Floating Drug Delivery Systems: A Review

Submitted: March 25, 2004; Accepted: May 30, 2005; Published: October 19, 2005

Shweta Arora,[1] Javed Ali,[1] Alka Ahuja,[1] Roop K. Khar,[1] and Sanjula Baboota[1]

[1]Department of Pharmaceutics, Faculty of Pharmacy, Hamdard University, New Delhi 110062, India

ABSTRACT

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. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. This review also summarizes the in vitro techniques, in vivo studies to evaluate the performance and application of floating systems, and applications of these systems. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form.

KEYWORDS: floating drug delivery systems, single unit, multiple units, evaluation in vitro and in vivo.

INTRODUCTION

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems 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. Basic human physiology with the details of gastric emptying, motility patterns, and physiological and formulation variables affecting the cosmic emptying are summarized.

Gastroretentive 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. 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.

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion,[2,3] flotation,[4] sedimentation,[5,6] expansion,[7,8] modified shape systems,[9,10] or by the simultaneous administration of pharmacological agents[11,12] that delay gastric emptying. Based on these approaches, classification of floating drug delivery systems (FDDS) has been described in detail. In vivo/in vitro evaluation of FDDS has been discussed by scientists to assess the efficiency and application of such systems. Several recent examples have been reported showing the efficiency of such systems for drugs with bioavailability problems.

Basic Gastrointestinal Tract Physiology

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.[13]

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours.[14] This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington.[15]

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
2. Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

Corresponding Author: Shweta Arora, Department of Pharmaceutics, Faculty of Pharmacy, Hamdard University, New Delhi 110062, India. Tel: +91 11 26444936; Fax: +91 11 26059663. E-mail: shweta_a3@hotmail.com

4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.[16]

Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric residence time and unpredictable gastric emptying rate.

Factors Affecting Gastric Retention

Gastric residence time of an oral dosage form is affected by several factors. To pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm.[15] The pH of the stomach in fasting state is ~1.5 to 2.0 and in fed state is 2.0 to 6.0. A large volume of water administered with an oral dosage form raises the pH of stomach contents to 6.0 to 9.0. Stomach doesn't get time to produce sufficient acid when the liquid empties the stomach, hence generally basic drugs have a better chance of dissolving in fed state than in a fasting state.

The rate of gastric emptying depends mainly on viscosity, volume, and caloric content of meals. Nutritive density of meals helps determine gastric emptying time. It does not make any difference whether the meal has high protein, fat, or carbohydrate content as long as the caloric content is the same. However, increase in acidity and caloric value slows down gastric emptying time. Biological factors such as age, body mass index (BMI), gender, posture, and diseased states (diabetes, Chron's disease) influence gastric emptying. In the case of elderly persons, gastric emptying is slowed down. Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down.[17]

The resting volume of the stomach is 25 to 50 mL. Volume of liquids administered affects the gastric emptying time. When volume is large, the emptying is faster. Fluids taken at body temperature leave the stomach faster than colder or warmer fluids. Studies have revealed that gastric emptying of a dosage form in the fed state can also be influenced by its size. Small-size tablets leave the stomach during the digestive phase while the large-size tablets are emptied during the housekeeping waves.

Timmermans and Andre[18] 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. 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.

It has been demonstrated using radiolabeled technique that there is a difference between gastric emptying times of a liquid, digestible solid, and indigestible solid. It was suggested that the emptying of large (>1 mm) indigestible objects from stomach was dependent upon interdigestive migrating myoelectric complex. When liquid and digestible solids are present in the stomach, it contracts ~3 to 4 times per minute leading to the movement of the contents through partially opened pylorus. Indigestible solids larger than the pyloric opening are propelled back and several phases of myoelectric activity take place when the pyloric opening increases in size during the housekeeping wave and allows the sweeping of the indigestible solids. Studies have shown that the gastric residence time (GRT) can be significantly increased under the fed conditions since the MMC is delayed.[19]

Several formulation parameters can affect the gastric residence time. More reliable gastric emptying patterns are observed for multiparticulate formulations as compared with single unit formulations, which suffer from "all or none concept." As the units of multiparticulate systems are distributed freely throughout the gastrointestinal tract, their transport is affected to a lesser extent by the transit time of food compared with single unit formulation.[20]

Size and shape of dosage unit also affect the gastric emptying. Garg and Sharma[21] reported that tetrahedron- and ring-shaped devices have a better gastric residence time as compared with other shapes. The diameter of the dosage unit is also equally important as a formulation parameter. Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm.

The density of a dosage form also affects the gastric emptying rate. A buoyant dosage form having a density of less than that of the gastric fluids floats. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period.

Timmermans et al studied the effect of buoyancy, posture, and nature of meals on the gastric emptying process in vivo using gamma scintigraphy.[22] 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 gastroduodenal 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 (Figure 1). It was also observed that of the floating and nonfloating units, the floating units were 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.

When subjects were kept in the supine position it was observed that the floating forms could only prolong their stay because of their size; otherwise the buoyancy remained no longer an advantage for gastric retention.

A comparison was made to study the affect of fed and nonfed stages on gastric emptying. For this study all subjects remaining in an upright position were given a light breakfast and another similar group was fed with a succession of meals given at normal time intervals. It was concluded that as meals were given at the time when the previous digestive phase had not completed, the floating form buoyant in the stomach could retain its position for another digestive phase as it was carried by the peristaltic waves in the upper part of the stomach.

Approaches to Design Floating Dosage Forms

The following approaches have been used for the design of floating dosage forms of single- and multiple-unit systems.[23]

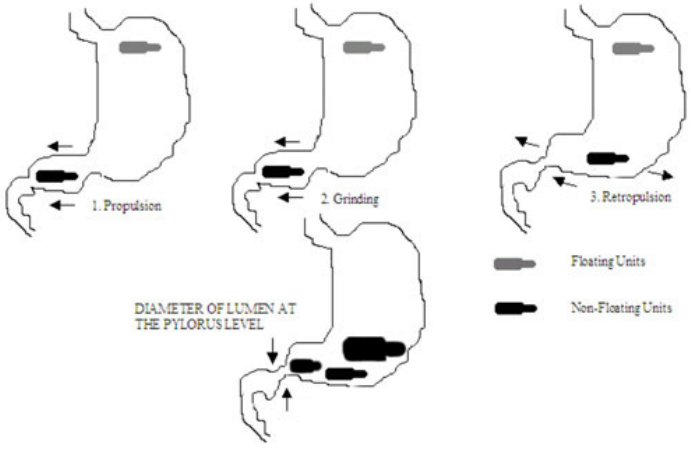

Figure 1. Intragastric residence positions of floating and nonfloating units.

Single-Unit Dosage Forms

In Low-density approach[4] the globular shells apparently having lower density than that of gastric fluid can be used as a carrier for drug for its controlled release. A buoyant dosage form can also be obtained by using a fluid-filled system that floats in the stomach.In coated shells[24] popcorn, poprice, and polystyrol have been exploited as drug carriers. Sugar polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been used to undercoat these shells. These are further coated with a drug-polymer mixture. The polymer of choice can be either ethylcellulose or hydroxypropyl cellulose depending on the type of release desired. Finally, the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration.

Fluid- filled floating chamber[25] type of dosage forms includes incorporation of a gas-filled floatation chamber into a microporous component that houses a drug reservoir. Apertures or openings are present along the top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein. The fluid present could be air, under partial vacuum or any other suitable gas, liquid, or solid having an appropriate specific gravity and an inert behavior. The device is of swallowable size, remains afloat within the stomach for a prolonged time, and after the complete release the shell disintegrates, passes off to the intestine, and is eliminated. Hydrodynamically balanced systems (HBS) are designed to prolong the stay of the dosage form in the gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form. The success of HBS capsule as a better system is best exemplified with chlordiazeopoxide hydrochloride. The drug is a classical example of a solubility problem wherein it exhibits a 4000-fold difference in solubility going from pH 3 to 6 (the solubility of chlordiazepoxide hydrochloride is 150 mg/mL and is ~0.1 mg/mL at neutral pH).

HBS of chlordiazeopoxide hydrochloride[26] had comparable blood level time profile as of three 10-mg commercial capsules. HBS can either be formulated as a floating tablet or capsule. Many polymers and polymer combinations with wet granulation as a manufacturing technique have been explored to yield floatable tablets.

Various types of tablets (bilayered and matrix) have been shown to have floatable characteristics. Some of the polymers used are hydroxypropyl cellulose, hydroxypropyl

methylcellulose, crosspovidone, sodium carboxymethyl cellulose, and ethyl cellulose.Self-correcting floatable asymmetric configuration drug delivery system[23]employs a disproportionate 3-layer matrix technology to control drug release.

The 3-layer principle has been improved by development of an asymmetric configuration drug delivery system in order to modulate the release extent and achieve zero-order release kinetics by initially maintaining a constant area at the diffusing front with subsequent dissolution/erosion toward the completion of the release process. The system was designed in such a manner that it floated to prolong gastric residence time in vivo, resulting in longer total transit time within the gastrointestinal tract environment with maximum absorptive capacity and consequently greater bioavailability. This particular characteristic would be applicable to drugs that have pH-dependent solubility, a narrow window of absorption, and are absorbed by active transport from either the proximal or distal portion of the small intestine.

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.

Multiple-Unit Dosage Forms

The purpose of designing multiple-unit dosage form is to develop a reliable formulation that has all the advantages of a single-unit form and also is devoid of any of the above mentioned disadvantages of single-unit formulations. In pursuit of this endeavor many multiple-unit floatable dosage forms have been designed. Microspheres have high loading capacity and many polymers have been used such as albumin, gelatin, starch, polymethacrylate, polyacrylamine, and polyalkylcyanoacrylate. Spherical polymeric microsponges, also referred to as "microballoons," have been prepared. Microspheres have a characteristic internal hollow structure and show an excellent in vitro floatability.[27] In Carbon dioxide–generating multiple-unit oral formulations[28] several devices with features that extend, unfold, or are inflated by carbon dioxide generated in the devices after administration have been described in the recent patent literature. These dosage forms are excluded from the passage of the pyloric sphincter if a diameter of ~12 to 18 mm in their expanded state is exceeded.

Classification of Floating Drug Delivery Systems (FDDS)

Floating drug delivery systems are classified depending on the use of 2 formulation variables: effervescent and noneffervescent systems.

Effervescent Floating Dosage Forms

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

Ichikawa et al[28] developed a new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills. 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. 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[28] (Figure 2, A and B).

Ichikawa et al[29] 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. This layer was further divided into 2 sublayers, 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.[29] It was shown that the swellable membrane layer played an important role in maintaining the buoyancy of the pills for an extended period of time. 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 a 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.

Yang et al[30] developed a swellable asymmetric triple-layer tablet with floating ability to prolong the gastric residence time of triple drug regimen (tetracycline, metronidazole,

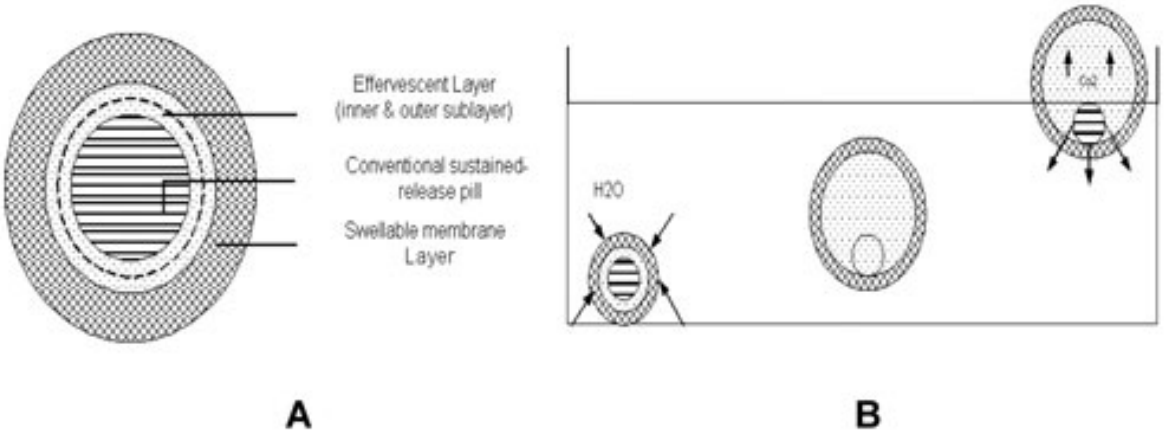

Figure 2. (A) Multiple-unit oral floating drug delivery system. (B) Working principle of effervescent floating drug delivery system.

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. The design of the delivery system was based on the swellable asymmetric triple-layer tablet approach. Hydroxypropylmethylcellulose and poly (ethylene oxide) were the major rate-controlling polymeric excipients. Tetracycline and metronidazole were incorporated into the core layer of the triple-layer matrix for controlled delivery, while bismuth salt was included in one of the outer layers for instant release. The floatation was accomplished by incorporatinga 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 (Figure 3).

Ozdemir et al[31] developed 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. The in vitro floating studies revealed that the lesser the compression force the shorter is the time of onset of floating, ie, when the tablets were compressed at 15 MPa, these could begin to float at 20 minutes whereas at a force of 32 MPa the time was prolonged to 45 minutes. 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.

Choi et al[32] 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. 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. It was concluded that calcium carbonate formed smaller but stronger beads than sodium bicarbonate. Calcium carbonate was shown to be a less-effective gas-forming agent than sodium bicarbonate but it produced superior floating beads with enhanced control of drug release rates. In vitro floating studies revealed that the beads free of gas-forming agents sank uniformly in the media while

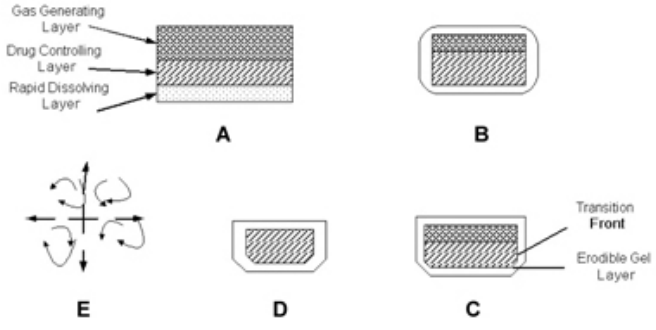

Figure 3. Schematic presentation of working of a triple-layer system. (A) Initial configuration of triple-layer tablet. (B) On contact with the dissolution medium the bismuth layer rapidly dissolves and matrix starts swelling. (C) Tablet swells and erodes. (D) and (E) Tablet erodes completely.

the beads containing gas-forming agents in proportions ranging from 5:1 to 1:1 demonstrated excellent floating (100%).

Li et al[33,34] evaluated the contribution of formulation variables on the floating properties of a gastro floating drug delivery system using a continuous floating monitoring device and statistical experimental design. The formulation was conceived using taguchi design. HPMC was used as a low-density polymer and citric acid was incorporated for gas generation. Analysis of variance (ANOVA) test on the results from these experimental designs demonstrated that the hydrophobic agent magnesium stearate could significantly improve the floating capacity of the delivery system. High-viscosity polymers had good effect on floating properties. The residual floating force values of the different grades of HPMC were in the order K4 M~ E4 M~K100 LV> E5 LV but different polymers with same viscosity, ie, HPMC K4M, HPMC E4M did not show any significant effect on floating property. Better floating was achieved at a higher HPMC/carbopol ratio and this result demonstrated that carbopol has a negative effect on the floating behavior.

Penners et al[35] 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. 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.

Fassihi and Yang[36] developed a zero-order controlled release multilayer tablet composed of at least 2 barrier layers and 1 drug layer. 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.

Talwar et al[37] 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. 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 be 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).

Two patents granted to Alza Corporation revealed a device having a hollow deformable unit that was convertible from a collapsed to expandable form and vice versa. The deformable unit was supported by a housing that was internally divided into 2 chambers separated by a pressure-sensitive movable bladder. The first chamber contained the therapeutic agent and the second contained a volatile liquid (cyclopentane, ether) that vaporized at body temperature and imparted buoyancy to the system. The system contained a bioerodible plug to aid in exit of the unit from the body.[38,39]

Baumgartner et al[40] developed a matrix-floating tablet incorporating a high dose of freely soluble drug. 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. In vivo experiments with fasted state beagle dogs revealed prolonged gastric residence time. On radiographic images made after 30 minutes of administration, the tablet was observed in animal's stomach and the next image taken at 1 hour showed that the tablet had altered its position and turned around. This was the evidence that the tablet did not adhere to the gastric mucosa. The MMC (phase during which large nondisintegrating particles or dosage forms are emptied from stomach to small intestine) of the gastric emptying cycle occurs approximately every 2 hours in humans and every 1 hour in dogs but the results showed that the mean gastric residence time of the tablets was 240 ± 60 minutes ($n = 4$) in dogs. The comparison of gastric motility and stomach emptying between humans and dogs showed no big difference and therefore it was speculated that the experimentally proven increased gastric residence time in beagle dogs could be compared with known literature for humans, where this time is less than 2 hours.

Moursy et al[41] developed sustained release floating capsules of nicardipine HCl. For floating, hydrocolloids of high viscosity grades were used and to aid in buoyancy sodium bicarbonate was added to allow evolution of CO_2. In vitro analysis of a commercially available 20-mg capsule of nicardipine HCl (MICARD) was performed for comparison. Results showed an increase in floating with increase in proportion of hydrocolloid. Inclusion of sodium bicarbonate increased buoyancy. The optimized sustained release floating capsule formulation was evaluated in vivo and compared with MICARD capsules using rabbits at a dose equivalent to a human dose of 40 mg. Drug duration after the administration of sustained release capsules significantly exceeded that of the MICARD capsules. In the latter case the drug was traced for 8 hours compared with 16 hours in former case.

Atyabi and coworkers[42] developed a floating system using ion exchange resin that was loaded with bicarbonate by mixing the beads with 1 M sodium bicarbonate solution. The loaded beads were then surrounded by a semipermeable membrane to avoid sudden loss of CO_2. Upon coming in contact with gastric contents an exchange of chloride and bicarbonate ions took place that resulted in CO_2 generation

thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads (Figure 4). 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).

Non-Effervescent Floating Dosage Forms

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

Thanoo et al[43] developed polycarbonate microspheres by solvent evaporation technique. Polycarbonate in dichloromethane was found to give hollow microspheres that floated on water and simulated biofluids as evidenced by scanning electron microscopy (SEM). 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.

Nur and Zhang[44] developed floating tablets of captopril using HPMC (4000 and 15 000 cps) and carbopol 934P. In vitro buoyancy studies revealed that tablets of 2 kg/cm^2 hardness after immersion into the floating media floated immediately and tablets with hardness 4 kg/cm^2 sank for 3 to 4 minutes and then came to the surface. Tablets in both cases remained floating for 24 hours. The tablet with 8 kg/cm^2 hardness showed no floating capability. 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.

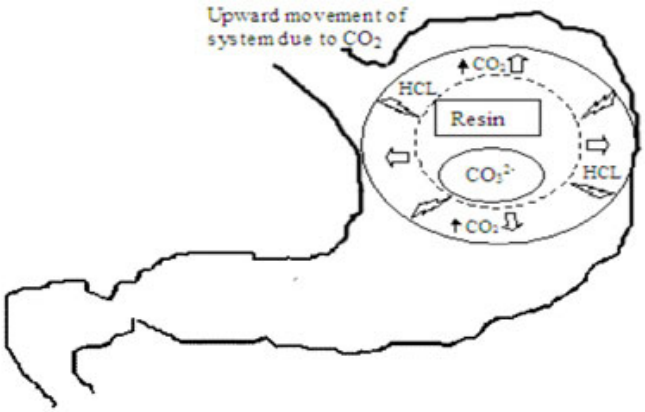

Figure 4. Pictorial presentation of working of effervescent floating drug delivery system based on ion exchange resin.

Bulgarelli et al[45] studied the effect of matrix composition and process conditions on casein gelatin beads prepared by emulsification extraction method. 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. It was observed that the percentage of casein in matrix increases the drug loading of both low and high porous matrices, although the loading efficiency of high porous matrices is lower than that of low porous matrices.

Fell et al[46] prepared floating alginate beads incorporating amoxycillin. The beads were produced by dropwise addition of alginate into calcium chloride solution, followed by removal of gel beads and freeze-drying. The beads containing the dissolved drug remained buoyant for 20 hours and high drug-loading levels were achieved.

Streubel et al[47] prepared single-unit floating tablets based on polypropylene foam powder and matrix-forming polymer. Incorporation of highly porous foam powder in matrix tablets provided density much lower than the density of the release medium. A 17% wt/wt foam powder (based on mass of tablet) was achieved in vitro for at least 8 hours. It was concluded that varying the ratios of matrix-forming polymers and the foam powder could alter the drug release patterns effectively.

Asmussen et al[48] invented a device for the controlled release of active compounds in the gastrointestinal tract with delayed pyloric passage, which expanded in contact with gastric fluids and the active agent was released from a multiparticulate preparation. It was claimed that the release of the active compound was better controlled when compared with conventional dosage forms with delayed pyloric passage.

El-Kamel et al[49] prepared floating microparticles of ketoprofen, by emulsion solvent diffusion technique. Four different ratios of Eudragit S 100 with Eudragit RL were used. The formulation containing 1:1 ratio of the 2 above-mentioned polymers exhibited high percentage of floating

particles in all the examined media as evidenced by the percentage of particles floated at different time intervals. This can be attributed to the low bulk density, high packing velocity, and high packing factor.

Illum and Ping[50] developed microspheres that released the active agent in the stomach environment over a prolonged period of time. 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.

Streubel et al[51] developed floating microparticles composed of polypropylene foam, Eudragit S, ethyl cellulose (EC), and polymethyl metha acrylate (PMMA) and were prepared by solvent evaporation technique. High encapsulation efficiencies were observed and were independent of the theoretical drug loading. Good floating behavior was observed as more than 83% of microparticles were floating for at least 8 hours. The in vitro drug release was dependent upon the type of polymer used. At similar drug loading the release rates increased in the following order PMMA < EC < Eudragit S. This could be attributed to the different permeabilities of the drug in these polymers and the drug distribution within the system.

Sheth and Tossounian[26] developed an HBS system containing a homogeneous mixture of drug and the hydrocolloid in a capsule, 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 (Figure 5).

Sheth and Tossounian[52] developed hydrodynamically balanced sustained release tablets containing drug and hydrophilic hydrocolloids, which on contact with gastric fluids at body temperature formed a soft gelatinous mass on the surface of the tablet and provided a water-impermeable colloid gel barrier on the surface of the tablets. The drug slowly released from the surface of the gelatinous mass that remained buoyant on gastric fluids (Figure 6, A and B).

Ushomaru et al[53] developed sustained release composition for a capsule containing mixture of cellulose derivative or a starch derivative that formed a gel in water and higher fatty acid glyceride and/or higher alcohol, which was solid at room temperature. The capsules were filled with the above mixture and heated to a temperature above the melting point of the fat components and then cooled and solidified.

Bolton and Desai[54] developed a noncompressed sustained release tablet that remained afloat on gastric fluids. The tablet formulation comprised 75% of drug and 2% to 6.5%

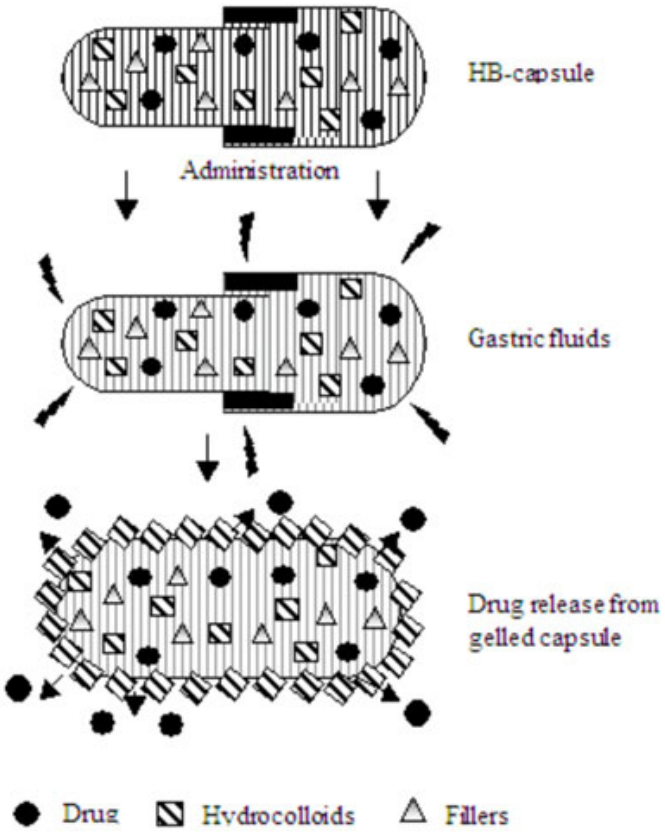

Figure 5. Working principle of hydrodynamically balanced system.

of gelling agent and water. The noncompressed tablet had a density of less than 1 and sufficient mechanical stability for production and handling.

Kawashima et al prepared multiple-unit hollow microspheres by emulsion solvent diffusion technique. Drug and acrylic polymer were dissolved in an ethanol-dichloromethane mixture, and poured into an aqueous solution of PVA with stirring to form emulsion droplets. The rate of drug release in micro balloons was controlled by changing the polymer-to-drug ratio. Microballoons were floatable in vitro for 12 hours when immersed in aqueous media. Radiographical studies proved that microballoons orally administered to humans were dispersed in the upper part of stomach and retained there for 3 hours against peristaltic movements.[55]

Dennis et al[56] invented a buoyant controlled release pharmaceutical powder formulation filled into capsules. It released a drug of a basic character at a controlled rate regardless of the pH of the environment. PH-dependent polymer is a salt of a polyuronic acid such as alginic acid and a pH-independent hydrocarbon gelling agent, hydroxypropylmethyl cellulose.

Spickett et al[57] invented an antacid preparation having a prolonged gastric residence time. It comprised 2 phases. The internal phase consisted of a solid antacid and the external

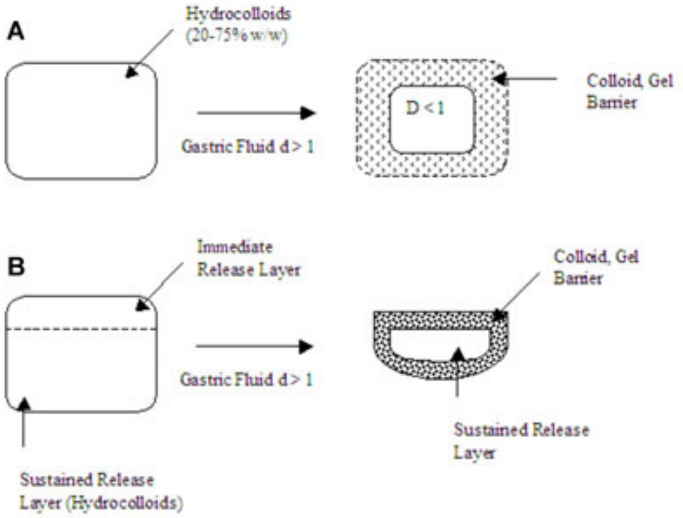

Figure 6. Intragastric floating tablets. (A) United States patent 4 167 558, September 11, 1979. (B) United States patent 4 140 755, February 20, 1979.

phase consisted of hydrophobic organic compounds (mono-, di-, and triglycerides) for floating and a non-ionic emulsifier.

Franz and Oth[58] described a sustained release dosage form adapted to release of the drug over an extended period of time. It comprised a bilayer formulation in which one layer consisted of drug misoprostal and the other had a floating layer. The uncompressed bilayer formulation was kept in a capsule and was shown to be buoyant in the stomach for 13 hours. The dosage form was designed in such a way that all the drug was released in the stomach itself.

Wu et al[59] developed 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 occurred.

Wong et al[60] developed a prolonged release dosage form adapted for gastric retention using swellable polymers. It consisted of a band of insoluble material that prevented the covered portion of the polymer matrix from swelling and provided a segment of a dosage form that was of sufficient rigidity to withstand the contractions of the stomach and delayed the expulsion of the dosage form from the stomach.

Mitra[61] developed a sustained release multilayered sheet-like medicament device. It was buoyant on the gastric contents and consisted of at least 1 dry, self-supporting carrier film of water-insoluble polymer. The drug was dispersed or dissolved in this layer and a barrier film overlaid the carrier film. The barrier film was compsosed of 1 water-insoluble layer and another water-soluble and drug-permeable polymer or copolymer layer. The 2 layers were sealed together in such a way that plurality of small air pockets were entrapped that gave buoyancy to the formulation.

Harrigan[62] developed an intragastric floating drug delivery system that was composed of a drug reservoir encapsulated in a microporous compartment having pores on top and bottom surfaces. However, the peripheral walls were sealed to prevent any physical contact of the drug in the reservoir with the stomach walls.

Joseph et al[25] 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. In vivo studies were performed in healthy male albino rabbits. Pharmacokinetic analysis was derived from plasma concentration vs time plot and revealed that the bioavailability from the piroxicam microspheres alone was 1.4 times that of the free drug and 4.8 times that of a dosage form consisting of microspheres plus the loading dose and was capable of sustained delivery of the drug over a prolonged period.

There are several commercial products available based on the research activity of floating drug delivery (Table 1).

Evaluation of floating drug delivery systems

Various parameters[17] that need to be evaluated in gastroretentive formulations include floating duration, dissolution profiles, specific gravity, content uniformity, hardness, and friability in case of solid dosage forms. In the case of multiparticulate drug delivery systems, differential scanning calorimetry (DSC), particle size analysis, flow properties, surface morphology, and mechanical properties are also performed.

The tests for floating ability (Table 2) and drug release are generally performed in simulated gastric fluids at 37ºC.

Table 1. Marketed Preparations of Floating Drug Delivery Systems[59]

S. no	Product	Active Ingredient	Reference No.
1	Madopar	Levodopa and benserzide	63
2	Valrelease	Diazepam	64
3	Topalkan	Aluminum magnesium antacid	65
4	Almagate flatcoat	Antacid	66
5	Liquid gavison	Alginic acid and sodium bicarbonate	67

Table 2. In Vitro Floating and Dissolution Performance

Drug (Polymer Used)	Floating Media/Dissolution Medium and Method	Ref
Pentoxyfillin (HPMC K4 M)	500 mL of artificial gastric fluid pH 1.2 (without pepsin) at 100 rpm using USP XXIII dissolution apparatus. The time taken by the tablet to emerge on the water surface (floating lag time) and time until it floats on water surface was measured.	40
Amoxicillin beads (Calcium alginate)	For dissolution: 900 mL of deaerated 0.1 M HCl (pH 1.2) at 37ºC ± 1ºC in USP XXII dissolution tester at 50 rpm.	46
Ketoprofen (Eudragit S100 Eudragit RL)	20 mL of simulated gastric fluid without pepsin, 50 mg of floating microparticles in 50-mL beakers were shaken horizontally in a water bath. % age of floating micro particles was calculated. For dissolution: 900 mL of either 0.1 N HCl or the phosphate buffer (pH 6.8) at 37ºC ± 0.1ºC in USP dissolution apparatus (I) at 100 rpm.	49
Verapamil (Propylene foam, Eudragit RS, ethyl cellulose, poly methyl meth acrylate)	30 mL of 0.1 N HCl (containing 0.02% wt/wt Tween 20), pH 1.2. Floatation was studied by placing 60 particles into 30-mL glass flasks. Number of settled particles was counted.	51
Captopril (Methocel K4M)	900 mL of enzyme-free 0.1 N HCl (pH 1.2) in USP XXIII apparatus II (basket method) at 37ºC at 75 rpm.	44
Theophylline (HPMC K4M, Polyethylene oxide)	0.1 N HCl in USP XXIII Apparatus II at 50 rpm at 37°C. Its buoyancy to upper 1/3 of dissolution vessel was measured for each batch of tablet.	23
Furosemide (β Cyclodextrin, HPMC 4000, HPMC 100, CMC, Polyethylene glycol)	For dissolution: continuous flow through cell gastric fluid of pH 1.2, 45–50 m N/m by adding 0.02% Polysorbate 20 (to reduce the surface tension), the flow rate to provide the sink conditions was 9mL/min.	32
Aspirin, Griseofulvin, p-Nitro Aniline (polycarbonate, PVA)	For dissolution: 500 mL of simulated gastric and intestinal fluid in 1000-mL Erlenmeyer flask. Flasks were shaken in a bath incubator at 37ºC.	43
Piroxicam (microspheres) (Polycarbonate)	For dissolution: 900 mL dissolution medium in USP paddle type apparatus at 37ºC at 100 rpm.	61
Ampicillin (Sodium alginate)	For dissolution: 500 mL of distilled water, JP XII disintegration test medium No.1 (pH 1.2) and No.2 (pH 6.8) in JP XII dissolution apparatus with paddle stirrer at 50 rpm.	68
Diclofenac (HPC-L)	An aliquot of 0.1 g of granules was immersed in 40 mL of purified water in a vessel at 37°C. Dried granules were weighed and floating percentage of granules was calculated. For dissolution: flow sampling system (dissolution tester: DT-300, triple flow cell) followed by 900 mL of distilled water in JP XII with paddles at 37 ºC ± 0.5ºC at 100 rpm.	69
Sulphiride (CP 934P)	For dissolution: 500 mL of each JP XII disintegration test medium No. 1 (pH 1.2) and No. 2 (pH 6.8) in JP XII dissolution apparatus at 37º C at 100 rpm.	70
Amoxicillin trihydrate (HPC)	For dissolution: 500–1000 mL (adequate to ensure sink conditions) of citrate/phosphate buffer of variable pH or solution of HCl (pH 1.2) in Erweka DT 6 dissolution tester fitted with paddles.	71
Ibuprofen, Tranilast (Eudragit S)	For dissolution: 900 mL dissolution medium (disintegration test medium No. 1 (pH 1.2) and No. 2 (pH 6.8) as specified in JP XI and as corresponding to USP XXI, paddle method at 37ºC at 100 rpm.	72
Isardipine (HPMC)	For dissolution: Method 1: 300 mL of artificial gastric fluid in a beaker, which was suspended in water bath at 37ºC agitated by magnetic stirrer and by bubbling CO_2 free air. Method 2: 500/1000 mL of 0.1 M HCl and surfactant lauryl sulfate dimethyl ammonium oxide with rotating paddle at 50 rpm.	73
Potassium chloride (Metolose S.M. 100, PVP)	For dissolution: tablet was mounted onto the perspex holder except one face of the matrix was set flush with one face of the holder at 37ºC and the other face of the tablet was prevented from the dissolution media by a rubber closure; good mixing was maintained in the receiver by a magnetic stirrer at 100 rpm.	74

Table 2. Continued

Drug (Polymer Used)	Floating Media/Dissolution Medium and Method	Ref
Verapamil (HPC-H, HPC-M, HPMC K15)	For dissolution: water in USP XXIII dissolution apparatus (method II) at 50 rpm.	75
PABA (Ethyl cellulose HPC-L)	70 mL of 50 mM acetate buffer with various pH (1–5) or viscosity (25–115 cps) in a 100-mL beaker at 37°C, 100 rpm. % age of floating pills was calculated. For dissolution: 50 mM acetate buffer (pH 4) in JP XI dissolution tester with paddles at 37ºC at 100 rpm.	76
Tetracycline, metronidazole, bismuth salt (Polyox, HPMC K4)	900 mL of 0.1 M HCl (pH 1.8) in USP dissolution apparatus at 50 rpm. The duration of floatation was observed visually.	30
Tranilast (Acrylic polymer, Eudragit RS)	Microballoons were introduced into 900 mL of disintegrating fluid solution no 1 (pH 1.2) containing Tween 20 (0.02% wt/vol) in USP XXII apparatus at 100 rpm . Percentage buoyancy was calculated.	55
Sotalol	Lag time required for the tablet to start floating on the top of the basket in dissolution apparatus was measured	77
Furosemide	Tablet were placed in a 400-mL flask at pH 1.2 and both the time needed to go upward and float on surface of the fluid and floating duration were determined.	31
Calcium carbonate (HPMC K4M, E4 M and Carbopol)	A continuous floating monitoring system was conceived. The upward floating force could be measured by the balance and the data transmitted to an online computer. Test medium used was 900 mL simulated gastric fluid (pH 1.2) at 37ºC.	33

Timmermans and Andre[18] characterized the buoyancy capability of floating forms and sinking of nonfloating dosage forms using an apparatus to quantitatively measure the total force acting vertically on the immersed object. It was given by the vectorial sum of buoyancy $F_{(b)}$ and gravitational forces $F_{(g)}$ acting on the test object.

$$F = F_{(b)} - F_{(g)} \tag{1}$$

Equation 1 can be rewritten as,

$$F = (d_f - d_s)gV = (d_f - W/V)gV \tag{2}$$

where F is the resultant weight of the object, d_f and d_s represent the fluid density and solid object density, g is the acceleration due to gravity and W and V are the weight and volume of the test objects. It can be seen from Equation 2 that if the resultant weight is more positive, better floating is exhibited by the object.

Li et al[33,34] invented an online continuous floating monitoring system that was a modification of the system described by Timmermans and Andre.[18] It was used to provide quantitative measurement of resultant floating force. The set-up consisted of an analytical balance connected with a computer. A capsule was inserted into the sample holder basket and the holder was immersed into the test medium (900 mL of simulated gastric fluid). A typical floating kinetic curve was obtained by plotting floating force vs time and 4 parameters were used to describe the floating properties of the capsules from this graph: F max, T max, Fr, and AUC f . Similar to Equation 2 conceived by Timmermans and Andre[18] the overall force that the capsule is subjected can be given by

$$F = (\rho_m - \rho_c)gVc \tag{3}$$

where ρ_m and ρ_c are the density of floating media and test object and Vc is the volume of the test object. In this equation, 2 parameters, ρ_c and Vc, are important for overall floating force. During the measurement of buoyancy, Vc increased due to swelling of polymer and ρ_c increased due to water uptake. This increase led to an upward rise in floating force curve, which reached a maximum (Fmax) and declined until an equilibrium was reached.

Table 2 gives dissolution tests generally performed using USP dissolution apparatus. USP 28 states "the dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of nonreactive material with not more than a few turns of a wire helix may be attached to the dosage units that would otherwise float.[78] However standard USP or BP methods have not been shown to be reliable predictors of in vitro performance of floating dosage forms.[24] Pillay and Fassihi[79] applied a helical wire sinker to the swellable floating system of theophylline, which is sparingly soluble in water and concluded that the swelling of the system was inhibited by the wire helix and the drug release also slowed down.

To overcome this limitation a method was developed in which the floating drug delivery system was fully submerged under a ring or mesh assembly and an increase in drug release was observed. Also, it was shown that the method was more reproducible and consistent. However no significant change in the drug release was observed when the proposed method was applied to a swellable floating system of diltiazem, which is a highly water-soluble drug. It was thus concluded that the drug release from swellable floating systems was dependent upon uninhibited swelling, surface exposure, and the solubility of the drug in water.

Surface morphology was observed by SEM, which serves to confirm qualitatively a physical observation relating to surface area. In preparation of SEM analysis, the sample was exposed to high vacuum during the gold-coating process, which was needed to make the sample conductive.

Kawashima et al[80] estimated the hollow structure of microspheres made of acrylic resins by measuring particle density (P_p) by a photographic counting method and a liquid displacement method. An image analyzer was used to determine the volume (v) of particles (n) of weight (w):

$$P = w/v \quad (4)$$

Porosity was measured by $\epsilon = (1 - P_p / P_t) \times 100$, where P_t is the true density.

Bulgarelli et al[45] developed casein gelatin beads and determined their porosity by mercury intrusion technique. The principle of this technique is that pressure (P) required to drive mercury through a pore decreases as described by the Washburn equation: $P = (-4\ \sigma \cos \theta)\ d$, where d is the pore diameter, σ is mercury / air interfacial tension, and θ is the contact angle at mercury air pore wall interface.

Sakuma et al[81] prepared radiolabeled anionic poly metha acrylic acid nanoparticles and the particle size of nonlabeleled nanoparticles was measured by dynamic spectrophotometry.

In vivo gastric residence time of a floating dosage form is determined by X-ray diffraction studies, gamma scintigraphy,[22] or roentgenography[82] (Table 3).

Applications of Floating Drug Delivery Systems

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.

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 short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. 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.

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 MICARD capsules (8 hours).[41]

Similarly a comparative study[63] between the Madopar HBS and Madopar standard formulation was done and it was shown that the drug was released up to 8 hours in vitro in the former case and the release was essentially complete in less than 30 minutes in the latter case.

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.

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.[84]

A bilayer-floating capsule was developed for local delivery of misoprostol, which is a synthetic analog of prostaglandin E1 used as a protectant of gastric ulcers caused by administration of NSAIDs. By targeting slow delivery of misoprostol to the stomach, desired therapeutic levels could be achieved and drug waste could be reduced.[86]

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.

A significant increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric-coated LASIX-long product (29.5%).[84]

Table 3. In Vivo Evaluation

Drug (Polymer)	Method	Ref
Tranilast (Eudragit S (BaSo4))	Two healthy male volunteers administered hard gelatin capsules packed with microballons (1000 mg) with 100 mL water. X-ray photographs at suitable intervals were taken.	55
Isardipine (HPMC)	Two phases: Phase I (fasted conditions): Five healthy volunteers (3 males and 2 females) in an open randomized crossover design, capsules ingested in sitting position with 100 mL of tap water. Phase II (fed states): Four subjects received normal or MR capsules in a crossover design after standard breakfast. Venous blood samples were taken in heparinized tubes at predetermined time intervals after dosing.	73
PABA+ Isosorbide dinitrate	Six healthy beagle dogs fasted overnight, then administered with capsules with 50 mL of water at 30 minutes after the meal. Control study: same amount of control pills without the effervescent layer were administered in the same protocol. The experimental design: Crossover design, 1-week washout time, plasma samples were taken by repeated venipuncture at upper part of the leg.	76
Hydrogel composites	Dogs (50 lbs) kept fasted and fed conditions. In each experiment (fed or fasted) 300 mL of water was given before administration of the capsules; X-ray pictures were taken.	83
Amoxycillin trihydrate	Six healthy fasted male subjects were selected; serum drug levels were compared in a single-dose crossover study following administration of tablets/capsules.	46
Floating beads	Gamma scintigraphy: In vivo behavior of coated and uncoated beads was monitored using a single channel analyzing study in 12 healthy human volunteers of mean age 34 yrs (22–49).	42
Pentoxyfillin	Four healthy beagle dogs (fasted for 24 hours). Tablet was administered with 100 mL of water for radiographic imaging. The animal was positioned in a right lateral/ventrodorsal recumbency.	40
Furosemide	Six purebred young male beagle dogs (9.6 to 14.3 kg), a 4-period crossover study balanced by residual effects was employed. Dogs were fasted overnight (water ad libitum), a catheter was inserted into right and left cephalic vein with 0.3 mL heparin lock, blood sampling was done at appropriate intervals.	84
Polystyrene nanoparticles	Dosing solution was administered to male SD strain rats fasted overnight The radioactivity was measured with a gamma counter or a β counter (small intestine was cut into 10-cm portions).	63
Piroxicam	Nine healthy male albino rabbits weighing 2.2–2.5 kg were divided into 3 groups and were fasted for 24 hours. First batch: fed with 20 mg of Piroxicam powder in a gelatin capsule. Second batch: 67% piroxicam loaded piroxicam microspheres (~20mg of drug). Third batch: 7 mg of piroxicam and 67% piroxicam-loaded piroxicam microspheres (~20 mg of drug).	61
Calcium alginate multiple units floating beads	Seven healthy males (21–55 years). After fasting from midnight the night before the subjects consumed cereal (30 g) with milk (150 ml) to which was added ~20 Ci .99 m Tc-DTPA. An anterior image of stomach was obtained with γ camera. Static 120-second anterior images were acquired at suitable intervals and subjects remained standing/sitting for the duration of the study.	85
Furosemide	Six healthy males (60–71 kg) aged between 25 and 32 years for X-ray detection. Labeled tablets were given to subjects with 200 mL of water after a light breakfast, following ingestion. Gastric radiography revealed the duration for which the tablet stayed in stomach was determined.	31
Sulphiride	Three 3.5-kg white male rabbits 10 mg of the drug/kg body weight was administered in a crossover manner with a 14-day washout period between dosing. Both IV and oral dosage form were given.	69

Miyazaki et al[87] conducted pharmacokinetic studies on floating granules of indomethacin prepared with chitosan and compared the peak plasma concentration and AUC with the conventional commercially available capsules. It was concluded that the floating granules prepared with chitosan were superior in terms of decrease in peak plasma concentration and maintenance of drug in plasma.

Ichikawa et al[76] 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. 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.[88]

In few cases the bioavailability of floating dosage form is reduced in comparison to the conventional dosage form. 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 gastroretentive 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.[89]

In some cases the reduction in bioavailability is compensated by advantages offered by FDDS, for example a hydrodynamically balanced system of L-dopa provided better control over motor fluctuations in spite of reduced bioavailability of up to 50% to 60% in comparison with standard L-dopa treatment. This could be attributed to reduced fluctuations in plasma drug levels in case of FDDS.[90,91]

Cook et al[92] concluded that iron salts, if formulated as an HBS, have better efficacy and lesser side effects.

FDDS also serves as an excellent drug delivery system for the eradication of *Helicobacter pylori*, which causes chronic gastritis and peptic ulcers. The treatment requires high drug concentrations to be maintained at the site of infection that is within the gastric mucosa. By virtue of its floating ability these dosage forms can be retained in the gastric region for a prolonged period so that the drug can be targeted.[93]

Katayama et al[68] developed a sustained release (SR) liquid preparation of ampicillin containing sodium alginate, which spreads out and aids in adhering to the gastric mucosal surface. Thus, the drug is continuously released in the gastric region.

Yang et al[30] 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 ulcers using HPMC and PEO as the rate-controlling polymeric membrane excipients. Results demonstrated that sustained delivery of tetracycline and metronidazole over 6 to 8 hours could be achieved while the tablets remained floating. It was concluded that the developed delivery system had the potential to increase the efficacy of the therapy and improve patient compliance.

Floating microcapsules of melatonin were prepared by ionic interaction of chitosan and a surfactant, sodium dioctyl sulfosuccinate that is negatively charged. The dissolution studies of the floating microcapsules showed zero-order release kinetics in simulated gastric fluid. The release of drug from the floating microcapsules was greatly retarded with release lasting for several hours as compared with nonfloating microspheres where drug release was almost instantaneous. Most of the hollow microcapsules developed showed floating over simulated gastric fluid for more than 12 hours.[94]

Sato and Kawashima[95] developed microballoons of riboflavin, which could float in JP XIII no 1 solution (simulated gastric fluid). These were prepared by an emulsion solvent technique. To assess the usefulness of the intragastric floating property of the developed microballoons of riboflavin, riboflavin powder, nonfloating microspheres of riboflavin, and floating microballoons of riboflavin were administered to 3 volunteers. Riboflavin pharmacokinetics was assessed by urinary excretion data. It could be concluded that although excretion of riboflavin following administration of floating microballoons was not sustained in fasted state, it was significantly sustained in comparison to riboflavin powder and nonfloating microspheres in the fed state. This could be due to the reason that the nonfloating formulation passes through the proximal small intestine at once from where riboflavin is mostly absorbed, while the floating microballoons gradually sank in the stomach and then arrived in the proximal small intestine in a sustained manner. Total urinary excretion (%) of riboflavin from the floating microballoons was lower than that of riboflavin powder. This was attributed to incomplete release of riboflavin from microballoons at the site of absorption.

Shimpi et al[96] studied the application of hydrophobic lipid, Gelucire 43/01 for the design of multi-unit floating systems of a highly water-soluble drug, diltiazem HCl. Diltiazem HCl-Gelucire 43/01 granules were prepared by the melt granulation technique. The granules were evaluated for in vitro and in vivo floating ability, surface topography, and in vitro drug release. In vivo floating ability was studied by

γ-scintigraphy in 6 healthy human volunteers and the results showed that the formulation remained in the stomach for 6 hours. It could be concluded that Gelucire 43/01 can be considered as an effective carrier for design of a multi-unit FDDS of highly water-soluble drugs such as diltiazem HCl.

A gastroretentive drug delivery system of ranitidine hydrochloride was designed using guar gum, xanthan gum, and hydroxy propyl methyl cellulose. Sodium bicarbonate was incorporated as a gas-generating agent. The effect of citric acid and stearic acid on drug release profile and floating properties was investigated. The addition of stearic acid reduces the drug dissolution due to its hydrophobic nature. A 3^2 full factorial design was applied to systemically optimize the drug release profile and the results showed that a low amount of citric acid and a high amount of stearic acid favor sustained release of ranitidine hydrochloride from a gastroretentive formulation. Hence, it could be concluded that a proper balance between a release rate enhancer and a release rate retardant could produce a drug dissolution profile similar to a theoretical dissolution profile of ranitidine hydrochloride.[97]

In a recent work by Sriamornsak et al,[98] a new emulsion-gelation method was used to prepare oil-entrapped calcium pectinate gel (CaPG) beads as a carrier for intragastric floating drug delivery. The gel beads containing edible oil were prepared by gently mixing or homogenizing an oil phase and a water phase containing pectin, and then extruded into calcium chloride solution with gentle agitation at room temperature. The oil-entrapped calcium pectinate gel beads floated if a sufficient amount of oil was used. Scanning electron photomicrographs demonstrated very small pores, ranging between 5 and 40 μm, dispersed all over the beads. The type and percentage of oil played an important role in controlling the floating of oil-entrapped CaPG beads. The oil-entrapped CaPG beads were a good choice as a carrier for intragastric floating drug delivery.

Reddy and Murthy[99] have discussed advantages and various disadvantages of single- and multiple-unit hydrodynamic systems.

Floating drug delivery is associated with certain limitations. Drugs that irritate the mucosa, those that have multiple absorption sites in the gastrointestinal tract, and those that are not stable at gastric pH are not suitable candidates to be formulated as floating dosage forms.

Floatation as a retention mechanism requires the presence of liquid on which the dosage form can float on the gastric contents. To overcome this limitation, a bioadhesive polymer can be used to coat the dosage so that it adheres to gastric mucosa,[100] or the dosage form can be administered with a full glass of water to provide the initial fluid for buoyancy. Also single unit floating capsules or tablets are associated with an "all or none concept," but this can be overcome by formulating multiple unit systems like floating microspheres or microballoons.[101]

Table 4 enlists examples of various drugs formulated as different forms of FDDS.

The use of large single-unit dosage forms sometimes poses a problem of permanent retention of rigid large-sized single-unit forms especially in patients with bowel obstruction,

Table 4. List of Drugs Formulated as Single and Multiple Unit Forms of Floating Drug Delivery Systems.

Tablets	Chlorpheniramine maleate[4]
	Theophylline[23]
	Furosemide[31]
	Ciprofolxacin[37]
	Pentoxyfillin[40]
	Captopril[44]
	Acetylsalicylic acid[52]
	Nimodipine[59]
	Amoxycillin trihydrate[71]
	Verapamil HCl[75]
	Isosorbide di nitrate[76]
	Sotalol[77]
	Atenolol[89]
	Isosorbide mono nitrate[100]
	Acetaminophen[102,103]
	Ampicillin[104]
	Cinnarazine[105]
	Diltiazem[106]
	Florouracil[107]
	Piretanide[108]
	Prednisolone[109]
	Riboflavin- 5′ Phosphate[110]
Capsules	Nicardipine[41]
	L- Dopa and benserazide[63]
	hlordiazepoxide HCl[64]
	Furosemide[84]
	Misoprostal[86]
	Diazepam[111]
	Propranlol[112]
	Urodeoxycholic acid[113]
Microspheres	Verapamil[27]
	Aspirin, griseofulvin, and p-nitroaniline[43]
	Ketoprofen[49]
	Tranilast[55]
	Iboprufen[80]
	Terfenadine[114]
Granules	Indomathacin[71]
	Diclofenac sodium[88]
	Prednisolone[115]
Films	Drug delivery device[62]
	Cinnarizine[106]
Powders	Several basic drugs[56]

intestinal adhesion, gastropathy, or a narrow pyloric opening (mean resting pyloric diameter 12.8 ± 7.0 mm). Floating dosage form should not be given to a patient just before going to bed as the gastric emptying of such a dosage form occurs randomly when the subject is in supine posture. One drawback of hydrodynamically balanced systems is that this system, being a matrix formulation, consists of a blend of drug and low-density polymers. The release kinetics of drug cannot be changed without changing the floating properties of the dosage form and vice versa.[18]

CONCLUSION

Drug absorption in the gastrointestinal tract is a 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. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique.

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. Ponchel G, Irache JM. Specific and non-specific bioadhesive particulate system for oral delivery to the gastrointestinal tract. *Adv Drug Del Rev.* 1998;34:191–219.

3. Lenaerts VM, Gurny R. Gastrointestinal Tract- Physiological variables affecting the performance of oral sustained release dosage forms. In: Lenaerts V, Gurny R, eds. *Bioadhesive Drug Delivery System.* Boca Raton, FL: CRC Press; 1990.

4. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled-release system for gastric retention. *Pharm Res.* 1997;14:815–819.

5. Rednick AB, Tucker SJ. Sustained release bolus for animal husbandry. US patent 3 507 952. April 22, 1970.

6. Davis SS, Stockwell AF, Taylor MJ, et al. The effect of density on the gastric emptying of single and multiple unit dosage forms. *Pharm Res.* 1986;3:208–213.

7. Urguhart J, Theeuwes F. Drug delivery system comprising a reservoir containing a plurality of tiny pills. US patent 4 434 153. February 28, 1994.

8. Mamajek RC, Moyer ES. Drug dispensing device and method. US Patent 4 207 890. June 17, 1980.

9. Fix JA, Cargill R, Engle K. Controlled gastric emptying. III. Gastric residence time of a non-disintegrating geometric shape in human volunteers. *Pharm Res.* 1993;10:1087–1089.

10. Kedzierewicz F, Thouvenot P, Lemut J, Etienne A, Hoffman M, Maincent P. Evaluation of peroral silicone dosage forms in humans by gamma-scintigraphy. *J Control Release.* 1999;58:195–205.

11. Groning R, Heun G. Oral dosage forms with controlled gastrointestinal transit. *Drug Dev Ind Pharm.* 1984;10:527–539.

12. Groning R, Heun G. Dosage forms with controlled gastrointestinal passage—studies on the absorption of nitrofurantion. *Int J Pharm.* 1989;56:111–116.

13. Desai S. A Novel Floating Controlled Release Drug Delivery System Based on a Dried Gel Matrix Network [master's thesis]. 1984 Jamaica, NY, St John's University.

14. Vantrappen GR, Peeters TL, Janssens J. The secretory component of interdigestive migratory motor complex in man. *Scand J Gastroenterol.* 1979;14:663–667.

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

16. Desai S, Bolton S. A floating controlled release drug delivery system: in vitro- in vivo evaluation. *Pharm Res.* 1993;10:1321–1325.

17. 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.

18. 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.

19. Mojaverian P, Ferguson RK, Vlasses PH, et al. Estimation of gastric residence time of the Heidelberg capsules in humans: effect of varying food composition. *Gastroenterology.* 1985;89:392–397.

20. Bechgaard H, Ladefoged K. Distribution of pellets in gastrointestinal tract. The influence on transit time exerted by the density or diameter of pellets. *J Pharm Pharmacol.* 1978;30:690–692.

21. Garg S, Sharma S. *Gastroretentive drug delivery systems. Business Briefing: Pharmatech 2003 Web Site. 5th edition. May 2003.* Available at: http://www.touchbriefings.com/cdps/cditem.cfm?NID=17&CID=5. Accessed: October 6, 2005.

22. 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.

23. Yang L, Fassihi R. Zero order release kinetics from self correcting floatable configuration drug delivery system. *J Pharm Sci.* 1996;85:170–173.

24. Burns SJ, Attwood D, Barnwell SG. Assesment of a dissolution vessel designed for use with floating and erodible dosage forms. *Int J Pharm.* 1998;160:213–218.

25. Joseph NJ, 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 Control Release.* 2002;79:71–79.

26. Sheth PR, Tossounian JL. Sustained release pharmaceutical capsules. US patent 4,126,672. November 21, 1978.

27. Soppimath KS, Kulkarni AR, Rudzinski WE, Aminabhavi TM. Microspheres as floating drug delivery system to increase the gastric residence of drugs. *Drug Metab Rev.* 2001;33:149–160.

28. 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.

29. Ichikawa M, Watanabe S, Miyake Y. Granule remaining in stomach. US patent 4 844 905. July 4, 1989.

30. 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.

31. 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.

32. Choi BY, Park HJ, Hwang SJ, Park JB. Preparation of alginate beads for floating drug delivery: effects of CO_2 gas forming agents. *Int J Pharm.* 2002;239:81–91.

33. Li S, Lin S, Daggy BP, Mirchandani HL, Chien TW. Effect of formulation variables on the floating properties of gastric floating drug delivery system. *Drug Dev Ind Pharm.* 2002;28:783–793.

34. Li S, Lin S, Chien TW, Daggy BP, Mirchandani HL. Statistical optimization of gastric floating system for oral controlled delivery of calcium. *AAPS PharmSciTech.* 2001;2:E1.

35. Penners G, Lustig K, Jorg PVG. Expandable pharmaceutical forms. US patent 5 651 985. July 29, 1997.

36. Fassihi R, Yang L. Controlled release drug delivery systems. US patent 5 783 212. July 21, 1998.

37. 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.

38. Michaels AS, Bashwa JD, Zaffaroni A. Integrated device for administering beneficial drug at programmed rate. US patent 3 901 232. August 26, 1975.

39. Michaels AS. Drug delivery device with self actuated mechanism for retaining device in selected area. US patent 3 786 813. January 22, 1974.

40. 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.

41. 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.

42. 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.

43. 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.* 1993;45:21–24.

44. Nur AO, Zhang JS. Captopril floating and/or bioadhesive tablets: design and release kinetics. *Drug Dev Ind Pharm.* 2000;26:965–969.

45. 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.

46. Whitehead L, Collett JH, Fell JT. Amoxycillin release from a floating dosage form based on alginates. *Int J Pharm.* 2000;210:45–49.

47. 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.

48. 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.

49. El-Kamel AH, Sokar MS, Al Gamal SS, Naggar VF. Preparation and evaluation of ketoprofen floating oral drug delivery system. *Int J Pharm.* 2001;220:13–21.

50. Illum L, Ping H. Gastroretentive controlled release microspheres for improved drug delivery. US patent 6 207 197. March 27, 2001.

51. Streubel A, Siepmann J, Bodmeier R. Floating microparticles based on low density foam powder. *Int J Pharm.* 2002;241:279–292.

52. Sheth PR, Tossounian JL. Novel sustained release tablet formulations. 4 167 558. September 11, 1979.

53. Ushomaru K, Nakachimi K, Saito H. Pharmaceutical preparations and a method of manufacturing them. US patent 4 702 918. October 27, 1987.

54. Bolton S, Desai S. Floating sustained release therapeutic compositions. US patent 4 814 179. March 21, 1989.

55. Kawashima Y, Niwa T, Takeuchi H, Hino T, Ito Y. Preparation of multiple unit hollow microspheres (microballoons) with acrylic resins containing tranilast and their drug release characteristics (in vivo). *J Control Release.* 1991;16:279–290.

56. Dennis A, Timminis P, Lel K. Buoyant controlled release powder formulation. US patent 5 169 638. December 8, 1992.

57. Spickett RGW, Vidal JLF, Escoi JC. Antacid preparation having prolonged gastric residence. US patent 5,288,506. February 22, 1993.

58. Franz MR, Oth MP. Sustained release, bilayer buoyant dosage form. US patent 5 232 704. August 3, 1993.

59. 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.

60. Wong PSL, Dong LC, Edgren DE, Theeuwes F. Prolonged release active agent dosage form adapted for gastric retention. US patent 6 120 803. September 19, 2000.

61. Mitra SB. Sustained release oral medicinal delivery device. US patent 4 451 260. May 29, 1984.

62. Harrigan BM. Drug delivery device for preventing contact of undissolved drug with the stomach lining. US patent 4 055 178. October 25, 1977.

63. Erni W, Held K. The hydrodynamically balanced system: a novel principle of controlled drug release. *Eur Neurol.* 1987;27:215–275.

64. Sheth PR, Tossounian J. The hydrodynamically balanced systems (HBS): a novel drug delivery system for oral use. *Drug Dev Ind Pharm.* 1984;10:313–339.

65. Degtiareva H, Bogdanov A, Kahtib Z, etal. . The use of third generation antacid preparations for the treatment of patients with nonulcerous dyspeosia and peptic ulcer complicated by reflux esophagus [in Chinese]. *Liakrs' ka sprava.* 1994;5-6:119–122.

66. Fabregas JL, Claramunt J, Cucala J, Pous R, Siles A. In vitro testing of an antacid formulation with prolonged gastric residence time (Almagate flot coat). *Drug Dev Ind Pharm.* 1994;20:1199–1212.

67. Washington N, Washington C, Wilson CG, Davis SS. What is liquid Graviscon? A comparison of four international formulations. *Int J Pharm.* 1986;34:105–109.

68. 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.

69. Yuasa H, Takashima Y, Kanaya Y. Studies on the development of intragastric floating and sustained release preparation. I. Application of calcium silicate as floating carrier. *Chem Pharm Bull (Tokyo).* 1996;44:1361–1366.

70. Kohri N, Naasani I, Iseki K. Improving the oral bioavailability of sulphiride by a gastric retained form in rabbits. *J Pharm Pharmacol.* 1995;48:371–374.

71. Hilton AK, Deasy PB. In vitro and in vivo evaluation of an oral sustained release floating dosage form of amoxycillin trihydrate. *Int J Pharm.* 1992;86:79–88.

72. Kawashima Y, Niwa T, Takeuchi H, Hino T, Itoh Y. Hollow microspheres for use as a floating controlled drug delivery system in stomach. *J Pharm Sci.* 1992;81:135–140.

73. Mazer N, Abhisch E, Gfeller JC, etal. . Intragastric behaviour and absorption kinetics of a normal and floating modified release capsules of isardipine under fasted and fed conditions. *J Pharm Sci.* 1988; 77:647–657.

74. Hashim H, Li WPA. Improving the release characteristics of water soluble drugs from hydrophilic sustained release matrices b in situ gas generation. *Int J Pharm.* 1987;35:201–209.

75. Chen GL, Hao WH. In vitro performance of floating sustained release capsules of verapamil. *Drug Dev Ind Pharm.* 1998;24:1067–1072.

76. Ichikawa M, Watanabe S, Miyake Y. A new multiple-unit oral floating dosage system. II: In vivo evaluation of floating and sustained-release characteristics with para amino benzoic acid and iso sorbide di nitrate as model drugs. *J Pharm Sci.* 1991;80:1153–1156.

77. Cheuh HR, Zia H, Rhodes CT. Optimization of Sotalol floating and bioadhesive extended release tablet formulation. *Drug Dev Ind Pharm.* 1995;21:1725–1747.

78. *USP 28 NF 23*. Rockville, MD: US Pharmacopeia; 2005:2413.

79. Pillay V, Fassihi R. Evaluation and comparision of dissolution data derived from different modified release dosage forms: an alternative method. *J Control Release.* 1998;55:45–55.

80. Kawashima Y, Niwa T, Takeuchi H, Hino T, Ito Y. Hollow microspheres for use as floating controlled drug delivery system in stomach. *J Pharm Sci.* 1992;81:135–140.

81. Sakuma S, Sudo R, Suzuki N, Kikuchi H, Akashi M, Hayashi M. Mucoadhesion of polystyrene nanoparticles having surface hydrophilic polymeric chains in gastrointestinal tract. *Int J Pharm.* 1999;177:161–172.

82. Babu VBM, Khar RK. In vitro and In vivo studies of sustained release floating dosage forms containing salbutamol sulphate. *Pharmazie.* 1990;45:268–270.

83. Chen J, Blevins WE, Park H, Park K. Gastric retention properties of superporous hydrogel composites. *J Control Release.* 2000;64:39–51.

84. Menon A, Ritschel WA, Sakr A. Development and evaluation of a monolithic floating dosage form for furosemide. *J Pharm Sci.* 1994; 83:239–245.

85. Whitehead L, Fell JT, Collett JH, Sharma HL, Smith A. In vivo study demonstrating prolonged gastric retention. *J Control Release.* 1998;55:3–12.

86. 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.

87. Miyazaki S, Yamaguchi H, Yokouchi C, Takada M, Huo WM. Sustained release and intra gastric floating granules of indomethacin using chitosan in rabbits. *Chem Pharm Bull (Tokyo).* 1988;36: 4033–4038.

88. Malcolm SL, Allen JG, Bird H, etal. . Single dose pharmacokinetics of Madopar HBS in volunteers. *Eur Neurol.* 1987;27:28S–35S.

89. Rouge N, Allémann E, Gex-Fabry M, et al. Comparative pharmacokinetic study of a floating multiple unit capsule, a high density multiple unit capsule and an immediate release tablet containing 25 mg atenolol. *Pharm Acta Helv.* 1998;73:81–87.

90. 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.

91. 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.

92. Cook JD, Carriaga M, Kahn SG, Schalch W, Skikne BS. Gastric delivery system for iron supplementation. *Lancet.* 1990;335:1136–1139.

93. Blaser MJ. Hypothesis on the pathogenesis and natural history of *Helicobacter pylori* induced inflammation. *Gastroenterology.* 1992; 102:720–727.

94. Gibaly EI. Development and evaluation of novel floating chitosan microcapsules: comparision with non floating chitosan microspheres. *Int J Pharm.* 2002;249:39–47.

95. Sato Y, Kawashima Y. In vitro and in vivo evaluation of riboflavin containing microballoons for a floating controlled drug delivery system in healthy human volunteers. *J Control Release.* 2003;93: 39–47.

96. Shimpi S, Chauhan B, Mahadik KR, Paradkar A. Preparation and evaluation of diltiazem hydrochloride-Gelucire 43/01 floating granules prepared by melt granulation. *AAPS PharmSciTech.* 2004;5: E43.

97. Dave BS, Amin AF, Patel MM. Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and in vitro evaluation. *AAPS PharmSciTech.* 2004;5:E34.

98. Sriamornsak P, Thirawong N, Puttipipatkhachorn S. Morphology and buoyancy of oil-entrapped calcium pectinate gel beads. *The AAPS Journal.* 2004;6:E24.

99. Reddy L, Murthy R. Floating dosage systems in drug delivery. *Crit Rev Ther Drug Carrier Syst.* 2002;19:553–585.

100. Chitnis V, Malshe VS, Lalla JK. Bioadhesive polymers synthesis, evaluation and application in controlled release tablets. *Drug Dev Ind Pharm.* 1991;17:879–892.

101. Rouge N, Leroux JC, Cole ET, Doelker E, Buri P. Prevention of sticking tendency of floating mini tablets filled into hard gelatin capsules. *Eur J Pharm Biopharm.* 1997;43:165–171.

102. Phuapradit W. Influence of Tablet Buoyancy on Oral Absorption of Sustained Release Acetaminophen Matrix Tablets [dissertation]. 1989, Jamaica, NY, St John's University.

103. Phuapradit W, Bolton S. Influence of tablet density on oral absorption of sustained release acetaminophen matrix tablets. *Drug Dev Ind Pharm.* 1991;17:1097–1107.

104. Gupta SK. Stability studies of ampicillin floating tablets (Ampiflot) and buffered Ampiflot [master's thesis]. 1987, Jamaica, NY, St John's University.

105. Machida Y, Inouye K, Tokumura T, Iwata M, Nagai T. Preparation and evaluation of intragastric buoyant preparations. *Drug Des Deliv.* 1989;4:155–161.

106. Gu TH, Chen SX, Zhu JB, Song DJ, Guo JZ, Hou JM. Pharmacokinetics and pharmacodynamics of diltiazem floating tablets [in Chinese] *Chung Kao Yao Li Hsuesh Pao.* 1992;13:527–531.

107. Watanbe K, Machida Y, Takayama M, Iwta M, Nagai T. Preparation and evaluation of intragastric floating tablets having pH independent buoyancy and sustained release property. *ArchPract Pharm Yakuzaigaku.* 1993;53:1–7.

108. Rouge N, Cole ET, Doelker E, Buri P. Buoyancy and drug release patterns of floating minutesitablets containing piretanide and atenolol as model drugs. *Pharm Dev Technol.* 1998;3:73–84.

109. Inouye K, Machida Y, Sannan T, Nagai T. Buoyant sustained release tablets based on chitosan. *Drug Des Deliv.* 1988;2: 165–175.

110. Ingani HM, Timmermans J, Moes AJ. Conception and in vivo investigation of peroral sustained release floating dosage forms with enhanced gastrointestinal transit. *Int J Pharm.* 1987;35:157–164.

111. Gustafson JH, Weissman L, Weinfeld RE, Holazo AA, Khoo KC, Kalpan SA. Clinical bioavailability evaluation of a controlled release formulation of diazepam. *J Pharmacokinet Biopharm.* 1981;9:679–691.

112. Khattar D, Ahuja A, Khar RK. Hydrodynamically balanced systems as sustained release dosage form for Propranalol hydrochloride. *Pharmazie.* 1990;45:356–358.

113. Simoni P, Cerre C, Cipolla A, etal. . Bioavailabilty study of a new sinking, enteric coated ursodeoxycholic acid formulation. *Pharmacol Res.* 1995;31:115–119.

114. Jayanthi G, Jayaswal SB, Srivastava AK. Formulation and evaluation of terfenadine microballoons for oral controlled release. *Pharmazie.* 1995;50:769–770.

115. Inouye K, Machida Y, Sannan T, Nagai T. Buoyant sustained release tablets based on chitosan. *Drug Des Deliv.* 1989;4: 55–67.