Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 3, Suppl 4, 2011

Review Article

GASTRO-RETENTIVE FLOATING DRUG DELIVERY SYSTEM- AN APPROACH IN GASTRO-RETENTIVE DRUG DELIVERY

PRAKASH RAJAK *[1], A BHATTACHARYA [2], NEHA SHARMA [3], MANJIR SARMA KATAKI [4], ANANYA RAJKUMARI [4]

[1] Institute of Pharmacy and Emerging Sciences, Baddi University of Emerging Sciences and Technology, Makhnumajra, Baddi, Distt. Solan, H.P.-173 205, [2] Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh -786004, Assam, India,[3] Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra – 13611, Haryana, India, [4] Abhilashi College of Pharmacy, Tanda, Mandi, Himachal Pradesh, Pin-175008, India. Email: prakashh2010@gmail.com

Received: 30 April 2011, Revised and Accepted: 6 May 2011

ABSTRACT

Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance, and cost-effective manufacturing process. In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits. One of the most widely gastro retentive drug delivery system. Several approaches are currently being used to prolong the GRT, including floating drug delivery systems (FDDS), also known as hydrodynamically balanced systems (HBS), swelling and expanding systems, high-density systems, and other delayed gastric emptying devices. Floating dosage forms are emerging as a promising dosage forms. Floating dosage form can be prepared as tablets, capsules by adding suitable ingredients as well as by adding gas generating agent. The purpose of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention.

Keywords: Gastro-Retentive drug delivery, Floating drug delivery, Gastric retention time.

INTRODUCTION

Drug delivery systems that can precisely control the release rates or target drugs to a specific body site have had an enormous impact on the health care system. Oral controlled release dosage forms have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. Although tremendous advance have been seen in oral controlled drug delivery system, this system has been of limited success in the case of drugs with poor absorption window throughout the GIT.

Several difficulties are faced in designing oral controlled release drug delivery system for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa [1]. Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed [2].

Gastric emptying of pharmaceuticals is highly variable and is dependent on the dosage form and the fed/fasted state of the stomach [3]. Normal gastric residence times usually range between 5 mints and 2 hrs. In the fasted state the electrical activity in the stomach, the interdigestive myoelectric cycle or migrating myoelectric complex (MMC) governs the activity and, hence, the transit of dosage forms. It is characterized by four phases:

Phase I Period of no contraction (40-60 minutes),

Phase II Period of intermittent contractions (20-40 minutes),

Phase III Period of regular contractions at the maximal frequency that travel distally also known as house keeper wave. (10-20 minutes),

Phase IV Period of transition between phase III and phase I (0-5 minutes) [4].

The attempts to develop gastro retentive drug delivery systems may be largely divided into two classes: those that rely on the natural physiology of the gastrointestinal tract and those that are designed to overcome it. Approaches such as size or floatation, which rely on delayed emptying from the stomach, depend on the normal physiological duration of the fed state of 4-8 hr, following a meal and rather reproducible transit time through the small intestine [5,6].

Gastro-retention is essential for drugs that are absorbed from the stomach, drugs that are poorly soluble or degraded by the higher pH of intestine, and drugs with an absorption which can be modified by changes in gastric emptying time. Gastro-retentive dosage forms are also useful for local as well as sustained drug delivery for certain conditions, like H. pylori infection which is the cause of peptic ulcers. This dosage form improves bioavailability, therapeutic efficacy and may even also allow a possible reduction in the dose because of steady therapeutic levels of drug, for example furosemide and ofloxacin. The reduction in fluctuations in therapeutic levels minimizes the risk of resistance especially in case of β-lactam antibiotics (Penicillins and Cephalosporins) [7].

In general, appropriate candidates for controlled release gastroretentive dosage forms (CRGRDF) are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT:

- Narrow absorption window in GI tract, e.g., riboflavin and levodopa
- Primarily absorbed from stomach and upper part of GIT, e.g., calcium supplements, chlordiazepoxide and cinnarizine.
- Drugs that act locally in the stomach, e.g., antacids and misoprostol.
- Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole.
- Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate

The need for gastro retentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems. These efforts resulted in GRDFs that were designed, in large part, based on the following approaches.

- Low density DF that causes buoyancy in gastric fluid.
- High density DF that is retained in the bottom of the stomach.
- Bioadhesion to stomach mucosa.
- Slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients [8].
- Expansion by swelling or unfolding to a large size which limits emptying of the DF through the pyloric sphincter [9].

Factors Controlling Gastric Retention of Dosage Forms

The gastric retention time (GRT) of dosage forms is controlled by several factors such as density and size of the dosage form, food intake, nature of the food, posture, age, sex, sleep and disease state of the individual (e.g., gastrointestinal diseases and diabetes) and administration of drugs such as prokinetic agents (cisapride and metoclopramide)

1. Density of dosage form

Dosage forms having a density lower than that of gastric fluid experience floating behavior and hence gastric retention. A density of <1.0 gm/cm3 is required to exhibit floating property. However, the floating tendency of the dosage form usually decreases as a function of time, as the dosage form gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium [10].

2. Size of dosage form

The size of the dosage form is another factor that influences gastric retention. The mean gastric residence times of non-floating dosage forms are highly variable and greatly dependent on their size, which may be small, medium, and large units. In fed conditions, the smaller units get emptied from the stomach during the digestive phase and the larger units during the housekeeping waves. In most cases, the larger the size of the dosage form, the greater will be the gastric retention time because the larger size would not allow the dosage form to quickly pass through the pyloric antrum into the intestine [11]. Thus the size of the dosage form appears to be an important factor affecting gastric retention.

Timmermans and Andre studied the effect of size of floating and nonfloating dosage forms on gastric emptying and concluded that the floating units remained buoyant on gastric fluids [12]. These are less likely to be expelled from the stomach compared with the nonfloating units, which lie in the antrum region and are propelled by the peristaltic waves.

3. Food intake and nature of food

Food intake, the nature of the food, caloric content, and frequency of feeding has a profound effect on the gastric retention of dosage forms. The presence or absence of food in the stomach influences the GRT of the dosage form. Usually, the presence of food increases the GRT of the dosage form and increases drug absorption by allowing it to stay at the absorption site for a longer time. In a gamma scintigraphic study of a bilayer floating capsule of misoprostol [13], the mean gastric residence time was 199 ± 69 minutes; after a light breakfast, a remarkable enhancement of average GRT to 618 ± 208 minutes was observed. The above results are supported by the experiments of Whitehead et al. which show an increase in the relative heights of the floating units after meal consumption [14].

4. Effect of gender, posture and age

A study by Mojaverian et al. found that females showed comparatively shorter mean ambulatory GRT than males, and the gastric emptying in women was slower than in men [15]. The authors also studied the effect of posture on GRT, and found no significant difference in the mean GRT for individuals in upright, ambulatory and supine state. On the other hand, in a comparative study in humans by Gansbeke et al. [16], the floating and non-floating systems behaved differently. In the upright position, the floating systems floated to the top of the gastric contents and remained for a longer time, showing prolonged GRT. But the non-floating units settled to the lower part of the stomach and underwent faster emptying as a result of peristaltic contractions, and the floating units remained away from the pylorus. However, in supine position, the floating units are emptied faster than non-floating units of similar size [17].

Timmermans et al. studied the effect of buoyancy, posture, and nature of meals on the gastric emptying process *in vivo* using gamma scintigraphy [18]. To perform these studies, floating and nonfloating capsules of 3 different sizes having a diameter of 4.8 mm (small units), 7.5 mm (medium units), and 9.9 mm (large units), were formulated. On comparison of floating and nonfloating dosage units, it was concluded that regardless of their sizes the floating dosage units remained buoyant on the gastric contents throughout their residence in the gastrointestinal tract, while the nonfloating dosage units sank and remained in the lower part of the stomach. Floating units away from the gastro duodenal junction were protected from the peristaltic waves during digestive phase while the nonfloating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase. It was also observed that of the floating and nonfloating units, the floating units had a longer gastric residence time for small and medium units while no significant difference was seen between the 2 types of large unit dosage forms.

Approaches to design floating dosage forms

The concept of Floating Drug Delivery System was described as a method for overcoming the difficulty experienced by some people of gagging or choking while swallowing medicine pills. It was suggested that this difficulty could be overcome by providing pills having density of less than 1.0 gm/ml, so that pills will float on water surface. Since then many types of gastric retention drug delivery systems were tested to overcome the limited region and times for drug absorption in gastrointestinal tract.

The main approaches that have been examined for gastro retentive dosage forms (GRDFs) are: low density of GRDF that cause buoyancy above gastric fluid (Floating system), high density which retain the dosage form in the body of stomach, concomitant administration of drugs or excipients which slow the motility of the GIT, bioadhesion to gastric mucosa, swelling to a large size which prevent emptying of dosage form through the pyloric sphincter [19,20].

Gastro-Retentive Floating Drug Delivery System

Floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation in plasma drug concentration. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration.

Types of Floating Drug Delivery Systems

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are:

A. Effervescent System, and

B. Non-Effervescent System.

A. Effervescent System

Effervescent systems include use of gas generating agents, carbonates (e.g. Sodium bicarbonate) and other organic acid(e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide(CO_2) gas, thus reducing the density of system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature.

The effervescent systems can be further classified into two types:

1) Gas Generating systems

2) Volatile Liquid/Vacuum Systems

1) Gas-generating Systems

(a) Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS)

These are as shown in Fig.1 and formulated by intimately mixing the CO_2 generating agents and the drug within the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate for a prolonged period. The drug is slowly released at a desired rate from the system and is expelled from the stomach. This leads to an increase in the gastro retentive time and a better control over fluctuation in plasma drug concentration.

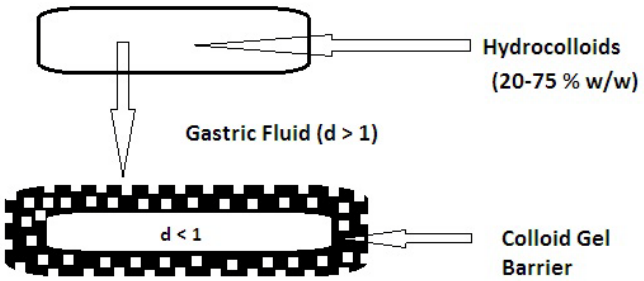

Fig. 1: Intragastric floating tablet

(b) Intra Gastric Bilayer Floating Tablets

These are also compressed tablet as shown in Fig 3 and contain two layers i.e.

i) Immediate release layer and

ii) Sustained release layer.

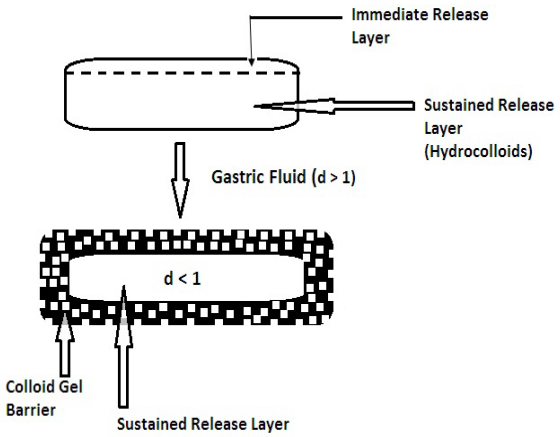

Fig. 2: Intra gastric floating bilayer tablet

(c) Multiple Unit type floating pills

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO_2 within the system. Fig 3.

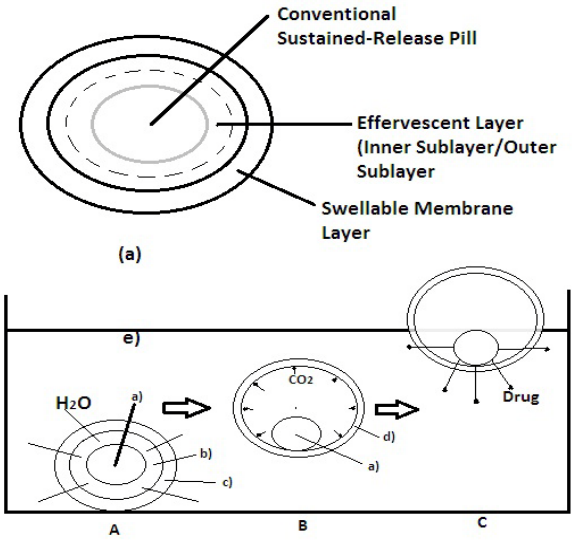

Fig. 3: (a) multiple-unit oral floating dosage system. (b) Stages of floating Mechanism

2) Volatile Liquid / Vacuum Containing Systems

(a) Intragastric Floating Gastrointestinal Drug Delivery System

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporous compartment, as shown in Fig 4.

(b) Inflatable Gastrointestinal Delivery Systems

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir into the gastric fluid. The system is shown in Fg.5.

(c) Intragastric Osmotically Controlled Drug Delivery System

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components: drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt.

An osmotic pressure is then created which acts on the collapsible bag and in turn forces the bag reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice. The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach. This system is shown in Fig.6

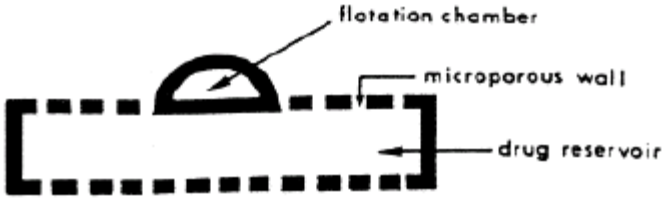

Fig. 4: Intragastric floating drug delivery device

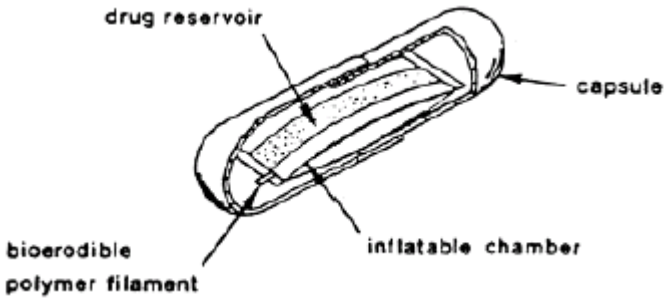

Fig. 5: Gastro-inflatable drug delivery device

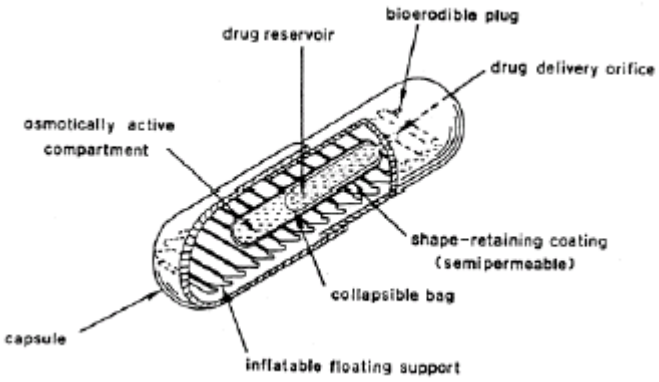

Fig. 6: Intragastric osmotic controlled drug delivery system

Fassihi and Yang developed a zero-order controlled release multilayer tablet composed of at least 2 barrier layers and 1 drug layer [21]. All the layers were made of swellable, erodible polymers and the tablet was found to swell on contact with aqueous medium. As the tablet dissolved, the barrier layers eroded away to expose more of the drug. Gas evolving agent was added in either of the barrier layers, which caused the tablet to float and increased the retention of tablet in a patient's stomach.

Ichikawa et al. developed a new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills [22]. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sub layers to avoid direct contact between the 2 agents. These sub layers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. It was found that the system had good floating ability independent of pH and viscosity and the drug (para-amino benzoic acid) released in a sustained manner.

Yang et al. developed a swellable asymmetric triple-layer tablet with floating ability to prolong the gastric residence time of triple drug regimen (tetracycline, metronidazole, and clarithromycin) in *Helicobacter pylori*–associated peptic ulcers using hydroxy propyl methyl cellulose (HPMC) and poly (ethylene oxide) (PEO) as the rate-controlling polymeric membrane excipients [23]. System was based on the swellable asymmetric triple-layer tablet approach. The floatation was accomplished by incorporating a gas-generating layer consisting of sodium bicarbonate: calcium carbonate (1:2 ratios) along with the polymers. The *in vitro* results revealed that the sustained delivery of tetracycline and metronidazole over 6 to 8 hours could be achieved while the tablet remained afloat. The floating feature aided in prolonging the gastric residence time of this system to maintain high localized concentration of tetracycline and metronidazole.

Atyabi and coworkers developed a floating system using ion exchange resin that was loaded with bicarbonate by mixing the beads with 1 M sodium bicarbonate solution [24]. The loaded beads were then surrounded by a semi permeable membrane to avoid sudden loss of CO_2. The *in vivo* behavior of the coated and uncoated beads was monitored using a single channel analyzing study in 12 healthy human volunteers by gamma radio scintigraphy. Studies showed that the gastric residence time was prolonged considerably (24 hours) compared with uncoated beads (1 to 3 hours).

Ichikawa et al. developed floating capsules composed of a plurality of granules that have different residence times in the stomach and consist of an inner foamable layer of gas generating agents [25]. This layer was further divided into 2 sub layers, the outer containing sodium bicarbonate and the inner containing tartaric acid. This layer was surrounded by an expansive polymeric film (composed of poly vinyl acetate [PVA] and shellac), which allowed gastric juice to pass through, and was found to swell by foam produced by the action between the gastric juices and the gas-generating agents. Two parameters were evaluated: the time for the pills to be floating (TPF) and rate of pills floating at 5 hours (FP_{5h}). It was observed that both the TPF and FP_{5h} increased as the percentage of swellable membrane layer coated on pills having an effervescent layer increased. As the percentage of swellable layer was increased from 13% to 25% (wt/wt), the release rate was decreased and the lag time for dissolution also increased. The percentage of swellable layer was fixed at 13% wt/wt and the optimized system showed excellent floating ability *in vitro* (TPF ~10 minutes and FP_{5h} ~80%) independent of pH and viscosity of the medium.

Ozdemir et al. developed floating bilayer tablets with controlled release for furosemide. One layer contained the polymers HPMC 4000, HPMC 100, and CMC (for the control of the drug delivery) and the drug [26]. The second layer contained the effervescent mixture of sodium bicarbonate and citric acid. Radiographic studies on 6 healthy male volunteers revealed 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. developed an expandable tablet containing mixture of polyvinyl lactams and polyacrylates that swell rapidly in an aqueous environment and thus reside in stomach over an extended period of time [27]. In addition to this, gas-forming agents were incorporated. As the gas formed, the density of the system was reduced and thus the system tended to float on the gastric contents.

Talwar et al. developed 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 [28]. The viscolysing agent initially and the gel-forming polymer later formed a hydrated gel matrix that entrapped the gas, causing the tablet to float and retained in the stomach or upper part of the small intestine (spatial control). The hydrated gel matrix created a tortuous diffusion path for the drug, resulting in sustained release of the drug (temporal delivery).

Baumgartner et al. developed a matrix-floating tablet incorporating a high dose of freely soluble drug [29]. The formulation containing 54.7% of drug, HPMC K4 M, Avicel PH 101, and a gas-generating agent gave the best results. It took 30 seconds to become buoyant.

Choi et al. prepared floating alginate beads using gas forming agents (calcium carbonate and sodium bicarbonate) and studied the effect of CO_2 generation on the physical properties, morphology, and release rates [30]. The study revealed that the kind and amount of gas-forming agent had a profound effect on the size, floating ability, pore structure, morphology, release rate, and mechanical strength of the floating beads. *In vitro* floating studies revealed that the beads free of gas-forming agents sank uniformly in the media while the beads containing gas-forming agents in proportions ranging from 5:1 to 1:1 demonstrated excellent floating (100%).

Moursy et al. developed sustained release floating capsules of nicardipine HCl [31]. For floating, hydrocolloids of high viscosity grades were used and to aid in buoyancy sodium bicarbonate was added to allow evolution of CO_2. Results showed an increase in floating with increase in proportion of hydrocolloid. Inclusion of sodium bicarbonate increased buoyancy.

B. Non Effervescent Systems

The non effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as chitosan and carbopol. The various types of this system are as follows:

1) Colloidal gel barrier system

Sheth and Tossounian first designated this ' hydrodynamically balanced system [32]. These types of systems contain drug with gel-forming hydrocolloids which allow them to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug at its absorption sites in the solution form for ready absorption. This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid as hydroxypropyl cellulose, hydoxyethyl cellulose, hydroxypropyl methyl cellulose (HPMC), polysaccharides and matrix-forming polymer such as polycarbophil, polyacrylate and polystyrene. This hydrocolloid hydrates and forms a colloidal gel barrier around its surface after coming in contact with gastric fluid and also helps in sustain releasing of drug.

2) Microporous compartment system

In this technology a drug reservoir is encapsulated inside a microporous compartment with pores along its top and bottom walls [33]. The peripheral walls of the drug reservoir compartment are completely sealed. This sealing prevents any direct contact of gastric surface with the undissolved drug. The floatation chamber containing entrapped air allows the delivery system to float over the gastric content in the stomach. Gastric fluid enters through an aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

3) Alginate Beads

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

4) Hollow Microspheres/Microballons

Hollow microspheres (microballons), loaded with drug in their outer polymer shells were prepared by a novel emulsion solvent diffusion method. The ethanol: dichloromethane solution of drug and enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 400 C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug. The microballons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours in vitro.

Streubel et al. developed floating microparticles composed of polypropylene foam, Eudragit S, ethyl cellulose (EC), and polymethyl metha acrylate (PMMA) and were prepared by solvent evaporation technique [34]. Good floating behavior was observed as more than 83% of microparticles were floating for at least 8 hours. At similar drug loading the release rates increased in the following order PMMA < EC < Eudragit S.

El-Kamel et al. prepared floating microparticles of ketoprofen, by emulsion solvent diffusion technique [11]. Four different ratios of Eudragit S 100 with Eudragit RL were used. The formulation containing 1:1 ratio of the 2 abovementioned polymers exhibited high percentage of floating particles in all the examined media as evidenced by the percentage of particles floated at different time intervals.

Bulgarelli et al. studied the effect of matrix composition and process conditions on casein gelatin beads prepared by emulsification extraction method [35]. Casein by virtue of its emulsifying properties causes incorporation of air bubbles and formation of large holes in the beads that act as air reservoirs in floating systems and serve as a simple and inexpensive material used in controlled oral drug delivery systems.

Illum and Ping developed microspheres that released the active agent in the stomach environment over a prolonged period of time [36]. The active agent was encased in the inner core of microspheres along with the rate-controlling membrane of a water-insoluble polymer. The outer layer was composed of bioadhesive (chitosan). The microspheres were prepared by spray drying an oil/water or water/oil emulsion of the active agent, the water-insoluble polymer, and the cationic polymer.

Fell et al. prepared floating alginate beads incorporating amoxicillin [37]. The beads containing the dissolved drug remained buoyant for 20 hours and high drug-loading levels were achieved.

Sheth and Tossounian developed an HBS system containing a homogeneous mixture of drug and the hydrocolloid in a capsule [38], which upon contact with gastric fluid acquired and maintained a bulk density of less than 1 thereby being buoyant on the gastric contents of stomach until all the drug was released.

Thanoo et al. developed polycarbonate microspheres by solvent evaporation technique [39]. High drug loading was achieved and drug-loaded microspheres were able to float on gastric and intestinal fluids. It was found that increasing the drug- to polymer ratio increased both their mean particle size and release rate of drug.

Streubel et al. prepared single-unit floating tablets based on polypropylene foam powder and matrix-forming polymer [40]. Incorporation of 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.

Nur and Zhang et al. developed floating tablets of captopril using HPMC (4000 and 15 000 cps) and carbopol 934P [41]. 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 center 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.

Asmussen et al. invented a device for the controlled release of active compounds in the gastrointestinal tract with delayed pyloric passage [42], which expanded in contact with gastric fluids and the active agent was released from a multiparticulate preparation.

Application of Floating Drug Delivery System

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

1. Sustained drug delivery

Hydrodynamically Balanced System (HBS) type dosage forms remain in the stomach for several hours, increase the gastric residence time and thus release the drug over a prolonged period of time. These dosage forms have bulk density less than one, relatively large in size and did not easily pass through pylorus.

Recently 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 *in vitro* MICARD capsules (8 hours) [43].

Similarly a comparative study between the Madopar HBS and Madopar standard formulation was done [44] and it was shown that the drug was released up to 8 hours in the former case and the release was essentially complete in less than 30 minutes in the latter case.

2. Site specific drug delivery

FDDS are particularly useful for drug having specific absorption from stomach or proximal part of the small intestine e.g. riboflavin, furosemide etc. In fact, the absorption of Captopril has been found to be site specific, stomach being the major site followed by duodenum. This property prompts the development of a monolithic floating dosage form for Captopril which could prolong the gastric residence time and thus increase the bioavailability. AUC obtained with the floating tablet was approximately 1.8 times that of conventional tablets. Recently, a bilayer floating capsule of misoprostol, which is a synthetic analog of prostaglandin E1, was developed and used as a protectant of gastric ulcers caused by administration of NSAIDs. By targeting slow delivery of misoprostol to the stomach, the desired therapeutic levels could be achieved and wastage of drug be reduced.

It has been reported that a monolithic floating dosage form of furosemide 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 [45].

A bilayer-floating capsule was developed for local delivery of misoprostol, which is a synthetic analog of prostaglandin E1. By targeting slow delivery of misoprostol to the stomach, desired therapeutic levels could be achieved and drug waste could be reduced [46].

3. Absorption enhancement

Drugs that have poor bioavailability because their absorption is restricted to upper GIT can be delivered specifically thereby improving their absolute bioavailability. A significant increase in the bioavailability of floating dosage form of captopril as compared to commercial available tablet.

Ichikawa et al. developed a multiparticulate system that consisted of floating pills of a drug (p- amino benzoic acid) having a limited absorption site in the gastrointestinal tract [47]. It was found to have 1.61 times greater AUC than the control pills.

The absorption of bromocriptine is limited to 30% from the gastrointestinal tract, however an HBS of the same can enhance the absorption. It was also studied that if metoclopramide is co delivered with bromocriptine, the side effects associated with high doses of bromocriptine can be prevented and the dosage from becomes therapeutically more potential [48].

4. There are some cases in which the relative bioavailability of floating dosage form is reduced as compared to conventional dosage form e.g. floating tablets of amoxicillin trihydrate has bioavailability reduced to 80.5% when compared with conventional capsules. In such cases, the reduction in bioavailability is compensated by the advantages offered by FDDS e.g. patients with advanced Parkinson's disease, experienced pronounced fluctuations in symptoms while treatment with standard L-dopa. A HBS dosage form provided a better control of motor fluctuations although its bioavailability was reduced by 50-60% of the standard formulation [49,50].

In a recent study 3 formulations containing 25 mg atenolol, a floating multiple-unit capsule, a high-density multiple-unit capsule, and an immediate-release tablet were compared with respect to estimated pharmacokinetic parameters. The bioavailability of the 2 gastro retentive preparations with sustained release characteristics was significantly decreased when compared with the immediate-release tablet. This study showed that it was not possible to increase the bioavailability of a poorly absorbed drug such as atenolol using gastroretentive formulations [51].

5. FDDS served as an excellent drug delivery system for the eradication of Helicobacter pylori, which is now believed to be causative bacterium for chronic gastritis and peptic ulcers. The patients require high concentration to be maintained at the site of infection that is within the gastric mucosa. The floating dosage form by virtue of its floating ability was retained in stomach and maintained high concentration of drug in the stomach.

Katayama et al. developed a sustained release (SR) liquid preparation of ampicillin containing sodium alginate, which spreads out and aids in adhering to the gastric mucosal surface [52]. Thus, the drug is continuously released in the gastric region.

Yang et al. developed a swellable asymmetric triple-layer tablet with floating ability to prolong the gastric residence time of triple drug regimen (tetracycline, metronidazole, clarithromycin) of Helicobacter pylori–associated peptic ulcer [53]. It was concluded that the developed delivery system had the potential to increase the efficacy of the therapy and improve patient compliance.

6. Floating system are particularly useful for acid stable drugs, drugs which are poorly soluble or unstable in intestinal fluids and for those which undergo abrupt changes in their pH-dependent solubility due to food, age and pathophysiological conditions of GIT. e.g. floating system for furosemide lead to potential treatment of Parkinson's disease.

Limitations

1. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.

2. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.

3. These systems require a high level of fluid in the stomach for drug delivery tom float and work efficiently-coat, water.

4. Not suitable for drugs that have solubility or stability problem in GIT.

5. Drugs which are irritant to Gastric mucosa are also not desirable or suitable.

6. The dosage form should be administered with a full glass of water (200-250 ml).

7. These systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract.

Future Potential

Gastro-retentive floating drug delivery system offers various future potential as evident from several recent publications. Drug absorption in the gastrointestinal tract is highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. FDDS promises to be a potential approach for gastric retention. Among the recently used clinical drugs several narrow absorption window drugs may benefit from compounding into a FDDS. Replacing parenteral administration of drugs to oral pharmacotherapy would substantially improve treatment. It may be believed that it can be possible with FDDS. Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavailability. Buoyant delivery system is also considered as a beneficial strategy for the treatment of gastric and duodenal cancers. The floating concept can be utilized in the development of various anti-reflux formulations. Developing a controlled release system for drugs which are potential to treat the Parkinson's disease, is also an important area of consideration.

REFERENCES

1. Hirtz J. The git absorption of drugs in man: a review of current concepts and methods of investigation. Br J Clin Pharmacol., 1985, 19:77S-83S.
2. Nayak BS, Ghosh SK, Patro KTB. Preparation and characterization of Famotidine microcapsule employing mucoadhesive polymers in combination to enhance gastro retention for oral delivery. International Journal of Pharmacy and Pharmaceutical Sciences. 2009,1(2): 112-120.
3. Chandira RM, Bhowmik D, Jayakar CB. Formulation and evaluation of gastro retentive drug delivery system of gastroprokinetic drug itopride hydrochloride. International Journal of Pharmacy and Pharmaceutical Sciences. 2010, 2(1):53-65.
4. Wilson CG, Washington N. Physiological pharmaceutics: biological barriers to drug absorption, Ellis Horwood, Chichester, 1989, 47-70.
5. Chin YW. Novel Drug Delivery Systems, EdN. 2nd, Vol. 50, Revised and Expanded Marcel Dekker, 140-155.
6. Gennaro RA Remington, "The Science and Practice of pharmacy",20 th Edn, vol.I, 903-913.
7. Singh BM, Kim KH. Floating drug delivery systems: an approach to controlled drug delivery via gastric retention. J. Control. Release, 2000, 63: 235-259.
8. Groning R, Heun G. Oral dosage forms with controlled gastrointestinal transit. Drug Dev. Ind. Pharm., 1984, 10: 527-539.
9. Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage forms. J. Control. Release, 2003, 90:143-162.
10. Timmermans J, Moes AJ. How well do floating dosage forms float. Int J Pharm., 1990, 62: 207- 16.
11. El-Kamel AH, Sokar MS, Gamal SS, Naggar VF. Preparation and evaluation of ketoprofen floating oral delivery system. Int J Pharm., 2001, 220: 13-21.
12. 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, 83:18-24.

13. Oth M, Franz M, Timmermans J, Moes AJ. The bilayer floating capsule: A stomach-directed drug delivery system for misoprostol. Pharm Res., 1992,9: 298-302.
14. Whitehead L, Fell JT, Collett JH, Sharma HL, Smith AM. Floating dosage forms: An in vivo study demonstrating prolonged gastric retention. J Control Release, 1998, 55: 3-12.
15. Mojaverian P, Vlasses PH, Kellner PE, Rocci Jr ML. Effects of gender, posture, and age on gastric residence time of an indigestible solid: Pharmaceutical considerations. Pharm. Res., 1988, 10: 639-44.
16. Gansbeke BV, Timmermans J, Schoutens A, Moes AJ. Intragastric positioning of two concurrently ingested pharmaceutical matrix dosage forms. Nucl Med Biol., 1991, 18: 711-18.
17. Timmermans J, Moes AJ. Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: New data for reconsidering the controversy. J Pharm Sci., 1994, 83: 18-24.
18. Timmermans J, Gansbeke VB, Moes AJ. Assessing by gamma scintigraphy the in vivo buoyancy of dosage forms having known size and floating force profiles as a function of time. Vol I. Proceedings of the 5th International Conference on Pharmacy Technology. Paris, France APGI., 1989, 42-51.
19. Banker GS, Rhodes CT. Modern Pharmaceutics.3rd edn., Marcel Dekker; New York, 1996. 678-721.
20. Howard CA, Pharmaceutical Dosage Form And Drug Delivery Systems, 7th edn, 229-243.
21. Fassihi R, Yang L. Controlled release drug delivery systems. US patent 5 783 212. July 21, 1998.
22. 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.
23. Yang L, Esharghi J, Fassihi R. A new intra gastric delivery system for the treatment of helicobacter pylori associated gastric ulcers: in vitro evaluation. J Control Release., 1999, 57:215-222.
24. Atyabi F, Sharma HL, Mohammed HAH, Fell JT. In vivo evaluation of a novel gastro retentive formulation based on ion exchange resins. J Control Release., 1996, 42:105-113.
25. Ichikawa M, Watanabe S, Miyake Y. Granule remaining in stomach. US patent 4 844 905. July 4, 1989.
26. 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.
27. Penners G, Lustig K, Jorg PVG. Expandable pharmaceutical forms. US patent 5 651 985. July 29, 1997.
28. Talwar N, Sen H, Staniforth JN. Orally administered controlled drug delivery system providing temporal and spatial control. US patent 6 261 601. July 17, 2001.
29. Baumgartner S, Kristel J, Vreer F, Vodopivec P, Zorko B. Optimisation of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm., 2000, 195:125-135.
30. Choi BY, Park HJ, Hwang SJ, Park JB. Preparation of alginate beads for floating drug delivery: effects of CO2 gas forming agents. Int J Pharm., 2002, 239:81-91.
31. Moursy NM, Afifi NN, Ghorab DM, El-Saharty Y. Formulation and evaluation of sustained release floating capsules of Nicardipine hydrochloride. Pharmazie., 2003, 58:38-43.
32. Sheth PR, Tossounian J. The hydrodynamically balanced system (HBSTM): A novel drug delivery system for oral use. Dev Ind Pharm., 1984, 10(2): 313-339
33. Harrigan RM. Drug delivery device for preventing contact of undissolved drug with the stomach lining. US Patent 4 055 178,. October 25, 1977
34. Streubel A, Siepmann J, Bodmeier R. Floating microparticles based on low density foam powder. Int J Pharm., 2002, 241:279-292.
35. Bulgarelli E, Forni F, Bernabei MT. Effect of matrix composition and process conditions on casein gelatin beads floating properties. Int J Pharm., 2000, 198:157-165.
36. Illum L, Ping H. Gastroretentive controlled release microspheres for improved drug delivery. US patent 6 207 197. March 27, 2001.
37. Whitehead L, Collett JH, Fell JT. Amoxycillin release from a floating dosage form based on alginates. Int J Pharm., 2000, 210:45-49.
38. Sheth PR, Tossounian JL. Sustained release pharmaceutical capsules. US patent 4,126,672. November 21, 1978.
39. Thanoo BC, Sunny MC, Jayakrishnan A. Oral sustained release drug delivery systems using polycarbonate microspheres capable of floating on the gastric fluids. J Pharm Pharmacol., 993, 45:21-24.
40. 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.
41. Nur AO, Zhang JS. Captopril floating and/or bioadhesive tablets: design and release kinetics. Drug Dev Ind Pharm., 2000, 26:965-969.
42. Asmussen B, Cremer K, Hoffmann HR, Ludwig K, Roreger M. Expandable gastroretentive therapeutic system with controlled active substance release in gastrointestinal tract. US patent 6 290 989. September 18, 2001.
43. Moursy NM, Afifi NN, Ghorab DM, El-Saharty Y. Formulation and evaluation of sustained release floating capsules of Nicardipine hydrochloride. Pharmazie., 2003, 58:38-43.
44. Erni W, Held K. The hydrodynamically balanced system: a novel principle of controlled drug release. Eur Neurol., 1987, 27:215-275.
45. Menon A, Ritschel WA, Sakr A. Development and evaluation of a monolithic floating dosage form for furosemide. J Pharm Sci., 1994, 83:239-245.
46. Oth M, Franz M, Timmermans J, Moes A. The bilayer floating capsule: a stomach directed drug delivery system for misoprostal. Pharm Res., 1992, 9:298-302.
47. Ichikawa M, Watanabe S, Miyake Y. A new multiple-unit oral floating dosage system. II: In vivo evaluation of floating and sustainedrelease characteristics with para amino benzoic acid and iso sorbide di nitrate as model drugs. J Pharm Sci., 1991, 80:1153-1156.
48. Malcolm SL, Allen JG, Bird H. Single dose pharmacokinetics of Madopar HBS in volunteers. Eur Neurol., 1987, 27:28S-35S.
49. Crevoisier C, Hoevels B, Zurcher G, Da Prada M. Bioavailability of L-dopa after Madopar HBS administration in healthy volunteers. Eur Neurol., 1987, 27:36S-46S.
50. Marion MH, Stochi F, Malcolm SL, Quinn NP, Jenner P, Marsden CD. Single dose studies of a slow release preparation of Levodopa and benserazide (Madopar HBS) in Parkinson's disease. Eur Neurol., 1987, 27:54S-58S.
51. Menon A, Ritschel WA, Sakr A. Development and evaluation of a monolithic floating dosage form for furosemide. J Pharm Sci., 1994, 83:239-245.
52. Katayama H, Nishimura T, Ochi S, Tsuruta Y, Yamazaki Y. Sustained release liquid preparation using sodium alginate for eradication of Helicobacter pylori. Biol Pharm Bull., 1999, 22:55-60.
53. Yang L, Esharghi J, Fassihi R. A new intra gastric delivery system for the treatment of helicobacter pylori associated gastric ulcers: in vitro evaluation. J Control Release., 1999, 57:215-222.