formulation studies, investigations have been undertaken in animals and humans to evaluate the intragastric retention performances of floating forms. These assessments were realised either indirectly through pharmacokinetic studies with a drug tracer, or directly by means of X-ray and gamma scintigraphic monitoring of the form transit in the GI tract. When a floating capsule is administered to the subjects with a fat and protein meal, it can be observed that it remains buoyant at the surface of the gastric content in the upper part of the stomach and moves down progressively while the meal empties. The reported gastric retention times range from 4 to 10 hours. Pharmacokinetic and bioavailability evaluation studies confirm the favourable incidence of this prolonged gastric residence time allows the permation of water.[13,14] Thus ,carbon dioxide is released causing the beads to float in the stomach.Other approach and materials that have ben reported are highly swellable hydrocolloids and light mineral oils ,a mixture of sodium alginate and sodium bicorbonate ,multiple unit floating pills that generate carbon dioxidewhen ingested ,floating minicapsules with a core of sodium bicarbonate ,lactose and polyvinyl pyrrolidone coated with hpmc and floating system based on ion exchange resin technology etc.[17]

Single Unit Systems

Non-Effervescent systems

In this type of FDDS, most commonly used Excipients are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene. The approach involves intimate mixing of the drug with gel forming hydrocolloids, which swell in contact with the gastric fluid after oral administration and maintains a relative integrity, shape and bulk density of less than a unity. Within th outer gelatinous barrier, the air entrapped by the swollen polymers confers to the buoyancy of these dosage forms.

Floating tablet

It's a matrix tablet with single layered or bi-layered. Matrix tablet were prepared by incorporating gel forming hydrocolloids like HPMC, which the most commonly used polymer for floating. Out of various grades of HPMC, low viscosity grade are use for floating purpose. Mixture of alginate and HPMC also prepared for floating tablet. Bilayer matrix tablet are prepared by providing polymers responsible for floating in one layer and drug loaded in other layer and so whole unit will float and will remain in the stomach. The other type of bilayer tablet is prepared by incorporating a loading dose of drug in one layer and remaining drug in other layer along with hydrocolloid for its sustained release effect.

Streubel *et al* [18] prepared single-unit floating tablets based on polypropylene foam powder (Accurel MP 1000®) and matrix-forming polymer. Highly porous foam powder in matrix tablets provided density much lower than the density of the release medium. It was concluded that varying the ratios of matrix-forming polymers and the foam powder could alter the drug release patterns effectively.

Wu *et al* [19] prepared floating sustained release tablets of nimodipine by using HPMC and PEG 6000. Prior to formulation of floating tablets, nimodipine was incorporated into poloxamer-188 solid dispersion after which it was directly compressed into

floating tablets. It was observed that by increasing the HPMC and decreasing the PEG 6000 content a decline in *In-vitro* release of nimodipine was observed.

Nur and Zhang [20] prepared floating tablets of captopril using HPMC (4000 and 15000 cps) and carbopol 934P. It was concluded that the buoyancy of the tablet is governed by both the swelling of the hydrocolloid particles on the tablet surface when it contacts the gastric fluids and the presence of internal voids in the centre of the tablet (porosity). A prolonged release from these floating tablets was observed as compared with the conventional tablets and a 24-hour controlled release from the dosage form of captopril was achieved.

Floating Capsules (HBS^{TM} Capsules)

It is Hydrodynamically Balanced System. It is a hard gelatin capsule containing drug with high level of one or more highly swellable gel forming hydrocolloids (20-75%) like HPMC, HPC, HEC, Na-CMC etc. Capsule shell dissolves in gastric fluids and hydrocolloids are hydrated to form colloidal gel barrier around its surface and maintains shape. Thus, the increase in volume leads to decrease the overall bulk density and imparts buoyancy. Gel structure controls rate of diffusion of fluid-in and drug- out making "Receding Boundary". After exterior surface dissolves/erodes, the immediate adjacent hydrocolloid layer is hydrated and process continues to give floating for extended period of time. The success of HBS capsule as a better system is exemplified with Chlordiazepoxide HCl. The drug is a classical example of solubility problem wherein it exhibits a 4000 fold difference in solubility going from pH 3-6.

Micro-porous reservoir

This device comprised of a drug reservoir encapsulated in microporous compartment having pores on its surface. A floating chamber was attached at one surface which gives buoyancy to entire device. Drug is slowly dissolves out via micro pores (figure.3).

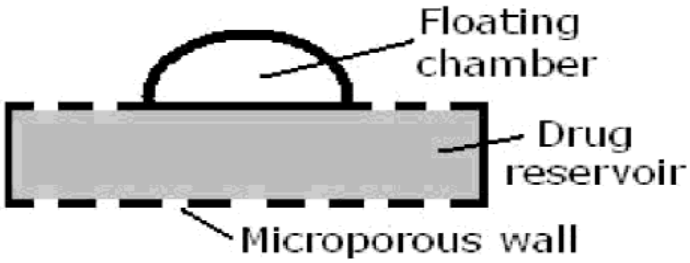

Figure 3. Design of Micro-porous reservoir

Effervescent system:(Gas-Generating Systems)

These buoyant systems utilized matrices prepared with swell able polymers like methocel, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate 15, 16 for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethylcellulose. The coating, which is insoluble but permeable.

Ozdemir *et al* [21] prepared floating bilayer tablets with controlled release for furosemide. 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 4000, HPMC 100, and CMC (for the control of the drug delivery) and the drug. The second layer contained the effervescent mixture of sodium bicarbonate and citric acid. Radiographic studies on 6 healthy male volunteers showed that floating tablets were retained in stomach for 6 hours and further blood analysis studies showed that bioavailability of these tablets was 1.8 times that of the conventional tablets. On measuring the volume of urine the peak diuretic effect seen in the conventional tablets was decreased and prolonged in the case of floating dosage form.

Penners *et al* [22] prepared an expandable tablet containing mixture of polyvinyl lactams andpolyacrylates that swell rapidly in an aqueous environment and thus stays in stomach over an extended period of time. In addition to this, gas-forming agents were also incorporated so as soon as the gas formed, the density of the system was reduced and thus the system tended to float on the gastric environment.

Talwar *et al* [23] prepared a once-daily formulation for oral administration of ciprofloxacin. The formulation was composed of 69.9% ciprofloxacin base, 0.34% sodium alginate, 1.03% xanthum gum, 13.7% sodium bicarbonate, and 12.1% cross-linked poly vinyl pyrrolidine. The cross linked PVP initially and the gelforming polymers later formed a hydrated gel matrix thatentrapped the gas, causing the tablet to float and be retained in the stomach The hydrated gel matrix created a diffusion path for the drug, resulting in sustained release of the drug.Single-unit formulations are associated with problems such as sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation. The main drawback of such system is "all or none" phenomenon. In such cases there is a danger of passing of the dosage form to intestinal part at the time of house-keeper waves. To overcome this difficulty multiple unit dosage forms are designed.

Multiple Unit Systems

Single unit dosage forms are associated with problems such as sticking together or being obstructed in the GIT, which may have a potential danger of producing irritation. Also there are chances of unreliability and incapability for producing results in prolonging residence time in the stomach when orally administered owing to their fotuitous (all or none) emptying process. On the other hand, multiple unit dosage forms appear to be better suited as they claim to reduce the inter subject variability in absorption and lower the probability of dose dumping. These dosage forms are available as powders, granules, beads, micro-spheres, micro-capsules, micro-balloons, etc.

Non-effervescent Systems

No much report was found in the literature on non-effervescent multiple unit systems, as compared to the effervescent systems. However, few workers have reported the possibility of developing such system containing indomethacin, using chitosan as the polymeric excipient. A multiple unit HBS containing indomethacin as a model drug prepared by extrusion process is reported.[24] A mixture of drug, chitosan and acetic acid is extruded through a needle, and the extrudate is cut and dried. Chitosan hydrates and floats in the acidic media, and the required drug release could be obtained by modifying the drug-polymer ratio.

Beads System

Calcium alginate/ Pectinate beads

Freeze dried calcium alginate beads are produce by dropping sodium alginate solution into aqueous solution of calcium chloride. So due to chemical reaction named as **Ionotropic gelation**, gelation take place and forms solid spherical gel beads, which are separated from solution and they are freeze dried at -40^{o}C for 24 hours. The resultant weight of beads is less giving buoyancy up to 12 hours. Similar to alginate, pectin can also be use for preparing gel beads. Combination of both means calcium-alginate-pectinate gel bead also tried, which gives fasten drug release as compare to only calcium pectinate beads.Calcium alginate beads also prepared with incorporation of Chitosan polymer so that it can incorporate air in beads.[25]

Oil entrapped gel beads

Vegetable oil is use as floating carrier as they are light weight and hydrophobic used for floating by incorporating it into gel matrix of beads. Oil entrapped beads are prepared by both calcium alginate bead and calcium pectinate beads. Pectin has some emulsification property, so aqueous solution of pectin is mix edible oil. Emulsion is obtained by homogenization. And this emulsion is extruded into calcium chloride solution to form beads which are separated, washed and dried (Figure 4).

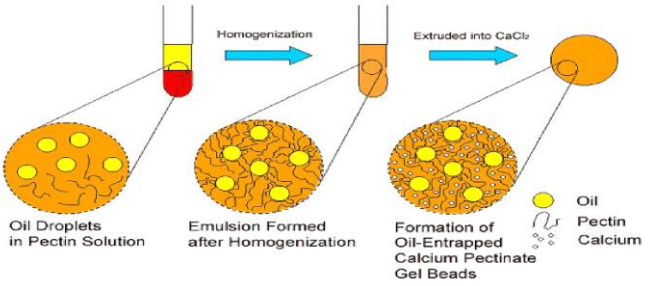

Figure 4. Prepartion of Oil entrapped gel beads

Effervescent systems

These are matrix type of systems prepared with the help of swellable polymers such as Methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid and citric acid. They are formulated in such a way that when in contact with the gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

Matrix tablets

Single layer matrix tablet is prepared by incorporating bicarbonates in matrix forming hydrocolloid gelling agent like HPMC, chitosan, alginate or other polymers and drug. Bilayer tablet can also be prepared by gas generating matrix in one layer and second layer with drug for its SR effect. Floating capsules also prepared by incorporating such mixtures. Triple layer tablet also prepared having first swellable floating layer, second sustained release layer of two drugs (Metronidazole and Tetracycline) and third rapid dissolving layer of bismuth salt. This tablet is prepared as single dosage form for Triple Therapy of H.Pylori.

Matrix tablets with carbopol

Carbopol is polymer which has pH dependent gelling property. It gels only at alkaline pH, so generally not gives gelling in acidic pH of gastric fluid and therefore not used as a swelling or matrixing polymer as HPMC and other used in GRDDS. But when gas generating bicarbonates are incorporated in it, due to generation of alkaline micro-environment by carbonate, Carbopol gives swelling and gelling. But this system not remains intact for long time; it can be coated with permeable elastic polymer like Eudragit to support integrity of core.

Coated effervescent core

Tablet is prepared with drug and effervescent material and then coated by polymeric coating of polymer like Eudragit RS with some plasticizer. Coating has higher elongation value and high water and low CO_2 gas permeability. So CO_2 gas generation makes floating system in gastric fluid. By using similar system, pulsatile system is also developed by using semipermeable coat which ruptures after predetermined time and release.Thus the whole system is now floating.Drug is released slowly from the drug compact made by high compression or by matrixing with polymer .As the drug release ,size of compact decreses and rubber disc is coming down due to pressure of spring. When all the drug is removed ,rubber disc came down to lowest position and horizontal –vertical orifice of disc matches with minipore made in side of the wall of HGC, CO_2 gas removes out of the system via orifice and minipore and system sink down and goes out of stomach and then out of body.

Porus beads system

Porous alginate beads are prepared by incorporating CO_2 gas generating agents like $NaHCO_3$ and $CaCO_3$. Bicarbonates are added with stirring into aqueous solution of sodium alginate and then mixture is added to solution of Calcium chloride with 10% acetic acid. So due to acetic acid and bicarbonate, CO_2 gas is generated and simultaneously gelling of beads by calcium ions are occurring producing the beads CO_2 which goes out during stirring and creating porous structures in calcium alginate beads.

Multiple films for floating

Two release controlling films(bigger than other films), one drug containing film and one effervescent film are prepared separately and assembled in such way that small sized drug and effervescent films are sandwiched .Two release controlling films(bigger than other films), one drug containing film and one effervescent film are prepared separately and assembled in such way that small sized drug and effervescent films are sandwiched between two bigger rate controlling films, and the periphery is sealed with small amount of polymer solution. So CO_2 gas generation inside assembly cause floating in gastric fluid.

Deformable unit with inflatable chamber

The system is kept in HGC which degrades in stomach to release system. This system is hollow deformable unit consists of two chambers separated by an impermeable, pressure responsive movable bladder. First chamber contains drug reservoir and second chamber contains volatile liquid like ether, cyclopentane, etc. which gasifies at body temperature to cause inflation of chamber in stomach. Inflation makes unit of lower density and gives buoyancy and also gives pressure on bladder to move and release drug from reservoir. The device may also consist of bioerodible plug that gradually dissolved, and after predetermined time (when all drug released), it unplugs system and gas release from system and system is then expelled out of body.

Osmotically controlled DDS

The system kept in HGC which degraded in stomach to release system. This system consist of mainly two different part attached with each other,one is floating part and other is osmotic controlled part. Floating part made up of deformable polymeric bag containing liquid that gasify at body temperature. Osmotic pressure controlling part consist of two part ,drug reservoir & osmotically active compartment. Inner drug reservoir is in impermeable collapsible bag along with drug delivery orifice &outer osmotically active compartment made up of the semipermeable membrane containing osmotically active salt. When the system in gastric fluids, inflation of floating part gives buoyancy and osmotic pressure generated in outer compartment due to fluid intake and drug is release due via orifice under osmotic pressure. Floating part also contains biodegradable plug that gradually dissolves /erodes & after predetermined time (when all the drug is released), it unplugs system and gas release from floating part and system is then expelled out of body (figure 5).

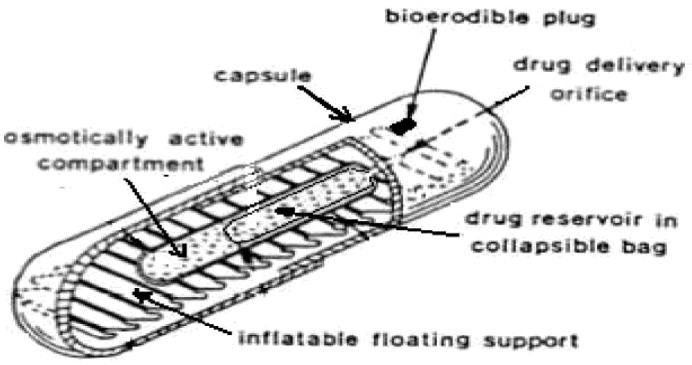

Figure 5. Design of Osmotically controlled DDS

Ichikawa *et al* [26] developed a new multiple type of floating dosage system having a pill in the core, composed of effervescent layers and swellable membrane layers coated on sustained release pills (shown in figure 3). The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sublayers to avoid direct contact between the 2 agents. These sublayers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37ºC, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO_2 was generated by the neutralization reaction between the 2 effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/ml.

Ikura *et al* [27] reported sustained release floating granules containing tetracycline hydrochloride. The granules are a mixture of drug granulates of two stages A and B, of which A contains 60 parts of HPMC, 40 parts of polyacrylic acid and 20 parts of drug and B contains 70 parts of sodium bicarbonate and 30 parts of tartaric acid. 60 parts by weight of granules of stage A and 30 parts by weight of granules of stage B are mixed along with a lubricant and filled into capsule. In dissolution media, the capsule shell dissolves and liberates the granules, which showed a floating time of more than 8 h and sustained drug release of 80% in about 6.5 h. Floating minicapsules of pepstatin having a diameter of 0.1-0.2 mm has been reported by Umezawa**.** [28] These minicapsules contain a central core and a coating. The central core consists of a granule composed of sodium bicarbonate, lactose and a binder, which is coated with HPMC. Pepstatin is coated on the top of the HPMC layer. The system floats because of the CO_2 release in gastric fluid and the pepstatin resides in the stomach for prolonged period.

Hollow Microspheres /Microballoons

Microballoons / hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion evaporation methods to prolong the gastric retention time (GRT) of the dosage form. Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin etc. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer polymer ratio and the solvent used for formulation. The microballoons floated continuously over the surface of an acidic dissolution media containing surfactant for >12 hours.[29] At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple-unit system and good floating.

Thanoo *et al* [30] developed Sustained release floating microspheres using polycarbonate were employing solvent evaporation technique.

Kawashima *et al* [31] described hollow microspheres (micro balloons) with drug in their outer polymer shells, prepared by a novel emulsion solvent diffusion method.

Joseph *et al* [32] developed a floating dosage form of piroxicam based on hollow polycarbonate microspheres. The microspheres were prepared by the solvent evaporation technique. Encapsulation efficiency of >95% was achieved.

Expandable System

After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus [33]. As a result, the dosage form is retained in the stomach for a long period of time. These systems are some times referred to as plug type systems because they tend to remain lodged at the pyloric sphincter. These polymeric matrices remain in the gastric cavity for several hours even in the fed state. Sustained and controlled drug release may be achieved by selecting a polymer with the proper molecular weight and swelling properties. As dosage form coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is a result of the presence of physical-chemical crosslink's in the hydrophilic polymer network. These cross-links prevent the dissolution of the polymer and thus maintain the physical integrity of the dosage form. A balance between the extent and duration of swelling is maintained by the degree of cross linking between the polymeric chains. A high degree of crosslinking retards the swelling ability of the system and maintains its physical integrity for a prolonged period. On the other hand, a low degree of cross-linking results in extensive swelling followed by the rapid dissolution of the polymer8. An optimum amount of cross-linking is required to maintain a balance between swelling and dissolution. The swollen system eventually will lose its integrity because of a loss of mechanical strength caused by abrasion or erosion or will burst into small fragments when the membrane ruptures because of continuous expansion[35]. These systems also may erode in the presence of gastric juices so that after a predetermined time the device no longer can attain or retain the expanded configuration.[34] The expandable GRDFs are usually based on following configurations:

- A small collapsed configuration which enables sufficient oral intake Expanded form that is achieved in the stomach and thus prevents passage through the pyloric sphincter.
- A smaller form that is achieved in the stomach when the retention is no longer required i.e. after the GRDF has released its active ingredient, thereby enabling evacuation.

Swelling System

These are the dosage forms, which after swallowing, swells to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a longer period of time. These systems may be named as 'plug type systems'. Sustained and controlled drug release may be achieved by selection of polymer of proper molecular weight and swelling of the polymer retards the drug release. on coming in contact with gastric fluid, the polymer imbibes water and swells (Figure 6).

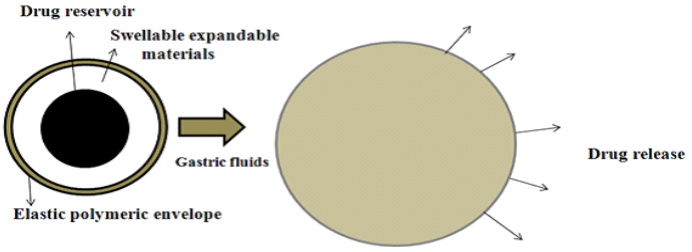

Figure 6. Sustained and controlled drug release in plug type system

Unfolding system

Unfolding systems are systems which are actually of larger size but they are folded to decrease size and kept in capsules. In stomach these systems comes out of capsules and unfolds to larger size. The important factor for unfolding system is shape memory. They should have sufficient shape memory such that they retain their unfolded (expanded) shape in stomach against gastric motility and not get folded again and escape out till the desired time interval (Figure 7).

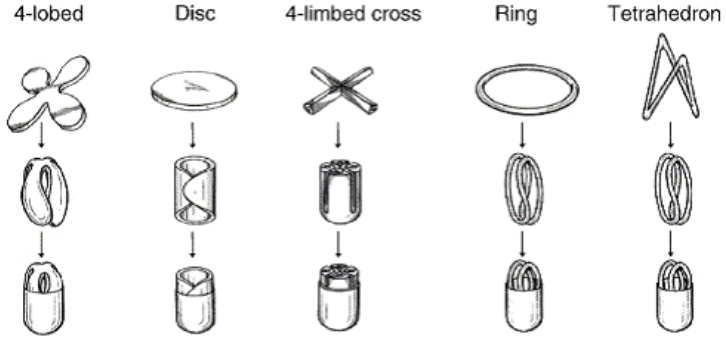

Figure 7. Various shapes of unfolding system

Raft Forming Systems

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO_2. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense and float on the gastric fluids.[36] Jorgen *et al* [37, 38] described an antacid raft forming floating system. The system contains a gel forming agent (e.g. alginic acid), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids. The raft thus formed floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus. A patent assigned to Reckitt and Colman Products Ltd., describes a raft forming formulation for the treatment of helicobacter pylori (H. Pylori) infections in the GIT. The composition contained drug, alginic acid, sodium bicarbonate, calcium carbonate, mannitol and a sweetener. These ingredients were granulated, and citric acid was added to the granules. The formulation produces effervescence and aerates the raft formed, making it float.

High Density Systems:[39, 40]

These systems with a density of about 3 g/cm^3 are retained in the antrum part of the stomach and are capable of withstanding its peristaltic movements. The only major drawbacks with such systems is that it is technically difficult to manufacture such formulations with high amount of drug (>50%) and to achieve a density of about 2.8 g/cm^3. It is necessary to use diluents like barium sulfate, zinc oxide, titanium dioxide, iron powder etc. to manufacture such high density formulations. Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations.

Bioadhesive Systems [41, 42]

Bio/mucoadhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the Gastro retention of drug delivery system (DDS) in the stomach by increasing the intimacy and duration of contact of drug with the biological membrane. A bio/muco-adhesive substance is a natural or synthetic polymer capable of producingan adhesive interaction based on hydration–mediated, bondingmediated or receptor mediated adhesion with a biological membrane or mucus lining of GI mucosa.

Polymers and other ingredients

Following types of ingredients can be incorporated into floating dosage form in addition to the drugs:

- **Hydrocolloids** (20%-75%): They can be synthetics, anionic or non-ionic like hydrophilic gums, modified cellulose derivatives.

eg. Acacia, pectin, Chitosan,agar, casein, bentonite, veegum, HPMC(K4M, K100M and K15M),Gellan gum(Gelrite®), Sodium CMC, MC, HPC.

- **Inert fatty materials**(5%-75%): Edible, inert fatty materials having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy Eg. Beeswax, fatty acids, long chain fatty alcohols, Gelucires® 39/01 and 43/01.
- **Effervescent agents:** Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate, CG (Citroglycine).
- **Release rate accelerants**(5%-60%): eg lactose, mannitol
- **Release rate retardants** (5%-60%): eg Dicalcium phosphate, talc, magnesium stearate
- **Buoyancy increasing agents**(upto80%): eg. Ethyl cellulose
- **Low density material:** Polypropylene foam powder (Accurel MP 1000®).

6. EVALUATION OF GASTRORETENTIVE DOSAGE FORM

(A) *In-Vitro* Evaluation [43, 44]

Floating Systems

(a) Buoyancy Lag Time

It is determined in order to assess the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. These parameters can be measured as a part of the dissolution test.

(b) Floating Time [46]

Test for buoyancy is usually performed in SGF-Simulated Gastric Fluid maintained at 37^0C. The time for which the dosage form continuously floats on the dissolution media is termed as floating time.

(c) Specific Gravity / Density

Density can be determined by the displacement method using Benzene as displacement medium.

(d) Resultant Weight [47]

Now we know that bulk density and floating time are the main parameters for describing buoyancy. But only single determination of density is not sufficient to describe the buoyancy because density changes with change in resultant weight as a function of time. For example a matrix tablet with bicarbonate and matrixing polymer floats initially by gas generation and entrapment but after some time, some drug is released and simultaneously some outer part of matrixing polymer may erode out leading to change in resultant weight of dosage form. The magnitude and direction of force/resultant weight (up or down) is corresponding to its buoyancy force (F_{buoy}) and gravity force (F_{grav}) acting on dosage form

$F = F_{buoy} – F_{grav}$

$F = D_f g V – D_s g V$

$F = (D_f – D_s) g V$

$F = (D_f – M/V) g V$

Where,

F = resultant weight of object D_f = Density of Fluid

D_S = Density of Solid object g = Gravitational force

M = Mass of dosage form V = Volume of dosage form

So when D_s, density of dosage form is lower, F force is positive gives buoyancy and when it is D_s is higher, F will negative shows sinking.

Swelling systems

(a) Swelling Index

After immersion of swelling dosage form into SGF at 37^0C, dosage form is removed out at regular interval and dimensional changes are measured in terms of increase in tablet thickness / diameter with time.

(b) Water Uptake

It is an indirect measurement of swelling property of swellable matrix. Here dosage form is removed out at regular interval and weight changes are determined with respect to time. So it is also termed asWeight Gain.

Water uptake = $W U = (W_t – Wo) \times 100 / W_o$

Where, W_t = weight of dosage form at time t

W_o = initial weight of dosage form

(c) Drug release

Dissolution tests are performed using the dissolution apparatus. Samples are withdrawn periodically from the dissolution medium with replacement and then analyzed for their drug content after an appropriate dilution.

Content uniformity, Hardness, Friability for Tablets and Drug loading, drug entrapment efficiency, particle size analysis, surface characterization for floating microspheres and beads. Drug loading is assessed by crushing accurately weighed sample of

beads or microspheres in a mortar and added to the appropriate dissolution medium which is then centrifuged, filtered and analyzed by various analytical methods like spectrophotometry. The percentage drug loading is calculated by dividing the amount of drug in the sample by the weight of total beads or microspheres. The particle size and the size distribution of beads or microspheres is determined in the dry state using the optical microscopy method. The external and cross-sectional morphology (surface characterization) is done by scanning electron microscope (SEM).[57]

(B) *In-Vivo* Evaluation

(a) Radiology

X-ray is widely used for examination of internal body systems. Barium Sulphate is widely used Radio Opaque Marker. So, BaSO4 is incorporated inside dosage form and X-ray images are taken at various intervals to view GR.[45]

(b) Scintigraphy

Similar to X-ray, emitting materials are incorporated into dosage form and then images are taken by scintigraphy. Widely used emitting material is 99Tc.

(c) Gastroscopy

Gastroscopy is peroral endoscopy used with fiber optics or video systems. Gastroscopy is used to inspect visually the effect of prolongation in stomach. It can also give the detailed evaluation of GRDDS.

(d) Magnetic Marker Monitoring

In this technique, dosage form is magnetically marked with incorporating iron powder inside, and images can be taken by very sensitive bio-magnetic measurement equipment. Advantage of this method is that it is radiation less and so not hazardous.

(e) Ultrasonography

Used sometimes, not used generally because it is not traceable at intestine.

(f) 13C Octanoic Acid Breath Test

13C Octanoic acid is incorporated into GRDDS. In stomach due to chemical reaction, octanoic acid liberates CO2 gas which comes out in breath. The important Carbon atom which will come in CO2 is replaced with 13C isotope. So time up to which 13CO2 gas is observed in breath can be considered as gastric retention time of dosage form. As the dosage form moves to intestine, there is no reaction and no CO2 release. So this method is cheaper than other.

7. APPLICATIONS

1. Sustained Drug Delivery

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of shortgastric residence time encountered with an oral CRformulation hence can be overcome with thesesystems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited. Eg. Sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours).[56]

2. Site-Specific Drug Delivery

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, eg, riboflavin and furosemide. Eg. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets.[48]

3. Absorption Enhancement

Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. Eg. A significantly increase in the bioavailability of floating dosage forms(42.9%) could b achieved as compared with commercially available LASIX tablets (33.4%) and enteric coated LASIX-long product (29.5%).[48]

Recent advances in stomach specific floating dosage forms

Jain *et al* [12] designed a controlled release system to increase GRT without contact with gastric mucosa. This was achieved through the preparation of floating microspheres by

emulsion solvent diffusion technique consisting of calcium silicate (FLR) as a porous carrier, repaglinide and a Eudragit polymer. The effect of various formulation and process variables were studied.

Chavanpatil *et al* [58] developed a gastroretentive dosage form for ofloxacin to be taken preferably once daily. The design ofthe delivery system based on a sustained release (SR) formulation with swelling and floating features in order to prolong gastric retention. Different polymers such as psyllium husk, HPMC K100M, crosspovidone and its combination were used and the formulations nwere evaluated for buoyancy, stability, drug content and drug release studies.

Ninan Ma *et al* [49] developed a type of multi-unit floating alginate (Alg) microspheres by the ionotropicgelation method with calcium carbonate (CaCO3) being used as gas-forming agent. Attempts were made to enhance the drug encapsulation efficiency and delay the drug release by adding chitosan (Cs) into the gelation medium and by coating with Eudragit, respectively. The gastrointestinal transit of optimized floating sustainedrelease microspheres was compared with that of the non floating system manufactured from identical material using the technique of gamma-scintigraphy in healthy human volunteers. It was found that the drug encapsulation efficiency of Cs–Alg microspheres was much higher than that of the Ca–Alg microspheres, and coating the microspheres with Eudragit RS could extend the drug release significantly. Both uncoating and coating microspheres were able to continuously float over the simulated gastric fluid (SGF) for 24 h *in vitro*. Prolonged gastricretention time (GRT) of over 5 h was achieved in the volunteer for the optimized coating floating microspheres (FM). In contrast, non-floating system (NFM) could be emptied within 2.5 hrs.

Strübing *et al* [50] investigated the mechanism of floating and drug release behaviour of poly (vinyl acetate)-based floating tablets with membrane controlled drug delivery. Propranolol HCl containing tablets with Kollidon® SR as an excipient for direct compression and different Kollicoat® SR 30 D/Kollicoat® IR coats varying from 10 to 20 mg polymer/cm^2 were investigated regarding drug release in 0.1 mole.lit-1 HCl. Furthermore, the onset of floating, the floating duration and the floating strength of the device were determined. In addition, benchtop MRI studies of selected samples were performed. Coated tablets with 10 mg polymer/cm2 SR/IR, 8.5:1.5 coat exhibited the shortest lag times prior to drug release and floating onset, the fastest increase in and highest maximum values of floating strength. The drug release was delayed efficiently within a time interval of 24 h by showing linear drug release characteristics.

Jang *et al* [51] has prepared a gastroretentive drug delivery system of DA-6034, a new synthetic flavonoid derivative, for the treatment of gastritis was developed by using effervescent floating matrix system (EFMS). The therapeutic limitations of DA-6034 caused by its low solubility in acidic conditions were overcome by using the EFMS, which was designed to cause tablets to float in gastric fluid and release the drug continuously. The release of DA-6034 from tablets in acidic media was significantly improved by using EFMS, which is attributed to the effect of the solubilizers and the alkalizing agent such as sodium bicarbonate used as gas generating agent. DA-6034 EFMS tablets showed enhanced gastroprotective effects in gastric ulcer-induced beagle dogs, indicating the therapeutic potential of EFMS tablets for the treatment of gastritis.

Sungthongjeen *et al* [52] have prepared a floating multilayer coated tablets based on gas formation. The system consists of a drug-containing core tablet coated with a protective layer (hydroxypropyl methylcellulose), a gas forming layer (sodium bicarbonate) and a gas-entrapped membrane, respectively. Eudragit® RL 30D was chosen as a gas-entrapped membrane due to its high flexibility and high water permeability. The obtained tablets enabled to float due to the CO2-gas formation and the gasentrapment by polymeric membrane. The effect of formulation variables on floating properties and drugrelease was investigated. The floating tablets using direct-compressed cores had shorter time to float andfaster drug release than those using wet-granulated cores. The increased amount of a gas forming agent did not affect time to float but increased the drug release from the floating tablets while increasing coating level of gasentrapped membrane increased time to float (more then 8 hours) and slightly retarded but sustained drug release.

Rajnikanth and Mishra[53] have developed a floating in situ gelling system of clarithromycin (FIGC) using gellanas gelling polymer and calcium carbonate as floating agent for potentially treating gastric ulcers, associatedwith Helicobacter pylori. Gellan based FIGC wasprepared by dissolving varying concentrations of gellan in deionized water to which varying concentrations of drug and sucralfate were dispersed well. The addition of sucralfate to the formulation significantly suppressed the degradation of clarithromycin at low pH. FIGC showed a significant anti-H. pylori effect than that of clarithromycin suspension. The in situ gel formulation with sucralfate cleared H.pylori more effectively than that of formulation without sucralfate. It was concluded that prolonged gastrointestinal residence time and enhanced clarithromycin stability resulting from the floating in situ gel of clarithromycin might contribute better for complete clearance of H. pylori.

Marketed Preparations [55, 3]

Table No. 1 Marketed preparations

S No	Brand Name	Description
1	Valreleas e®	Floating capsule *Diazepam* (15mg) Hoffmann-LaRoche, USA
2	Madopar ®	HBS(Prolopa® HBS) Floating, CR capsule *Benserazide* (25mg) and *LDopa*(100mg)Roche Products, USA **Liquid Gaviscon®** Effervescent Floating liquid alginate preparations Al hydroxide (95 mg), MgCarbonate (358 mg) GlaxoSmithkline,India
3	Topalkan ®	Floating liquid alginate preparation *Al – Mg antacid* Pierre Faber Drug, France
4	Almagate Flotcoat ®	Floating dosage form Al – Mg antacid
5	Conviron ®	Colloidal gel forming FDDS *Ferrous sulphate* Ranbaxy, India
6	Cytotech ®	Bilayer floating capsule *Misoprostol* (100µg/200µg) Pharmacia, USA
7	Cifran OD®	Gas-generating floating form *Ciprofloxacin* (1gm) Ranbaxy, India

Drugs Used In The Formulations Of Stomach Specific Floating Dosage Form:[35, 54, 55]

- **Floating microspheres** – Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Ketoprofen Piroxicam, Verapamil, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol , Tranilast and Terfinadine
- **Floating granules** - Diclofenac sodium, Indomethacin and Prednisolone
- **Films** – Cinnarizine , Albendazole
- **Floating tablets and Pills** - Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxycillin trihydrate, Atenolol, Fluorouracil, Isosorbide mononitrate Para- aminobenzoic acid, Piretanide , Theophylline, Verapamil hydrochloride, Chlorpheniramine maleate, Aspirin, Calcium Carbonate, Fluorouracil, Prednisolone, Sotalol, pentoxyfilline and Diltiazem HCl.
- **Floating Capsules** - Chlordiazepoxide hydrogen chloride, Diazepam, Furosemide, Misoprostol, L-Dopa, Benserazide, Ursodeoxycholic acid and Pepstatin, and Propranolol.

8. CONCLUSION & FUTURE PROSPECT

Based on the literature surveyed, it may be concluded that stomach specfic gastroretentive drug delivery offers various potential advantages for drug with poor bioavailability and narrow absorption window due their absorption is restricted to the upper gastrointestinal tract(GIT) and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability. Due to complexity of pharmacokinetics and pharmacodynamics parameters, in vivo studies are required to establish the optional dosage form for a specific drug. Some of the unresolved, critical issues like the quantitative efficiency of floating delivery systems in the fasted and fed states, role of buoyancy in enhancing GRT of FDDS and more than that formulation therefore it is an ideal dosage form to be given locally to eradicate H.Pylori, responsible for gastric ulcers world wide. All these gastroretentive drug delivery systems (high density, floating, expandable or unfoldable or swelling, bioadhesive, etc.) are interesting and present their own advantages and disadvantages. Now, a lot of work is running to develop different types of gastroretentive delivery systems of various drugs. In the future, it is expected that they will become of increasing importance, ultimately leading to improved efficiencies of various types of pharmacotherapies.

REFERENCES

1. Garg S, Sharma S. Gastroretentive drug delivery system. Business Briefing Pharmtech. 2003; 160-166.
2. Arrora S, Ali J, Khar R K, Baboota S. Floatng drug delivery systems: A review. AAPS Pharm Sci. Tech 2005; 6 (3): 372-390.
3. Chawala G, Gupta P, Koradia V, Bansal AK. Gastroretention a means to Address Regional Variability in Intestinal Drug Absorption. Pharmaceutical Technology. 2003; 50-68.
4. Reddy L H, Murthy R H. Floating dosage systems in drug delivery, Crit. Rev. Ther. Drug Carrier Syst. 2002; 19 (6): 553-585.
5. Yang L, Fassihi R. Zero order release kinetics from self correcting floatable configuration drug delivery system. J Pharm Sci. 1996; 85: 170Y173.
6. Davis SS, Stockwell AF, Taylor M J. The effect of density on the gastric emptying of single and multiple-unit dosage forms. Pharm Res. 1986; 3: 208-213.
7. Desai S, Bolton S. A floating controlled release drug delivery system: *in vitro-in vivo* evaluation. Pharm Res. 1993; 10: 1321-1325.
8. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release. 2000; 63: 235-259.

9. Gupta P, Vermani K, Garg S. Hydrogels: From Controlled Release to pH Responsive Drug Delivery. Drug Discovery Today 2002; 7 (10): 569-579.
10. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled release system for gastric retention. Pharm. Res. 1997; 14: 815-819.
11. Kawashinia Y, Niwa T, Takcuchi H, Hino T, Itoh Y. Hallow microspheres for use as a floating controlled drug delivery system in the stomach. J Pharm. Sci.1992; 81(2): 135-140**.**
12. Jain SK, Awasthi AM, Jain NK, Agarwal GP. Calcium silicate based microspheres of repaglinide for gastroretentive floating drug delivery: preparation and *in-vitro* characterization. J Control Release. 2005; 107: 300-309.
13. Sato Y, Kawaafaima Y, Takenchi H. *In-vitro* and *in-vivo* evaluation of riboflavin containing microoballoons for floating controlled delivery system in healthy humans. Int. J Pharm. 2004; 275: 75-82.
14. Seth PR, Tossounian J. The hydrodynamically balanced system HBSTM: A novel drug delivery system for oral use, Drug Dev. Ind. Pharm. 1984; 10: 313-339.
15. Nayak AK, Maji R, Das B. Gastroretentive drug delivery systems: A review. Asian J Pharm. Clinical Res. 2010; 3 (1): 2-10.
16. Dave BS, Amin AF, Patel M. Gastrorentive drug delivery system of ranitidine HCl formulation and in vitro evaluation. AAPS Pharma Sci. Tech. 2004; 5: 1-10.
17. Stockwell AF, Davis SS, walker SE. *In-vitro* evaluation of alginate gel system as sustainedrelease drug delivery system. J Control Release. 1986; 3: 167-175.
18. Streubel A, Siepmann J, Bodmeier R. Floating matrix tablets based on low density foam powder: effect of formulation and processing parameters on drug release. Eur. J Pharm. Sci. 2003; 18: 37-45.
19. Wu W, Zhou Q, Zhang HB, Ma GD, Fu CD. Studies on Nimodipine sustained release tablet capable of floating on gastric fluids with prolonged gastric resident time. Yao Xue Xue Bao. 1997; 32: 786-790.
20. Nur AO, Zhang JS. Captopril floating and/or bioadhesive tablets: design and release kinetics. Drug Dev. Ind. Pharm. 2000; 26: 965-969.
21. Ozdemir N, Ordu S, OzkanY. 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.
22. Penners G, Lustig K, Jorg PVG. Expandable pharmaceutical forms. US patent 1997; 5: 651-985.
23. Talwar N, Sen H, Staniforth JN. Orally administered controlled drug delivery system providing temporal and spatial control. US patent 6261601. 2001.
24. Tardi P, Troy H. European patent no. EP 1432402. 2002.
25. Talukdar R, Fassihi R. Gastroretentive delivery systems: hollow beads. Drug Dev. Ind. Pharm. 2004; 30: 405-12.
26. Ichikawa M, Watanabe S, Miyake Y. A new multiple unit oral floating dosage system I: Prepration and *in-vitro* evaluation of floating and sustained-release kinetics. J Pharm.Sci. 1991; 80: 1062-1066.
27. Ikura, Hiroshi, Suzuki, Yoshiki. United States Patent 4777033.1988.
28. Umezawa, Hamao. United States Patent 4101650. 1978. 2924.
29. Garg R, Gupta GD. Progress in controlled gastroretentive delivery systems. Trop. J Pharm. Res. 2008; 7(3): 1055-1066.
30. Thanoo BC, Sunny MC, Jayakrishnan A. Oral sustained-release drug delivery systems using polycarbonate microspheres capable of floating on the gastric fluid. J Pharm. Pharmacol. 1993; 45: 21-24.
31. Sato Y, Kawashima Y, Takeuchi H, Yamamoto H. *In-vivo* evaluation of riboflavin containing microballoons for floating controlled drug delivery system in healthy human volunteers. J Cont. Rel. 2003; 93: 39-47.
32. Joseph NH, Laxmi S, Jayakrishnan A. A floating type oral dosage from for piroxicam based on hollow microspheres: *In-vitro* and *In-vivo* evaluation in rabbits. J Cont. Rel. 2002; 79: 71-79.
33. Caldwell LJ, Gardner CR, Cargill RC. Drug Delivery Device Which Can Be Retained in the Stomach for a Controlled Period of Time. US Patent No. 4735804. 5 April 1988.
34. Klausner EA, Lavy E, Stepensky D, Friedman M, Hoffman A. Novel gastroretentive dosage form:evaluation of gastroretentivity and its effect on riboflavin absorption in dogs. J Pharm. Res. 2002; 19: 1516-1523.
35. Rouge N, Cole ET, Doelker E, Buri P. Buoyancy and drug release patterns of floating mini tablets containing piretanide and atenolol as model drugs. Pharm. Dev. Technol. 1998; 3: 73-84.

36. Washington N. Investigation into the barrier action of an alginate gastric reflux suppressant. Liquid Gaviscon. Drug Investig. 1987; 2; 23-30.
37. Foldager J, Toftkjor H. Antacid composition. US Patent 5068109.1991.
38. Fabrcgas JL, Cucala CG, Pous J, Sites RA. *In-vitro* testing of an antacid formulation with prolonged gastric residence time. Drug Dev. Ind. Pharm. 1994; 20: 1199-1212.
39. Clarke GM, Newton JM, Short MD. Gastrointestinal transit of pellets of differing size and density. Int. J Pharm. 1993; 100 (1-3): 81-92.
40. Clarke GM, Newton JM., Short MD. Comparative gastrointestinal transit of pellet systems of varying density. Int. J Pharm. 1995; 114 (1): 1-11.
41. Gupta PK, Robinson JR. Oral Controlled- Release Delivery, in Treatise on Controlled Drug Delivery. A. Kydonieus, Eds., Marcel Dekker, New Jersey, 1992; 255-310.
42. Park K, Robinson JR. Bioadhesive Polymers as Platforms for Oral-Controlled Drug Delivery: Method to Study Bioadhesion. Int. J Pharm. 1984; 19 (1): 107-127.
43. Desai S, Bolton S. A floating controlled release system: *In-vitro/In-vivo* valuation. Pharm. Res. 1993; 10: 1321-1325.
44. Patel VF, Patel NM. Yeole P G. Studies on formulation and evaluation Ranitidine floating tablets. Ind. J Pharm. Sci., 2005, 67 (6): 703-709.
45. Harries D, Sharma HL. GI transit of potential bioadhesive formulations in man: A scintigraphic study. J Cont. Rel. 1990; 12 (1): 45-53.
46. Burns SJ, Corness D, Hay G. Development and validation of an *In-vitro* dissolution method for a floating dosage form with biphasic release characteristics. Int. J Pharm. 1995; 121: 37-34.
47. Timmermans J, Andre JM. Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: New data for reconsidering the controversy. J Pharm Sci. 1994; 83: 18Y24.
48. Moursy NM, Afifi NH, Ghorab DM, El-Saharty Y. Formulation and evaluation of sustained release floating capsules of Nicardipine hydrochloride. Pharmazie. 2003; 58: 38-43.
49. Ninan M , Lu X, Wanga Q, Zhanga X. Development and evaluation of new sustained release floating microspheres. Int. J Pharm. 2008; 358: 82-90.
50. Strübing S, Abbouda T, Renata C, Metza H. New insights on poly (vinyl acetate)-based coated floating tablets: Characterisation of hydration and CO_2 generation by benchtop MRI and its relation to drug release and floating strength. European J Pharm. and Biopharm. 2008; 69: 708-717.
51. Janga S, Lee J, Park S. Gastroretentive drug delivery system of DA-6034, a new flavonoid derivative, for the treatment of gastritis. Int. J Pharm. 2008; 356: 88-94.
52. Sungthongjeena S, Sriamornsak P, Puttipipatkhachorn S. Design and evaluation of floating multi-layer coated tablets based on gas formation. Euro. J Pharm. and Biopharm. 2008; 69: 255-263.
53. Rajinikanth P, Mishra B. Floating in situ gelling system for stomach site-specific delivery of clarithromycin to eradicate H.pylori. J Cont. Rel. 2008; 25: 33-41.
54. Cheuh HR., Zia H, Rhodes CT. Optimization of Sotalol floating and bioadhesive extended release tablet formulation. Drug Dev. Ind. Pharm. 1995; 21: 1725-1747.
55. Vyas SP, Khar RK. Gastroretentive systems. In: Controlled drug Delivery. Vallabh Prakashan, Delhi, India. 2006; 197-217.
56. Fell JT, Whitehead L, Collet H. Prolonged gastric trtention using floating dosage forms. Pharm. Technol. 2000; 24 (3): 82-90.
57. Agnihotri SA, Jawalkar SS, Aminabhavi TM. Controlled release of cephalexin through gellan gum beads: Effect of formulation parameters on entrapment efficiency, size, and drug release. Eur. J Pharm. Biopharm. 2006; 63: 249–261.
58. Chavanpatil M, Jain P, Chaudhari S, Shear R, Vavia P. Development of sustained release gastroretentive drug delivery system for ofloxacin: *In-vitro* and *In-vivo* evaluation. Int. J Pharm. 2005; 304: 178-184.