Floating Drug Delivery System

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A R T I C L E   I N F O

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A B S T R A C T

The purpose of writing this review to compile the current technological development of floating drug delivery system (FDDS), advantages and future potential for oral controlled drug delivery. The review includes various approaches which are currently utilized in the prolongation of the gastric residence time (GRT) and their classification. This review also summarizes various in vitro and in vivo techniques to evaluate the performance and application of these systems.

Introduction

The design of an oral controlled drug delivery system (DDS) should be primarily aimed at achieving more predictable and increased bioavailability of drugs. However, the development process is precluded by several physiological difficulties such as an inability to restrain and localize the DDS within desired regions of gastrointestinal (GI) tract and the highly variable nature of gastric emptying process. It can be anticipated that depending upon the physiological state of the subject and the design of pharmaceutical formulations, the emptying process can last from a few minutes to 12 hours. This variability, in turn, may lead to unpredictable bioavailability and time to achieve peak plasma levels, since the majority of drugs are preferentially absorbed in the upper part of intestine.

Furthermore, the relatively brief gastric emptying time (GET) in humans, which normally averages 2–3 hours through the major absorption zone (stomach or upper part of the intestine), can result in incomplete drug release from the DDS, leading to diminished efficacy of the administered dose. Thus, control of placement of a DDS in a specific region of the GI tract offers numerous advantages, especially for drugs exhibiting an absorption window in the GI tract or drugs with a stability problem. Overall, the intimate contact of the DDS with the absorbing membrane has the potential to maximize drug absorption and may also influence the rate of drug absorption. These considerations have led to the development of oral controlled release (CR) dosage forms possessing gastric retention capabilities.[1]

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time (GRT) using gastroretentive dosage forms (GRDFs). GRDF can remain in the gastric region for several hours and hence significantly prolong the GRT of the drugs. Prolonged gastric retention improves the bioavailability, reduces drug waste, and improves solubility of 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. Gastroretention helps to provide better availability of new products with new therapeutic possibility and substantial benefits for patients. So, GRDFs will provide us new and important therapeutic options.[2]

Davis, in 1968, firstly described the concept of floating drug delivery system (FDDS) after gagging or choking was experienced by some persons, while swallowing medicinal pills. The researcher suggested that such difficulty could be overcome by providing pills having a density of less than 1.0 g/ml, so that the pill will float on water surface. Since then, several approaches have been proposed for ideal floating delivery systems like formulating low-density dosage form that remains buoyant above the gastric fluid (floating dosage form) or high-density dosage form that is retained at the bottom of the stomach, imparting bioadhesion to the stomach mucosa, reducing motility of the GI tract by concomitant administration of drugs or pharmaceutical excipients, expanding...
Digestive motility pattern and comprises continuous contraction changes from fasted to that of fed state. This is also known as intends to prolong the GI retention time.

Phase IV : Period of transition between Phase III and Phase I and lasts from 4 to 6 minutes
Phase II (Preburst phase) : Period of intermittent contraction and of similar duration. As the phase progresses, the intensity and frequency also increases gradually
Phase III (burst phase) : Period of regular contraction at the maximal frequency lasting from 4 to 6 minutes
Phase I (basal phase) : Period of no contraction lasting from 40 to 60 minutes

A complete cycle of these four phases has an average duration of 90–120 minutes. Phase III has a housekeeping role and serves to clear all indigestible materials from the stomach and the small intestine. Consequently, any CR gastrointestinal drug delivery system (GIDS) designed to stay during the fasted state should be capable of resisting the housekeeping action of phase III if one intends to prolong the GI retention time.

After the ingestion of a mixed meal, the pattern of contraction changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contraction as in phase II of fasted state. These contractions result in reducing the size of food particles (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.

**Approaches to Gastric Retention**

Over the last three decades, various approaches have been pursued to increase the retention of an oral dosage form in the stomach, which are discussed below.

**Floating drug delivery system or hydrodynamically balanced system**

FDDS or hydrodynamically balanced system (HBS) has a bulk density lower than gastric fluids and thus remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in plasma drug concentrations in some cases.

**Swelling systems**

Swelling type dosage forms are such that after swallowing, these products swell to an extent that prevents their exit from the stomach through the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be referred to as “plug type systems” since they exhibit a tendency to remain lodged at the pyloric sphincter. Upon coming in contact with gastric fluid, the polymer imbibes water and swells.

**Bioadhesive system**

These systems are used to localize a delivery device within the lumen and cavity of the body to enhance the drug absorption process in a site-specific manner. The approach involves the use of bioadhesive polymer that can adhere to the epithelial surface of the GI tract. The proposed mechanism of bioadhesion is the formation of hydrogen and electrostatic bonding at the mucus–polymer boundary. Rapid hydration in contact with gastric fluid, the polymer imbibes water and swells.

**Modified-shape system**

Modified-shape systems are nondisintegrating geometric shapes molded from silastic elastomer or extruded from polyethylene blends which extend the GRT, depending on size, shape and flexural modulus of the drug delivery device.

**High-density formulations**

High-density formulations include coated pellets which have a density greater than that of the stomach contents (−1.004 g/cm³). These systems having density of −3 g/cm³ are retained in the rugae of the stomach. This is accomplished by coating the drug with a
heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder, etc. The only major drawback with such systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and to achieve the required density of 2.4–2.8 g/cm³.

**Factors Affecting Gastric Retention**

There are several factors that can affect gastric emptying (and hence GRT) of an oral dosage form.[12-13] These factors are as follows.

**Density**

GRT is a function of dosage form buoyancy that is dependent on the density. 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.

**Size**

Dosage form units with a diameter of less than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.

**Shape of dosage form**

Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT = 90–100% retention at 24 hours compared with other shapes.

**Single or multiple unit formulation**

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

**Fed or unfed state**

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the MMC that occurs every 1.5–2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

**Nature of meal**

Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

**Caloric content**

GRT can be increased by 4–10 hours with a meal that is high in proteins and fats.

**Frequency of feed**

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

**Gender**

Mean ambulatory GRT in males (3.4 ± 0.6 hours) is lesser compared with their age- and race-matched female counterparts (4.6 ± 1.2 hours), regardless of the weight, height and body surface.

**Age**

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

**Posture**

Gastric emptying is favored while standing and lying on the right side since the normal curvature of the stomach provides a downhill path, whereas lying on the left side or in supine position retards it.

**Disease states**

Diseases like gastroenteritis, gastric ulcer, pyloric stenosis, diabetes and hypothyroidism retard gastric emptying, while partial or total gastrectomy, duodenal ulcer and hyperthyroidism promote it.

**Concomitant drug administration**

Drugs that retard gastric emptying include poorly soluble antacids (aluminum hydroxide), anticholinergics (atropine, propantheline), narcotic analgesics (morphine) and drugs such as tricyclic antidepressants (imipramine, amitriptyline), metoclopramide, domperidone, cisapride stimulate gastric emptying.

**Technological Developments in Floating Drug Delivery System**

Based on the mechanism of buoyancy, two distinctly different technologies, i.e., non-effervescent and effervescent systems, have been utilized in the development of FDDS.[16-18] The various approaches used and their mechanisms of buoyancy are discussed in the following subsections.

**Non-effervescent floating drug delivery system**

*Hydrodynamically balanced intragastric delivery system*

The hydrodynamically balanced GIDSs, in either capsule or
tablet form, are designed to prolong GI residence time in an area of the GI tract, to maximize the drug reaching its absorption site in solution state, and hence, ready for absorption. It is prepared by incorporating a high level (20–75% w/w) of one or more gel-forming hydrocolloids, e.g., hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcellulose into the formulation and then compressing these granules into a tablet (or encapsulating into capsules). On contact with gastric fluid, the hydrocolloid in this intragastric floating device starts to become hydrated and forms a colloid gel barrier around its surface with its thickness growing with time. This gel barrier controls the rate of solvent penetration into the device and the rate of drug release from the device. It maintains a bulk density of less than 1 and thus remains buoyant in the gastric fluid inside the stomach for up to 6 hours.

**Bilayer tablet**

A bilayer tablet can be prepared to contain one immediate-release layer and one SR layer. After the initial dose is delivered by the immediate release layer, the SR layer absorbs the gastric fluid and forms a colloidal gel barrier on its surface. This produces a bulk density lesser than that of the gastric fluid and remains buoyant in the stomach for extended period of time.

GIDS can be made to float in the stomach by incorporating a floating chamber, which may be a vacuum or filled with a harmless gas.

A drug reservoir is encapsulated inside a microporous compartment with apertures along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the stomach mucosal surface with the undissolved drug.

In the stomach, the flotation chamber causes the GIDS to float in the gastric fluids. Fluids enter through the apertures, dissolve the drug, and carry the drug solute out of the DDS for controlled transport to the intestine for absorption.

**Effervescent floating drug delivery system**

These buoyant delivery systems utilize matrices prepared with swellable polymers such as methocel or polysaccharides, e.g., chitosan (Cs), and effervescents components, e.g., sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature. The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gelified hydrocolloid. This produces an upward motion of dosage form and maintains it buoyancy.

Recently, a multiple-unit type of floating pill, which generates carbon dioxide gas, has been developed. The system consists of SR pills as seeds surrounded by double layers. The inner layer is an effervescent layer containing both sodium bicarbonate and tartaric acid. The outer layer is a swellable membrane layer containing mainly polyvinyl acetate and purified shellac. Moreover, the effervescent layer is divided into two sublayers to avoid direct contact between sodium bicarbonate and tartaric acid. Sodium bicarbonate is contained in the inner sublayer and tartaric acid in the outer layer. When the system is immersed in a buffer solution at 37°C, it sinks at once in the solution and forms swollen pills, like balloons, with a density much lower than 1 g/ml. The reaction is due to carbon dioxide generated by neutralization in the inner effervescent layer with the diffusion of water through the outer swellable membrane layer.

The system, when starting floating within 10 minutes and approximately 80% remains floating over a period of 5 hours, irrespective of pH and viscosity of the test medium.

A floating system utilizing ion-exchange resins has been developed. The system consists of resin beads which are loaded with bicarbonate and a negatively charged drug that is bound to the resin. The resultant beads are then encapsulated in a semipermeable membrane to overcome rapid loss of carbon dioxide. Upon arrival in the acidic environment of stomach, an exchange of chloride and bicarbonate ions takes place, as expected. As a result of this reaction, carbon dioxide is released and trapped in the membrane, thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads. In contrast, the uncoated beads sink quickly. Radioactivity measurement by scintigraphy showed that gastric residence was substantially prolonged, compared with a control, when the system was given after a light, mainly liquid meal. Furthermore, the system was capable of slow release of drug, a property which widens the scope of such a floating system for SR preparation of drugs possessing negative charge since they can be easily bound to the resin in combination with bicarbonate ions.

Two patents on FDDS issued to the Alza Corporation disclosed drug delivery devices for the controlled and continuous administration of medicinal agents.

**Inflatable gastrointestinal drug delivery system**

The residence time of the drug delivery device in the stomach can also be sustained by incorporation of an inflatable chamber which contains a liquid, e.g., ether, which gasifies at body temperature to cause the chamber to inflate in the stomach.

**Intragastric osmotically controlled drug delivery system**

It is composed of an osmotic pressure controlled drug delivery and an inflatable floating support in a bioerodible capsule. When the drug delivery device reaches the site of drug administration, e.g., the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable floating support is made from a deformable hollow polymeric bag that contains a liquid which gasifies at body temperature to inflate the bag.

Although single-unit floating dosage forms have been extensively studied, these single-unit dosage forms have the disadvantage of an all or nothing emptying process, while the multiple unit particulate system passes through the GIT to avoid the vagaries of gastric emptying and thus releases the drug more uniformly. The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave birth to oral controlled drug delivery and led to development of gastroretentive floating microspheres (FM). FM are gastroretentive delivery systems based on non-effervescent approach. Gastroretentive FM is low-density systems which have sufficient buoyancy to float over gastric contents and remain in stomach for a prolonged period. As the system floats over gastric contents, the drug is released slowly at the desired rate, resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. Hollow microspheres are prepared by solvent diffusion and evaporation methods to create the hollow
inner core. The polymers studied for the development of such systems include cellulose acetate, Chitosan, Eudragit, methocel, polyacrylates, polyvinyl acetate, carbopel, agar, polyethylene oxide and polycarbonates.

**Compilation of Different Works Cited in the Literature**

In recent years, scientific and technological advancements have been made in the research and development of rate-controlled oral DDS by overcoming physiological adversities such as short GRT and unpredictable GET. Several approaches are currently utilized in the prolongation of the GRT, including FD DDS, also known as HBS, swelling and expanding system, polymeric bioadhesive system, modified-shape system, high-density system and other delayed gastric emptying devices.

The works cited in the literature are compiled below.

Rao et al. [20] formulated and optimized the FD DDS containing cephalixin using 2 factorial design. Floating tablets were prepared by direct compression method incorporating HPMC K4M, xanthan gum, guar gum, sodium bicarbonate and tartaric acid as gas generating agent. The influence of independent variables like polymer:polymer ratio, polymer type and tartaric acid on floating lag time and cephalexin release profile was studied.

Sauzet et al. [21] developed an innovative floating GRDF. The technology developed induces a low-density dosage form containing high active pharmaceutical ingredient (API) concentration by using a hydrophobic dusty powder excipient under specific conditions. The new dosage form was obtained by state of the art wet granulation manufacturing process. An experimental design using a discrete variable and four mixture variables was developed in order to optimize API concentration and buoyancy of the new dosage form. An apparatus was developed to measure the apparent density of floating tablet. The GRDF was characterized for apparent density, buoyancy, porosity and dissolution using in vitro experimentations.

Zhao et al. [22] designed an experiment to assess the safety, tolerability and pharmacokinetics of phenoprolamine hydrochloride floating sustained tablets (PHFST) in healthy Chinese subjects. One hundred and sixteen volunteers were randomized into single or multiple dose groups for oral administration of 30–240 mg of PHFST once or 60–120 mg twice daily. Safety and tolerability were appraised by monitoring adverse events and laboratory parameters. Pharmacokinetics was assessed by determining the plasma concentrations of phenoprolamine hydrochloride with a validated high performance liquid chromatography (HPLC) method. The mean Cmax of PHFST is proportional to dose, but not the area under the curve AUC. Oral dosing regimen selected for subsequent Phase II/III clinical trials was 60 mg of PHFST, b.i.d., and a dose of up to 120 mg, b.i.d. may be used to achieve better antihypertensive effect.

Khan et al. [23] investigated preparation and in vitro evaluation of gastroretentive floating tablet of theophyline. Two hydrophilic cellulose derivatives, Methocel K100M and Methocel K15MCR, were evaluated for their gel forming and release controlling properties. Sodium bicarbonate and citric acid were incorporated as gas generating agents. The effects of soluble components (sodium bicarbonate and citric acid), gel forming agents and amount variation of theophyline on drug release profile and floating properties were investigated.

Gattani et al. [24] formulated and evaluated floating multiparticulate oral DDS of diltiazem hydrochloride, which can provide SR. The work also aims to study various parameters affecting the behavior of floating multiparticulate in oral dosage form. FM were prepared by non-aqueous emulsification solvent evaporation technique using ethyl cellulose (EC) and Eudragit RS-100 as the rate controlling polymer. The in vitro performance was evaluated by the usual pharmacopeiaal and other tests such as drug–polymer compatibility, (% yield, particle size analysis, drug entrapment efficiency, surface topography, in vitro floatability and release studies. The data obtained in this study thus suggest that a microparticulate floating dosage form of diltiazem hydrochloride can be successfully designed to give controlled delivery and improved oral bioavailability.

Stops et al. [25] designed floating calcium alginate beads to improve drug bioavailability from oral preparations and compared with that from many commercially available and modified release products. A model drug, riboflavin, was also incorporated into the formula. The aims of the current work were to obtain information regarding the structure, floating ability and changes that occurred when the dosage form was placed in aqueous media and to investigate riboflavin release from the calcium alginate beads in physiologically relevant media prior to in vivo investigations. The characterization studies showed that the calcium alginate beads could be considered as a potential gastroretentive dosage form.

Ma et al. [26] prepared a type of multi-unit floating alginate (Alg) microspheres by the ionotropic gelation method with calcium carbonate (CaCO3) used as gas-forming agent. Attempts were made to enhance the drug encapsulation efficiency and delay the drug release by adding Cs into the gelation medium and by coating with Eudragit, respectively. The gastrointestinal transit of optimized floating SR microspheres was compared with that of the non-floating system manufactured from identical material using the technique of gamma-scintigraphy in healthy human volunteers. Prolonged gastric retention time (GRT) of over 5 hours was achieved in the volunteer for the optimized coating FM. In contrast, non-floating system (NFM) could be emptied within 2.5 hours. In the present study, a multi-unit system with excellent floating ability, optimum drug entrapment efficiency and suitable drug release pattern has been developed.

Jang et al. [27] developed a gastroretentive DDS of DA-6034, a new synthetic flavonoid derivative, for the treatment of gastritis, by using effervescent floating matrix system (EFMS). The therapeutic limitations of DA-6034 caused by its low solubility in acidic conditions were overcome by using the EFMS, which was designed to cause tablets to float in the gastric fluid and release the drug continuously. DA-6034 EFMS tablets showed enhanced gastroprotective effects in gastric ulcer-induced beagle dogs, indicating the therapeutic potential of EFMS tablets for the treatment of gastritis.

Shishu et al. [28] investigated the development and evaluation of single-unit floating tablets of 5-fluorouracil (5-FU). Tablet was designed to prolong the GRT, increase drug bioavailability and target the stomach cancer. The formulations were optimized for the type of filler like lactose, microcrystalline cellulose (MCC) and dicalcium phosphate (DCP) as well and for different viscosity grades and concentrations of HPMC and concentrations. The anti-tumor activity of 5-FU was studied in albino female mice (Balb/c strain) using benzo(a)pyrene [B(a)P] to induce stomach tumors. It was found that the tumor incidence was reduced by 75% using FDDS of 5-FU, whereas only a 25% reduction was observed using the conventional tablet form of 5-FU.

Gooed [29] developed SR levodopa minitablets (MT), prepared by melt granulation and subsequent compression, which are designed to float over an extended period of time. The importance of the
composition and manufacturing parameters of the MT on their floating and dissolution properties was then examined. The investigation showed that MT composition and MT diameter had the greatest influence on drug release, which was sustained for more than 8 hours. By using the same formulation, the best floating properties were obtained with 3 mm MT prepared at low compression forces ranging between 50 and 100 N.

Bajpai et al.[30] studied the drug release behavior of vitamin B2 loaded superporous floating hydrogels which were prepared through rapid copolymerization of acrylamide and acrylic acid in the presence of model drug using NaHCO₃ as a porogen and tetraethylmethylenediamine as a catalyst. The gels prepared with 0.12 and 0.58 mM of cross linker remained buoyant for nearly 96 hours, but showed different release behaviors. The sample with 0.12 mM of cross linker released almost 100% drug within 2 hours in a simulating gastric fluid of pH 1.2, while the sample with 0.58 mM of cross linker demonstrated a slower release which was extended over a period of 30 hours. The gels offer their strong candidature for prolonged gastric delivery of drugs for the treatment of gastric disorders.

Tanwar et al.[31] prepared and evaluated FM of verapamil hydrochloride for improving the drug bioavailability by prolongation of GRT. Cellulose acetate, acrycoat S100 and eudragit S100 microspheres loaded with verapamil hydrochloride were prepared by solvent diffusion evaporation method. The prepared microspheres exhibited prolonged drug release and remained buoyant for more than 12 hours. Radiographic images of dog stomach revealed that cellulose acetate microspheres loaded with barium sulfate floated on the gastric fluid for about 3.2 hours.

Sriamornsak et al.[32] investigated pectin as a carrier for an intragastric floating drug delivery by means of calcium pectinate gel (CaPG) beads. The CaPG beads containing carbonate salt as a gas-forming agent were prepared by dispersing carbonate salt in pectin solution and then extruding into either neutral or acidified solution of calcium chloride. The effects of selected factors such as type of carbonates, percentage of carbonates, degree of methylesterification (DE) of pectin, type of gelation medium, drug loading and drying method on morphology, floating and release properties were investigated.

Roy et al.[33] conceptualized a specific technology based on combining floating and pulsatile principles to develop DDS intended for chronotherapy in nocturnal acid breakthrough. In this study, investigation of the functionality of the outer polymer coating to predict lag time and drug release was statistically analyzed using the response surface methodology (RSM). Results revealed that both the coating composition and coating level are significant factors affecting drug release profile. The optimized formulation prepared according to computer-determined levels provided a release profile, which was close to the predicted values. The proposed mathematical model is found to be robust and accurate for optimization of time-lagged coating formulations for programmable pulsatile release of ranitidine hydrochloride, consistent with the demands of nocturnal acid breakthrough.

Meka et al.[34] developed a gastroretentive FDDS with multiple-unit MT based on gas formation technique for furosemide. The system consists of core units (solid dispersion of furosemide:povidone and other excipients), prepared by direct compression process, which are coated with two successive layers, one of which is an effervescent (sodium bicarbonate) layer and the other one an outer polymeric layer of polymethacrylates. The rapid floating and the CR properties were achieved in this study. The in vivo GRT was examined by radiograms and it was observed that the units remained in the stomach for about 6 hours.

Rao et al.[35] prepared and evaluated FM of rosiglitazone maleate for the prolongation of GRT. The microspheres were prepared by solvent diffusion–evaporation method using EC and HPMC. A full factorial design was applied to optimize the formulation. The results of 3² full factorial design revealed that the concentration of ethylcellulose 7 cps (X1) and stirring speed (X2) significantly affected drug entrapment efficiency, percentage release after 8 hours and particle size of microspheres.

Deepaa et al.[36] developed FM of cefpodoxime proxetil in order to achieve an extended retention in the upper GIT, which may result in enhanced absorption and thereby improved bioavailability. The microspheres were prepared by non-aqueous solvent evaporation method using polymers such as HPMC K15M, EC in different ratios and cefpodoxime proxetil in each formulation. The best drug release profiles were seen with formulation 2 at the ratio of drug to polymer of 1:2.

Patil et al.[37] prepared FM of acyclovir using different viscosities of EC to achieve an extended retention in upper GIT, which may result in enhanced absorption and thereby improves bioavailability. The FM were prepared by emulsion solvent diffusion technique and triethylic citrate was used as a plasticizer. The microspheres were evaluated for particle size analysis, drug entrapment, floating ability, in vitro drug release and characterized by scanning electron microscopy and X-ray diffractometry. The in vitro release study indicated that when the polymer concentration was increased and the drug loading was decreased, the release of drug from microspheres was decreased.

Ali et al.[38] developed an HBS of metformin as a single-unit floating capsule. Various grades of low-density polymers were used for the formulation of this system. Capsules prepared with HPMC K4M and EC gave the best in vitro percentage release and were taken as the optimized formulation. In vivo studies were carried out in rabbits to assess the buoyancy as well as the pharmacokinetic parameters of the formulation using gamma scintigraphy. The formulation remained buoyant during 5 hours of study in rabbits. The comparative pharmacokinetic study was performed by administration of the optimized HBS capsules and immediate release capsules, both with radiolabeled metformin, using gamma counter. There was an increase in AUC in optimized HBS capsules of metformin when compared with immediate release formulation.

Badve et al.[39] developed hollow calcium pectinate beads for floating-pulsatile release of diclofenac sodium intended for chronopharmacotherapy. In vivo studies by gamma scintigraphy determined on rabbits showed gastroretention of beads up to 5 hours. The floating beads provided the expected two-phase release pattern with initial lag time during floating in acidic medium, followed by rapid pulse release in phosphate buffer. This approach suggested the use of hollow calcium pectinate microparticles as promising floating-pulsatile DDS for site- and time-specific release of drugs acting as per chronotherapy of diseases.

Jain et al.[40] developed a CR system to increase its residence time in the stomach without contact with the mucosa. This aim was achieved through the preparation of FM by the emulsion solvent diffusion technique consisting of calcium silicate Florite RE, FLR) as a porous carrier, repaglinide, an oral hypoglycemic agent, and Eudragit as a polymer. Incorporation of FLR in the microspheres proved to be an effective method to achieve the desired release behavior and buoyancy. The designed systems, combining excellent buoyant ability and suitable drug release pattern, could possibly be advantageous in terms of increased bioavailability of repaglinide.
Sato et al. developed riboflavin containing microballoons (MB) possessing a spherical cavity enclosed within a hard polymer shell as a dosage form characterized by excellent buoyancy in the stomach. MB were prepared by the emulsion solvent diffusion method using enteric acrylic polymers. Riboflavin containing MB were administered orally to each of three healthy volunteers. The pharmacokinetics of riboflavin was investigated by analysis of the urinary excretion. The objective of the investigation was to assess the usefulness of intragastric buoyancy properties in terms of sustained pharmacological action in humans.

Sato et al. developed hollow floatable microspheres with enteric acrylic polymers such as Eudragit S 100 by the emulsion solvent diffusion method. Five different drugs exhibiting distinct water solubilities, such as aspirin, salicylic acid, ethoxybenzamide, indomethacin and riboflavin, could be enclosed in the shell of MB, forming a matrix-like structure, and the release properties of these five drugs entrapped within MB were investigated.

El-Kamel et al. designed an SR system for ketoprofen to increase its residence time in the stomach without contact with mucosa through the preparation of MB by the emulsion solvent diffusion technique. The floating multi-unit system for ketoprofen was prepared using Eudragit RS 100 (ES) alone or in a mixture with the permeable Eudragit RL (ERL). The floating microparticles of ketoprofen prepared with a suitable ratio of ES 100 to ERL provided a convenient dosage form for achieving best performance regarding flow, release and floating properties.

Ohta et al. developed a simple method for the preparation of a silica gel based controlled delivery system with high drug content. Drug (theophylline) loading was carried out by immersing the silica gel in a pre-heated drug solution or suspension. In the next step, the drug-loaded silica gel was coated with HPMC and an aqueous dispersion of EC (Aquacoat) to control the drug release.

Shah et al. prepared in situ cubic phase transforming system of glyceryl monooleate (GMO) which offers protection to the metalloenzyme, seratiopeptidase (STP), in gastric environment and provides delayed and controlled release with no initial burst after oral administration. Effect of magnesium trisilicate (MTS) on floating, proteolytic activity and drug release was studied.

Sato et al. investigated the intragastric behavior of 99mTc-labeled MB and non-floating microspheres (NF) of riboflavin following oral administration in fasted and fed humans by gamma scintigraphy. Simultaneously, pharmacokinetic examination of riboflavin released from MB and NF was conducted in fasted and fed human subjects. The investigation suggests that MB are very useful for improving drug bioavailability, resulting in a more sustained pharmacological action.

Dave et al. developed a gastroretentive DDS of ranitidine hydrochloride using guar gum, xanthan gum, and HPMC. 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. A 3² 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 favored SR of ranitidine hydrochloride from a gastroretentive formulation.

Sato et al. prepared MB of riboflavin by the emulsion solvent diffusion method. The objective of the investigation was to assess the usefulness of intragastric buoyant properties in terms of sustained pharmacological action in humans. NF were prepared in order to effect comparison with MB; moreover, in vivo evaluation of MB and NF in humans was conducted. Pharmacokinetics was examined via analysis of urinary excretion of riboflavin adopted as a model drug following oral administration of MB.

Sato et al. investigated the physiochemical properties to determine the buoyancy of hollow microspheres. It was found that preparation temperature determined the formation of cavity inside the microspheres and the surface smoothness, which in turn determine the floatability and the drug release rate of the MB. The correlation between the buoyancy of MB and there physical properties, e.g., apparent density and roundness of MB was elucidated. The drug loading efficiency of MB with various types of drug was investigated and correlated with the distribution coefficient of drug between dichloromethane and water.

Streubel et al. developed a single-unit FDDS of diltiazem, theophylline and verapamil, which was based on low-density foam power and matrix-forming polymer(s). The drug release patterns can effectively be adjusted by varying simple formulation parameters such as the “matrix-forming polymer/foam power” ratio, initial drug loading, tablet height and diameter, type of matrix-forming polymer, addition of water-soluble and water-insoluble fillers and the use of polymer blends. Thus, desired release profiles adapted to the pharmacokinetic/pharmacodynamic properties of the incorporated drug can easily be provided.

EL-Gibaly et al. prepared floating microcapsules containing melatonin by the ionic interaction of Cs and a negatively charged surfactant, sodium diocyl sulfosuccinate (DOS). The effect of various factors (cross-linking time, DOS and Cs concentration, as well as drug/polymer ratio) on microcapsule properties was evaluated. Cs concentration and drug/polymer ratio had a remarkable effect on drug entrapment in DOS/Cs microcapsules.

Patel et al. prepared FM of metformin hydrochloride by non-aqueous emulsification solvent evaporation technique using EC as the rate-controlling polymer. The experimental design supported product development and optimization procedure yielded the desired microspheres with drug release equivalent to those of the marketed single-unit dosage forms with the added advantage of floatability in gastric juice for prolonged slow release.

Choi et al. prepared alginate beads of riboflavin for FDDS. The effects of gas-forming agents CaCO₃/NaHCO₃ on beads' size, floating ability, pore structure, morphology, release rate and mechanical strength of floating beads were investigated. In general, CaCO₃ formed smaller and stronger floating beads than NaHCO₃. Although CaCO₃ is a less effective gas-forming agent than NaHCO₃, it produced superior floating beads with enhanced control of drug release rates.

Srivastava et al. prepared FM of cimetidine by the solvent evaporation method using the polymers HPMC and EC. In vitro data obtained for FM showed excellent floatability, good buoyancy and prolonged drug release. Microspheres of different sizes and drug content could be obtained by varying the formulation variables.

Bulgarelle et al. prepared casein–gelatin beads of fluorescein sodium by emulsification extraction method. Casein emulsifying properties cause air bubble incorporation and the formation of large holes in the beads. The study shows that cavities act as an air reservoir and enable the beads to float. Therefore, casein seems to be a material suitable for the inexpensive formation of reservoirs for floating systems.

Krogel et al. developed and evaluated floating and pulsatile DDS of chlorpheniramine maleate based on a reservoir system consisting of a drug-containing effervescent core and a polymeric coating. Ideally, the expansion of the core could result in

1. a floating dosage form with a prolonged residence time and extended drug release or
2. a pulsatile dosage form, in which the drug is released rapidly in a time-controlled fashion after rupturing of the coating.

In order to achieve these goals, the properties of the effervescent core and the coating were investigated and optimized.

Sakr et al. developed a programmable CR DDS. The device in the form of a non-digestible oral capsule was designed to utilize an automatically operated geometric obstruction that keeps the device floating in the stomach and prevent it from passing through the remainder of the GIT. Different viscosity grades of HPMC were employed as model eroding matrices.

Iannuccelli et al. carried a preformulation study to optimize the in vitro floating ability of an air compartment multiple-unit system. Each unit was formed by a coated bead composed of a calcium alginate core separated by an air compartment from a calcium alginate/polyvinyl alcohol (PVA) membrane. The floating ability increased with the increase in PVA concentration and molecular weight and it was found to be excellent when using PVA 100,000 at a concentration of at least 5%.

Yang et al. proposed a new strategy for the triple drug treatment (tetracycline, metronidazole and bismuth salt) of Helicobacter pylori associated peptic ulcers. The design of the delivery system was based on the swellable asymmetric triple layer tablet approach, with floating feature in order to prolong the GRT of delivery system. The floating feature could possibly prolong the GRT of this system to maintain high localized concentration of tetracycline and metronidazole. The developed delivery system has the potential to increase the efficacy of the therapy for H. pylori associated ulcers and to improve patient compliance.

Streubel et al. developed floating microparticles composed of polypropylene foam, Eudragit RS, EC, and polymethyl metha acrylate (PMMA) 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 RS. This could be attributed to the different premeabilities of the drug in these polymers and drug distribution within the system.

Iannuccelli et al. assayed the intragastric behavior of a floating multiple-unit system in humans. The floating unit used in this study was composed of a calcium alginate core separated by an air compartment from a calcium alginate/polyvinyl alcohol membrane. In the fasted state, the intragastric buoyancy of the system did not influence its GRT. In the fed state after the meal, all floating units showed a floating time (FT) of about 5 hours and a GRT prolonged by about 2 hours over the control. In the fed state after a succession of meals, most of the floating units showed an FT of 6 hours and a GRT prolonged by about 9 hours over the control.

Whitehead et al. developed freeze-dried calcium alginate multiple-unit floating dosage forms (FDFs) which demonstrated favorable in vitro floating characteristics. The aim of this study was to investigate the in vivo behavior of this system compared to a multiple-unit non-floating dosage form manufactured from an identical material. The results of this study suggest that in the fed state, these FDFs have the potential for sustained drug delivery for either local or systemic purposes.

Burns et al. developed a dissolution method for a floating dosage form using HALO propranolol capsules containing propranolol base dissolved in oleic acid. A modified paddle dissolution method, in which the paddle blades were set to the surface of the dissolution medium, was shown to be effective for assessing HALO propranolol capsules, characterized by having both rapid release and SR properties.

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

Bussemeyer et al. developed and evaluated an alternative pulsatile DDS consisting of a drug containing hard gelatin capsule, a swelling layer and an insoluble polymeric coating, which used only approved excipients and was prepared by standard pharmaceutical procedures. The lag time was controlled by the hydration/expansion of the swelling layer and subsequent complete rupturing of the polymer coating, allowing a fast drug release.

Basak et al. developed a floating matrix tablet of ciprofloxacin using gas generating agent (sodium bicarbonate) and hydrophilic polymer (HPMC). Formulation was optimized on the basis of floating time and in vitro drug release. It is evident from this investigation that gas powered floating matrix tablet could be a promising delivery system for ciprofloxacin with SR action and improved drug availability.

Yang et al. developed a novel, multiple- and concentrations unit FDDS of microspheres with MB inside, from xanthan gum (XG) and gelatin (GA), by a water-in-oil method using theophylline as the model drug. Four formulations with different ratios of the two polymers were prepared, and size distribution, encapsulation efficiency, floating behavior, release and morphology were investigated.

Jain et al. prepared floating flaps containing albendazole and closantel by casting techniques, employing poly (di-lactide-co-glycolate, 75:25) Eudragit RL 100 and Eudragit RS 100, along with polyethylene glycol 400 as plasticizer. This study was conducted with an objective to develop SR floating flap for continuous administration of low level of anthelmintics such as albendazole and closantel and controlling helminthes in grazing ruminants through prolonged reduction in levels of pasture contamination prior to and during periods when development and survival of face living stages are particularly favored.

Patel et al. developed intragastric FDDS of cefuroxime axtil. The full factorial design was employed to evaluate contribution of HPMC K4M/HPMC K100 LV ratio (polymer blend) and sodium lauryl sulfate (SLS) on drug release from HPMC matrices. It was found that polymer blend and SLS significantly affect the time required for 50% of drug release, percentage drug release at 12 hours, release rate constant and diffusion exponent.

Shimpi et al. 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. In vivo floating ability was studied by gama-scintigraphy in six healthy human volunteers and the results showed that the formulation remained in the stomach for 6 hours.

Patel et al. prepared floating tablets of ranitidine hydrochloride and optimized the process for type of filler; different viscosity grades
of HPMC and its concentration. Two fillers, namely, Avicel pH 102 and Tablettose 80, were used. Three different viscosity grades of HPMC were used. It was observed that type of filler and viscosity had a major influence on drug release from hydrophilic matrices as well as on floating properties.

Muthusamy et al.\textsuperscript{[72]} prepared lansoprazole floating micro pellets by emulsion solvent diffusion technique to improve their residence time in the stomach, without contact with the mucosa. The prepared floating micro pellets can be used for SR in gastric media for more than 12 hours, thereby improving the oral bioavailability of lansoprazole by increasing GRT because it helps to retain in the stomach for a longer period.

EL-Kamal et al.\textsuperscript{[73]} prepared ketoprofen floating microparticles by emulsion solvent diffusion technique using Eudragit RS and Eudragit RL in a ratio of 1:1 and studied the gastric ulcerogenic effect of ketoprofen floating microparticles in comparison with the plain ketoprofen. The ketoprofen loaded microparticles were found to be less ulcerogenic and they protected the stomach probably by preventing the intimate contact of ketoprofen with gastric mucosa.

Gohel et al.\textsuperscript{[74]} developed a more relevant in vitro dissolution method to evaluate a carbamazepine FDDS. Carbamazepine floating tablets were prepared by wet granulation technique. The performance of the modified dissolution apparatus was compared with US Pharmacopeia (USP) dissolution apparatus 2. The drug release followed zero-order kinetics. The proposed test may show good in vitro–in vivo correlation since an attempt is made to mimic the in vivo conditions such as gastric volume, gastric emptying and gastric acid secretion rate.

Marketed Products of FDDS

The last three decades of intensive research work has resulted in the development of the five commercial FDDS [Table 1].

Advantages of FDDS

Sustained drug delivery

Drug absorption from oral CR dosage forms is often limited by the short GRT available for absorption. However, HBS type dosage form can remain in the stomach for several hours, and therefore, significantly prolongs the GRT of numerous drugs. These special dosage forms are light, relatively large in size and do not easily pass through the pylorus which has an opening of approximately 0.9–1.9 cm.\textsuperscript{[75]} These systems have a bulk density of < 1 as a result of which they can float on the gastric contents. The assumed prolongation in the GRT is postulated to cause sustained drug release behavior.

<table>
<thead>
<tr>
<th>Table 1: Marketed preparations of floating drug delivery system</th>
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<tr>
<td><strong>Product</strong></td>
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<tr>
<td>Madopar</td>
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<tr>
<td>Valrelease</td>
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<tr>
<td>Topalkan</td>
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<tr>
<td>Almagate Flatcoat</td>
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<td>Liquid Gavison</td>
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</table>

Site-specific drug delivery

A floating dosage form is a feasible approach, especially for drugs such as furosemide and riboflavin, which have limited absorption site in the upper small intestine. In fact, the absorption of furosemide has been found to be site-specific, the stomach being the major site of absorption, followed by the duodenum. This property prompted the development of a monolithic floating dosage form of furosemide, which could prolong the GRT, and thus, its bioavailability was increased.\textsuperscript{[76]} FDDS can be used as carriers for drugs with so-called absorption window, those substances, for example, antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides, and tetracyclines) are taken up only from very specific sites of the GI mucosa. In addition, by continually supplying the drug to most efficient site of absorption, the dosage form may allow for more effective oral use of peptide and protein drug such as calcitonin, erythropoietin, vasopressin, insulin, low molecular weight heparin and LHRH.

Absorption enhancement

Drugs that have poor bioavailability because their absorption is restricted to the upper GI tract can be delivered efficiently, thereby maximizing their absorption and improving their absolute bioavailabilities.

Reduce side effect

FDDS of non-steroidal anti-inflammatory drugs is very effective for CR as well as it reduces the major side effect of gastric irritation; for example, FM of indomethacin are quiet beneficial for rheumatic patients.

Pharmacokinetic advantages

FDDS provides an easy way of maintaining constant blood level with an ease of administration and better patient compliance. Floating dosage form with SR characteristics can also be expected to reduce the variability in transit performance and various pharmacokinetic parameters.

Apart form the aforementioned advantages, floating systems are particularly useful for acid soluble drugs, drugs which are poorly soluble or unstable in intestinal fluids and those which may undergo abrupt changes in their pH-dependent solubility due to factors such as food, age and pathophysiological conditions of the GI tract.

FDDS can greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentration at the gastric mucosa, thus eradicating H. pylori from the submucosal tissue of the stomach and making it possible to treat stomach and duodenal ulcers, gastritis and esophagitis. The development of such systems allows administration of non-systemic, controlled release antacid formulations containing calcium carbonate and also locally acting antulcer drug in the stomach, e.g., lansoprazole. Buoyant microparticles are considered as a beneficial strategy for the treatment of gastric and duodenal cancers.
Evaluation of Gastroretentive Dosage Forms

FDDS is evaluated for its effect on GRT. The various parameters include their micrometric properties such as particle size, tapped density, compressibility index, true density and flow properties. The test for buoyancy and in vitro drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 37°C. Dissolution tests are performed using the USP dissolution apparatus. Samples are withdrawn periodically from the dissolution medium, replenished with the same volume of fresh medium each time and then analyzed for their drug contents after an appropriate dilution. In vivo evaluation for gastroretention is carried out by means of X-ray and/or gamma scintigraphic monitoring of the dosage form transit in the GI tract. The modern technique of gamma scintigraphy now makes it possible to follow the transit behavior of dosage form in human volunteers in a non-invasive manner.

Limitations

One of the disadvantages of floating systems is that they require a sufficiently high level of fluids in the stomach for the drug delivery buoy to float therein and to work efficiently. However, this limitation can be overcome by coating the dosage form with bioadhesive polymers, thereby enabling them to adhere to the mucous lining of the stomach wall. Alternatively, the dosage form may be administered with a glass full of water (200–250 ml). Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids. Drugs such as nifedipine, which is well absorbed along the entire GI tract and undergoes significant first-pass metabolism, may not be desirable candidates for FDDS, since the slow gastric emptying may lead to reduced systemic bioavailability of FDDS for drugs that are irritant to gastric mucosa.

Future Prospects

In recent years, scientific and technological advancements have been made in the research and development of rate-controlled oral drug delivery system by overcoming physiological adversities such as short GRT and unpredictable GET. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery system (FDDS), also known as hydrodynamically balanced system (HBS), swelling and expanding system, polymeric bioadhesive system, modified-shape system, high-density system and other delayed gastric emptying devices.

FDDS has emerged as an efficient means of controlling release of many drugs. The control of GI transit profiles could be the focus for the next two decades and this might result in the availability of new products with new therapeutic possibilities and substantial benefit for patients. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large numbers of companies are focusing toward commercializing this technique.

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