RECENT ADVANCEMENT IN FLOATING DRUG DELIVERY SYSTEM AND CURRENT APPROACHES

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ABSTRACT
The purpose of writing this review on FDDS was to compile the recent literature with special focus on the approaches, principal mechanism and recent advancement of floatation to achieve gastric retention. FDDS are designed to prolong the gastric residence time after oral administration, at particular site and controlling the release of drug especially useful for achieving controlled plasma levels as well as improving bioavailability. FDDS have bulk density less than gastric fluids that have sufficient buoyancy to float over the gastric contents and remain in the stomach for longer duration of time without affecting gastric emptying rate and thereby improve the bioavailability of drugs. Several approaches are currently utilized in the prolongation of GRT including floating drug delivery system, swelling and expanding systems, polymeric bioadhesive systems, high density systems, modified shape systems and other delayed gastric emptying devices. Floating dosage forms are emerging as promising dosage forms which can be prepared as tablets, capsule by adding suitable ingredients as well as by gas generating agents. Various components like hydrocolloids, inert fatty materials and buoyancy increasing agents can be used to formulate floating dosage forms. Various categories like antacids, antidiabetic, antifungal and anticancer drugs are formulated into FDDS. FDDS provides local delivery to specific region like stomach and proximal part of the small intestine and it also shows better bioavailability and improved therapeutic activity and substantial benefits to
patients. The recent development of FDDS such as physiological and formulation variables affecting gastric retension approaches to design single unit and multiple unit floating systems and their classification such as effervescent and non effervescent systems and formulation aspects are covered in detail. This review.

**KEYWORDS:** Floating drug delivery system, approaches, application, marketed products, mechanism, recent advancements, patents, manufacturing techniques, characterization.

**INTRODUCTION**

The oral route is the most promising route of drug delivery. Controlled-release drug delivery system (CRDDS) provide drug release at a predetermined, predictable and controlled rate and provide the benefits like maintenance of optimum therapeutic drug concentrations in blood with predictable and reproducible release rates for extended time period; enhancement of duration of activity for short half life drugs; elimination of side effects; reducing frequency of dosing and wastage of drugs; optimized therapy and better patient compliance.

Effective oral drug delivery may depend upon factors such as gastric emptying process, gastrointestinal transit time of dosage forms, drug release from the dosage form and site of absorption of drugs. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profile, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed. The gastric emptying of dosage forms in humans is affected by several factors. Because of which wide inter and intra subject variations are observed.

Since many drugs are well absorbed in the upper part of the gastrointestinal tract, such high variability may lead to non uniform absorption and makes the bioavailability unpredictable. Hence a beneficial delivery system would be one which possess the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site (i.e, upper part of the small intestine).

The identification of new diseases and the resistance shown towards the existing drugs called for the introduction of new therapeutic molecules. In response, a large number of chemical
entities have been introduced of which some have absorption all over the gastrointestinal tract (GIT), some have absorption window (i.e., absorption sites, especially the upper part of the small intestine) and some drugs have poor solubility in intestinal media. The drugs belonging to the second and third categories and the drugs which are required for local action in the stomach, require a special delivery system.

**Definition:** Floating system or dynamically controlled systems are low density systems that have sufficiently buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. This results in an increased gastric retension time and a better control of the fluctuations in plasma drug concentrations. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres.¹

**Advantages of floating drug delivery system**

1) Improved drug absorption, because of improved gastric residence time and more time spent by the dosage form at its absorption site.
2) Controlled delivery of drugs
3) Delivery of drugs for local action in the stomach.
4) Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
5) Treatment of gastrointestinal disorders such as gastro-oesophageal reflux.
6) Simple and conventional equipment for manufacture.
7) Ease of administration and better patient compliance.
8) Site specific drug delivery.²

**Disadvantages of floating drug delivery system**

1) There are certain situations where gastric retension is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of such drugs in the stomach is unwanted.
2) Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems.
3) Furthermore, other drugs, such as Isosorbite Dinitrate that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retension.²
CURRENT APPROACHES TO GASTRIC RETENTION

A) Bio/Mucoadhesive systems
Bio/Mucoadhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the GRT of drug delivery system (DDS) in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane. The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDDS based on bioadhesive/mucoadhesive polymers. The ability to provide adhesion of a drug (or a delivery system) to the GI walls provides a longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect.[3]

B) Swelling and expanding systems
There are the dosage forms, which after swallowing swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be named as “plug type systems,” since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18mm in their expanded state. The formulation is designed for gastric retension ad controlled delivery of the drug into the gastric cavity for several hours even in the fed state. The balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system maintaining its physical integrity for prolonged period.[4]

C) High density system
These systems with a density of about 3g/cm³ are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8g/cm³ acts as a threshold value after which such systems can be retained in the lower part of the stomach. High density formulations includes coated pellets. Coating is done by heavy inert materials such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc.[5]

D) Low density systems
To avoid premature evacuation of drug through the pyloric sphincter low density systems (≤1g/cm³) with immediate buoyancy have been developed. They are made of low density materials, entrapping oil or air. Most are multiple unit systems, and are also called microballoons because of low density core.[4]
E) Raft forming systems

The basic mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. The raft floats because of the buoyancy created by the formation of CO$_2$ and acts as a barrier to prevent the reflux of gastric contents like HCl and enzymes into the oesophagus. Usually, the system contains a gel forming agents and alkaline bicarbonate or carbonates responsible for the formation of to make the system less dense and floats on the gastric fluids.\cite{6}

F) Magnetic systems

This approach to enhance the GRT is based on the simple principle that the dosage form contains a small internal magnet, and a magnet is placed on the abdomen over the position of the stomach. Although magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance. The technological approach in rabbits with bioadhesive granules containing ultra-fine ferrite. They guided them to oesophagus with an external magnet for the initial 2 minutes and almost all the granules were retained in the region after 2 hours.\cite{7}

G) Floating Systems

Floating drug delivery systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the released of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. Floating systems can be classified into two distinct categories:- Non effervescent systems and effervescent systems.\cite{8}

Floating systems are classified into two types 1) Effervescent systems 2) Non effervescent systems.

1. Effervescent systems:- These are matrix type of systems prepared with the help of swellable polymers such as methyl cellulose and chitosan and various effervescent compounds, eg. Sodium bicarbonate, tartaric acid and citric acid. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1.\cite{9}
Effervescent systems are classified into two types i) Gas generating systems ii) Volatile liquid systems.

i) **Gas generating systems:** These are matrix type of systems prepared with the help of swellable polymers such as methyl cellulose and chitosan and various effervescent compounds, eg. Sodium bicarbonate, tartaric acid and citric acid. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. [9]

ii) **Volatile liquid systems:** The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid eg. Ether, cyclopentane, that gasifie at body temperature to cause inflation of chamber in the stomach. [10]

2. **Non effervescent systems:**- One or more gel forming, highly swellable cellulosic hydrocolloids Hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcellulose, polysaccharides or matrix forming polymers (eg. Polycarbophil, polyacrylates and polystyrene) are incorporated in high level (20-75%) to tablets or capsules. [11]

These are further classified as

i) **Colloidal gel barrier systems:** Hydrodynamically balance systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporates a high level of one or more gel forming highly swellable cellulose type hydrocolloids eg. HEC, HPMC, NaCMC, polysaccharides and matrix forming polymer such as polycarbophil, polyacrylates and polystyrene incorporated either in tablets or in capsules. On coming in contact with gastric fluids, he hydrocolloids in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than a unity and confers buoyancy to this dosage form. [10]

ii) **Microporous compartment systems/Hollow microspheres:** This technology is based on the encapsulation of drug reservoir inside a microporous compartment with aperture along its top and bottom wall. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolved drug. In stomach the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the aperture, dissolves the drug, and carries the dissolved drug for continuous transport across the intestine for absorption. [12]
iii) Alginate beads: Multiple unit floating dosage form have been developed from freeze dried calcium alginate. Spherical beads of approximately 2.5mm in diameter can be prepared by dropping a sodium alginate solution into a aqueous solution of calcium chloride causing precipitation of calcium alginate. The beads are then separated snap and frozen in liquid nitrogen, and freeze dried. This results in the formation of aporous sytems which remain buoyant in the stomach.[12]

iv) Hydrodynamically balanced systems: This system contains drug with gel forming hydrocolloids formulated into single unit dosage form. Upon contact with gastric fluids, the hydrocolloids swells to form a gel barrier which facilitates the system to remain buoyant in the stomach.[4]

v) Layered tablets: These may be of single layer and double layer

a) Single layered floating tablets: This type of tablet contains drug mixed with gel forming hydrocolloids and other excipients. Upon contact with gastric fluids, the hydrocolloid swell and maintain bulk density less than one and hence remain buoyant in the stomach.

b) Double layer floating tablets: This type of tablet contains two layers, one of which is immediate release layer and the other is sustained release layer containing drug and hydrocolloids which remains in the stomach for prolonged period of time.[4]

Recent advances in floating dosage forms

Recent advancement in floating dosage forms includes Tablet, Capsule, Pellets, Gel systems, Microspheres are discussed below.

A. Tablets

1. Treatment of hypertension: i) Floating tablets of Atenolol were prepared using HPMC K4M, K15M, HPMC K100M (as a release retardant polymers), sodium bicarbonate (as the gas generating agent), microcrystalline cellulose, and other excipients like magnesium stearate and talc by direct compression method are prepared to increase the gastric retension and to improve the bioavailability of the drug. The floating tablets extended the drug release upto 8 hour. Atenolol is an antihypertensive drug.[13]

ii) Floating drug delivery system of antihypertensive drug Propanolol HCl were prepared by using a synthetic hydrophilic polymer polyethyleneoxide of different grade such as PEO WSR N-12K and PEO 18 NF as release retarding polymers, calcium carbonate as gas
generating agent and other excipients like magnesium stearate by direct compression method which exhibited higher retarding properties and good buoyancy properties. Propanolol HCl is an antihypertensive drug used in the treatment of hypertension.\cite{14}

**2. Treatment of gastric disorders:** Floating tablets of Metoclopramide HCl were prepared by using HPMC K4M, Eudragit RS 100, guar gum as polymers, sodium bicarbonate (as gas generating agent) and other excipients like PVP K30 and lactose by direct compression method. The developed floating tablet of Silymarin may be used to prolong drug release for at least 12 hours thereby improving the bioavailability and patient compliance. Metoclopramide is Antidopaminergic and GI stimulant.\cite{15}

**3. Treatment of ulcer:** i) Floating matrix tablets for Curcumin were prepared using psyllium husk as release controlling polymer and to compare the release pattern with synthetic polymers like HPMC K15M and HPMC K100M and other excipients like sodium bicarbonate, citric acid magnesium stearate, talc, PVP K30, hydrochloric acid, potassium chloride potassium dihydrogen phosphate and disodium hydrogen phosphate. Release rate of the formulation containing psyllium husk in combination with HPMC K15M more than the formulation containing similar amount of HPMC K100M which enhanced the floating duration and helps to maintain the dimensional stability. Curcumin is a diarylheptanoid used in the treatment of ulcer.\cite{16}

ii) Gastroretentive drug delivery of Troxipide were prepared using polymers Pluronic F127 and Polyox 205 WSR, and other excipients like sodium bicarbonate, citric acid, dicalcium phosphate, talc and magnesium stearate by direct compression technique, which exhibited prolonged drug release of more than 10 hours and site specific drug delivery. Increased gastric residence time and enhanced bioavailability can be achieved. Troxipide is a novel gastroprotective agent with antiulcer, anti-inflammatory and mucus secreting properties.\cite{17}

**4. Treatment of muscular pain:** Floating matrix tablet of Tizanidine HCl were prepared by using effervescent gas generating systems by incorporating sodium bicarbonate by wet granulation method. Various viscosity grade polymers like HPMC (K4M and K400M) and Psyllium Husk are used which plays a major role in controlling the drug release and improves the gastric residence time for 12 hours which increases bioavailability of the drug thus reduces frequency of dosing. Tizanidine HCl act as an agonist on centrally acting \(\alpha_2\) adrenergic receptors, as it is an imidazoline derivative. It also act as an prokinetic agent
which restore motility throughout the GI tract. Tizanidine HCl is a muscle relaxant used in management of spasticity.\[18\]

5. Treatment of bacterial infections:- Floating tablets of Ofloxacin were prepared using HPMC K4M, K15M, carbopol 934P chitosan and magnesium stearate by direct compression method. Floating tablets exhibited prolonged and controlled drug release upto 99% which increased its gastric residence time and improved bioavailability, thus reduces frequency of dosing with better patient compliance. Ofloxacin is synthetic antibiotic consider to be a second generation fluoroquinolone.\[19\]

B. Capsules
1. Treatment of viral infection: Oseltamivir capsules were prepared by using various excipients like pregelatinized starch, croscarmelose sodium, povidone K30, talc, and sodium stearyl fumerate by both wet granulation and dry granulation method. Capsules were stable, pharmaeutically equivalent, low cost and quality improved. Oseltamivir is an antiviral drug, neuroaminidase inhibitor used in the treatment and prophylaxis of both influenza A and influenza B.\[20\]

2. Treatment of bacterial infection: Hydrodynamically balanced system for third generation Cephalosporin as single unit floating capsules were prepared using polymers like HPMC K4M, ethyl cellulose and PEG 6000. All the HBS capsules of Cefixime Trihydrate exhibited prolonged drug release upto 12 hours compared to capsule containing only pure drug. The HBS capsules were stable. Cefixime trihydrate is an antibacterial agent.\[21\]

3. Treatment of ulcer: Floating ring capsules dosage form of Levofloxacin were prepared using HPMC, sodium CMC, sodium alginate and carbopol 934 P. The capsules exhibited prolonged drug release upto 8 hours which improved gastric residence time and bioavailability. Levofloxacin is an antifulcer agent.\[22\]

4. Treatment of parkinsonism disease: Floating capsule of Antiparkinsonism drug were prepared using polymers like HPMC (K15M, K100M), BHA, BHT and citric acid. Capsules exhibited prolonged drug release upto 12 hours, Capsules were found to be stable with increased gastric residence time and improved bioavailability.\[23\]
C. Microballoons

1. Treatment of hypertension: i) Hollow microballoons of Telmisartan were prepared using polymers like Hydroxypropylmethylcellulose (HPMC), Eudragit RS100 as polymers and dichloromethane, ethanol and polyvinylalcohol as organic solvents by emulsion solvent diffusion technique in order to extend the drug release for about 12 hours in the upper GIT, which may result in enhanced absorption and thereby improved bioavailability. Telmisartan is a non peptide angiotensin II receptor antagonist.\[24\]

ii) Pentoxifylline loaded microballoons were prepared using different concentrations of polymers like HPMC K4M and ethyl cellulose and tween 80. Ethanol and dichloromethane as organic solvent. The floating microballoons have been utilized to obtain prolonged and uniform release in the stomach and to prolong gastric residence time. Pentoxifylline trisubstituted xanthine derivative is an haemorrheologic agent used for the treatment of peripheral arterial disease and intermittent claudication.\[25\]

2. Treatment of diabetes: i) Floating microballoons of Glipizide were prepared using hydrophilic polymers Hydroxypropylmethylcellulose (HPMC) and Eudragit RS100. PVA, dichloromethane and ethanol as organic solvents by emulsion solvent evaporation technique showed excellent floatability, good buoyancy and prolonged drug release of 12 hours. Which increased its gastric residence time and improve bioavailability. Glipizide is an effective antidiabetic drug particularly in type II diabetes mellitus (non insulin dependent diabetes mellitus).\[26\]

ii) Hollow microballoons loaded with Nateglinide were prepared in their outer polymer shell using eudragit RS100 as a polymer by emulsion solvent diffusion method in order to achieve an extended release in the upper GIT, which may result in reduction in dosing frequency thereby improving patient compliance. The prepared microspheres exhibited prolonged drug release (24hrs) and remained buoyant for ≥ 12 hours. Nateglinide is an antidiabetic drug belongs to the meglitinide category.\[27\]

3. Treatment of gastric disorders: Domperidone loaded microballoons were prepared using polymers like Eudragit RS 100, HPMC PVA, Ethanol, dichloromethane as organic solvents and monostearin as membrane forming agent. The designed system, combining excellent buoyant ability and suitable drug release pattern over 12 hours and increased bioavailability
of Domperidone. Domperidone is a synthetic benzimidazole compound that act as a dopamine D2 receptor antagonist.[28]

4. Treatment of muscular pain: Microballoons of Baclofen were prepared by solvent diffusion and evaporation procedure using various combinations of ethylcellulose (release retardant) and HPMC K4M (release modifier) dissolved in a mixture of dichloromethane and methanol. The buoyant Baclofen microballoons provide a promising gastroretentive drug delivery system to deliver Baclofen in spastic patients with sustained release rate of not less than 10 hours. Baclofen is a skeletal muscle relaxant.[29]

D. Microspheres

1. Treatment of diabetes: i) Glipizide floating microspheres were prepared using varying concentrations of eudragit RS 100 HPMC, dichloromethane, ethanol and polyvinylalcohol as organic solvents by emulsification solvent diffusion method. Floating microspheres of Glipizide may prolong drug release of 12 hours, thereby improving bioavailability and enhance opportunity of absorption in stomach. Glipizide is a second generation oral sulfonylurea hypoglycemic agent used in lowering the blood sugar levels in patients with non insulin dependent diabetes mellitus.[30]

   ii) Glimipride microspheres were prepared using polymers such as ethylcellulose and eudragit R100 and eudragit RL100, eudragit RS 100 and dichloromethane .PVA as organic solvents were successfully prepared by emulsification solvent evaporation method. Microspheres showed improved bioavailability and giving a prolonged drug release for 12 hours. Microspheres exhibited improved oral bioavailability and increased gastric residence time. Glimipride is an antidiabetic drug used in the treatment of type II diabetes (non insulin dependent diabetes mellitus).[31]

   iii) Resin-based multiparticles of Repaglinide were prepared using polymers like cholestyramine resin, ethylcellulose, sodium bicarbonate and dichloromethane and PVA as organic solvents for encapsulation. Floating microspheres containing drug resin complex were able to sustain the drug release in an effective manner for 8 hours and proven in vivo effectiveness by reducing blood glucose level for a longer duration. Repaglinide, a fast and short acting meglitinide analog.[32]
iv) Floating microspheres of Nateglinide were prepared using polymers like sodium alginate, eudragit RS 100 and dichloromethane, acetonitrile and PVA as organic solvents by emulsion gelation method. Microspheres of Nateglinide can sustain the drug release for 12 hours which increased the gastric residence time and enhanced bioavailability. Nateglinide is an oral antihyperglycemic agent used for the treatment of non-insulin dependent diabetes mellitus.\[33]\n
2. Treatment of leukemia: Dastanib floating microspheres were prepared using biocompatible polymers like eudragit S100 ethylcellulose and dichloromethane, methanol, glyceryl monostearate and PVA as organic solvents by emulsion solvent diffusion method. Microparticulate floating dosage form of Dastanib can be successfully designed to give prolonged release of drug between 85-93% and hence improved bioavailability. Dastanib is a tyrosine kinase inhibitor.\[34]\n
3. Treatment of ulcer: Microspheres of Pantoprazole were prepared using polymers like polyvinylpyrrolidone and hydroxypropylmethylcellulose were developed by coacervation technique. Microspheres of Pantoprazole were able to sustain the drug release of 88% and hence improved gastric retention time and enhanced bioavailability can be achieved. Pantoprazole is a proton pump inhibitor used in the treatment of ulcer.\[35]\n
E. Microcarriers (Beads)

1. Treatment of ulcer: Floating microcarriers of Famotidine were prepared using eudragit S100 as a polymer and dichloromethane, ethanol and PVA as organic solvents by modified solvent evaporation technique. Microcarriers showed prolonged drug release upto 20 hours, hence increased the gastric residence time in the stomach and improved bioavailability. Microcarriers are used to target stomach ulcers. Famotidine is a competitive histamine H-2 receptor antagonist which is used to treat peptic ulcer and gastroesophageal reflux disease.\[36]\n
2. Treatment of bacterial infection: Floating microcarriers of Cefixime were prepared using sodium alginate and HPMCK5 in different concentrations and with constant concentration of calcium chloride and light liquid paraffin by emulsion gelation method. The prepared Cefixime floating microcarriers exhibited prolonged drug release (12 hours)and remained buoyant for ≥10 hours. Cefixime is a third generation antibiotic used in the treatment of urinary tract infection bronchitis and gonorrhoea.\[37]\n
3. Treatment of gastric disorders: Alginate based floating pellets of Bromhexine were prepared using hydroxypropylmethylcellulose (HPMC) (HPMC K4M and HPMC K100LV), sodium alginate, calcium chloride by extrusion/spheronisation technique. Floating pellets showed prolonged drug release with improved gastric residence time and bioavailability. Bromhexine is an expectorant and mucolytic agent.\(^{[38]}\)

4. Treatment of hypertension: i) Alginate poloxamer floating beads of Losartan potassium were prepared using different concentrations of sodium alginate as the foam stable agent, calcium chloride and poloxamer (poloxamer 188 and poloxamer 407) as a foaming agent by foam technology. The gastroretentive floating beads of Losartan Potassium were formulated to increase the residence time in the stomach and to sustain the release behaviour of the drug upto 73-88\% and increases drug bioavailability. Losartan potassium is an angiotensin receptor blocker used to treat hypertension.\(^{[39]}\)

ii) Hollow calcium alginate beads were prepared for floating pulsatile release of Valsartan intended for chronopharmacotherapy using potassium bicarbonate, methanol, acetic acid and sodium alginate and calcium chloride as a crosslinking agent. The prepared beads exhibited drug release upto 6 hours which increased the gastric residence time and improved bioavailability. Floating pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release. Valsartan is an angiotensin receptor blocker used to treat hypertension.\(^{[40]}\)

5. Treatment of diabetes: Sustained release floating beads of Metformin hydrochloride were prepared using sodium alginate, HPMC, calcium chloride and sodium bicarbonate. The prepared beads showed controlled release and alginate could be serve as an effective carrier for highly water soluble antihyperglycaemic agents like MH for the sustained release drug delivery upto 12 hours which increased the gastric residence time ad improved bioavailability. Metformin HCl is an antidiabetic agent used in the treatment of type II (non insulin dependent) diabetes mellitus.\(^{[41]}\)

F. Pulsatile drug delivery system

1. Treatment of acute migraine attacks: Modified pulsincap drug delivery system of Rizatriptan benzoate were prepared using polymers like HPMC K4M and methanol as organic solvent by wet granulation method. Pulsincap formulation of Rizatriptan Benzoate successfully targeted to colon for the treatment of migraine. Drug release over a period of 5-
18 hrs can be achieved from treated gelatin capsule and hydrogel plug which increased the gastric residence time and improved bioavailability. Rizatriptan Benzoate is a serotonin 5-H1 receptor agonist.\cite{42}

2. Treatment of ulcer: Pulse type profile of Lansoprazole using hydrophilic polymers HPMC (HPMC K4M, HPMC K15M, HPMC K100M), dibasic calcium phosphate, microcrystalline cellulose and other excipients like sodium starch glycollate, lake sunset yellow, lake quinolone yellow, magnesium stearate, sodium hydroxide, potassium dihydrogen phosphate and HCl by compression coating technique. By combining different HPC viscosity grades it is possible to obtain a time lags of 3 to 9 hours. Compression coating tablets utilizing HPMC in the outer shell gives timed release profile. The use of hydrophilic polymer with erodible and gellable properties in the dry coating development of pulse type drug release achieved. The formulation is administered at bed time provides nocturnal recovery of gastric acid secretion by releasing drug from formulation in time controlled manner. Lansoprazole is a proton pump inhibitor used to treat ulcer.\cite{43}

3. Treatment of hypertension: i) Press coated floating pulsatile drug delivery system of Lisinopril were prepared using superdisintegrants like crosspovidone and crosscarmellose sodium by direct compression method. A press coated tablet (barrier-layer) contained the polymer carrageenan, xanthan gum, HPMC K4M and HPMC K15M. The buoyant layer was optimized with HPMC K100M, sodium bicarbonate and citric acid and other excipients used are lactose, magnesium stearate. Pulsatile system exhibited drug release upto 99% which increased gastric residence time and improved bioavailability. Lisinopril is an angiotensin-converting enzyme (ACE inhibitor), primarily used for the treatment of hypertension, congestive heart failure and heart attack. It belongs to BCS class III.\cite{44}

ii) Compression coated floating pulsatile drug delivery system of Bisoprolol was developed using polyox WSR 205 and polyox WSR N12 K, HPMC K4M, HPMC K100M, crosscarmellose sodium, microcrystalline cellulose and other excipients like magnesium stearate sodium bicarbonate and citric acid by direct compression method. Floating pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release at 4 hours which improved bioavailability and increased gastric residence time. Bisoprolol is a cardioselective β1 adrenergic blocking agent.\cite{45}
2. Treatment of inflammation and pain: Floating press coated pulsatile release of Aceclofenac tablets were prepared using sodium starch glycolate, hydroxypropylmethylcellulose and other excipients like sodium bicarbonate and magnesium stearate by direct compression method. Floating press coated pulsatile drug delivery system intended for treatment of early morning stiffness and symptomatic relief from pain in patients with rheumatoid arthritis with a distinct predetermined lag time of 8 hours which increased the gastric residence time and improved bioavailability. Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID). [46]

3. Treatment of bacterial infection: Gastroretentive floating pellets of Metronidazole were prepared by ionic gelation using different quantities of sodium alginate, calcium chloride, liquid paraffin and psyllium husk. Floating pellets exhibited drug release for more than 12 hours. Such kind of dosage forms may provide an extension of drug presence in the upper part GI tract resulting enhanced absorption and improved bioavailability for the treatment against protozoa and bacteria. Metronidazole is used in the treatment of bacterial vaginosis, trichomoniasis, amoebiasis and is also used in the combination with other drugs to treat Helicobacter H. Pylori that causes stomach or intestinal ulcers. [47]

G. Multiple unit FDDS

1. Treatment of ulcer: i) Oil entrapped floating beads of Famotidine were prepared by ionotropic gelation method using polymers like sodium alginate, pectin, HPMC K4M with calcium chloride as curing agent and various concentrations of mineral oil as floating agent. Floating beads exhibited drug release of more than 24 hours which increased its gastric residence time and improved bioavailability. Famotidine is a H2 receptor blocker. [48]

ii) GDDS of Ranitidine HCl were prepared using different polymers of ionotropic gelation method with polymers like sodium alginate, HPMC and other excipients like calcium chloride, pectin, acetic acid and HCl as polymers and CaCO3 as the buoyancy providing agents. GFDDS formulations of Ranitidine HCl were controlled for a period of more than 14 hours which increased the gastric residence time and enhanced bioavailability. Ranitidine is an anti-ulcer drug and works on H2 receptor mainly in stomach. [49]

2. Treatment of hypertension: Multiple unit floating drug delivery system consisting of porous carrier calcium silicate, Diltiazem Hydrochloride, a cardiovascular drug, HPMC K4M, carbopol 934P, calcium silicate and ethanol, chloroform as organic solvents. All
formulations remained buoyant up to 8 hours which increases its gastric residence time and improved bioavailability. The total amount of drug release from all the granules batch ranged from 68% to 85%. Diltiazem hydrochloride is a calcium channel blocker belongs to the benzothiazepine family used for the treatment of hypertension and angina.\[50\]

3. Treatment of diabetes: Floating microspheres of Glipizide were prepared using polymeric material such as chitosan, sodium alginate and other excipients like calcium carbonate, calcium chloride and glacial acetic acid by ionotropic gelation method. Formulated microspheres exhibited prolonged drug release and remain buoyant for more than 12 hours which increased the gastric residence time and improved bioavailability. Glipizide is an oral hypoglycemic agent.\[51\]

4. Treatment of bacterial infection: Multiple unit floating beads of Clarithromycin prepared from sodium alginate solution containing HPMC (K100M) and sunflower oil. Floating beads showed floating lag time below 2 minutes and showed total floating duration more than 10 hours which increased its gastric residence time and improved bioavailability. Clarithromycin is a macrolide antibiotics which is used to treat bacterial infections.\[52\]

5. Treatment of viral infections: Hydrodynamically balanced gastroretentive systems of non effervescent formulation of Acyclovir prepared with novel lipoidal carriers like gleucrine 43/01, gleucrine 50/02, compritol A70 888, geleol pellets, HPMC (K4M, K15M, K100M), PVP K30, Isopropyl alcohol. The systems showed prolonged drug release of 12 hours which increased the gastric residence time and improved bioavailability with patient compliance. Acyclovir is an antiviral drug used to treat infections caused by herpes virus.\[53\]

H. Floating gel systems

1. Treatment of ulcer: i) Floating oral in situ gel of Ranitidine HCl, were prepared using sodium alginate as a polymer and CaCO\(_3\) was used as crosslinking agent and other excipients like sodium citrate, D-sorbitol. In situ forming polymeric formulations drug delivery system is in sol form before administration in the body, but once administered, undergoes gelation in situ to form a gel. Floating in situ gel exhibited prolonged drug release up to 8 hours which increased the gastric residence time and improved bioavailability. Ranitidine HCl is a H\(_2\)-receptor antagonist and mainly used clinically as inhibitors of gastric acid secretion in treatment of peptic ulcers.\[54\]
ii) Gastroretentive floating in situ gel of Ranitidine hydrochloride was prepared using polymers like sodium alginate, HPMC and other excipients like sodium bicarbonate, sodium citrate, sorbitol, calcium chloride, HCl. Gastroretentive in situ gel of Ranitidine used to increase the residence time in the stomach and to sustain the release upto 8 hours that lead to increase gastric residence time and improved drug bioavailability. Ranitidine is H₂ receptor antagonist used in the treatment of peptic ulcer.[55]

iii) Gastroretentive drug delivery system of Ornidazole in situ gelling system were prepared by using polymers like gellan gum, sodium alginate and other excipients like sodium citrate, calcium carbonate, as a gelling polymer and CaCl₂ as across linking agent. Formed gel showed prolonged gastric residence time upto 12 hours and enhanced Ornidazole stability which contribute better patient compliance. While reduce frequency of dosing and by acceptable sustained release of dosage forms Ornidazole in the stomach to promote a fast and effective eradication of H.pylori to cure peptic ulcer.[56]

2. Treatment of bacterial infection: i) Gastroretentive in situ gelling system of Metronidazole were prepared using polymers like sodium alginate, methylcellulose, HPMC, NaCMC and other excipients like CaCO₃/NaHCO₃, methyl paraben, propyl paraben. The in situ gel exhibits drug release upto 6 hours which increased the gastric residence time and improved bioavailability. The prepared in situ gelling formulations of Metronidazole could float in the gastric conditions and release the drug in controlled manner. The prepared formulations appear to be promising drug delivery system of localized delivery of Metronidazole for better treatment of peptic ulcer disease caused by H.Pylori. Metronidazole is a nitroimidazole used to treat amoebiasis, vaginitis, trichomonas infection.[57]

ii) Floatable in situ gel of Ofloxacin were prepared using polymers like sodium alginate, HPMC (K4M, K15M, K100M), and other excipients like calcium carbonate, sodium bicarbonate, methyl paraben, propyl paraben, aspartame, HCl. Drug release obtained is 16 hours which increased the gastric residence time and improved bioavailability. The developed floating in situ gel could perform better than conventional dosage form leading to improved efficacy and better patient compliance. Ofloxacin is a synthetic fluorinated carboxyquinolone that has a broad spectrum of activity.[58]

3. Treatment of hypertension: Floating in situ gel of Ramipril were prepared using different concentrations of gelling polymer such as sodium alginate, gellan gum and calcium...
carbonate. Floating in situ gel of Ramipril is used to increase the gastric residence time in the stomach and modulate the release behaviour of Ramipril up to 99% for 12 hours with improved bioavailability. Ramipril is an angiotensin converting enzyme inhibitor (ACE) used in the treatment of hypertension.\[59\]

I. Bioadhesive systems

1. Treatment of hypertension: i) Bioadhesive tablets of Diltiazem HCl were prepared using polymers carbopol 934, HPMC K4M, microcrystalline cellulose, and other excipients like talc and magnesium stearate by direct compression technique. Floating bioadhesive tablets of Diltiazem Hydrochloride were prepared with good bioadhesion and controlled release up to 12 hours which prolonged the gastric residence time and improved bioavailability. Diltiazem Hydrochloride is a calcium channel blocker used in the treatment of hypertension and angina.\[60\]

ii) Floating mucoadhesive Dipyridamole tablets were prepared using various concentrations of HPMC K4M, carbopol 934P and other excipients like magnesium stearate, lactose, conc HCl and sodium bicarbonate for swelling, mucoadhesive and floating behaviour respectively. The tablets are prepared by direct compression technique. The tablets had considerable bioadhesion along with considerable floating and swelling behaviour with good release pattern up to 12 hours. Dipyridamole is a BCS class III drug having low solubility and high permeability.\[61\]

2. Treatment of bacterial infection: i) Floating bioadhesive tablets of Ciprofloxacin HCl were prepared using polymers like xanthan gum, guargum, chitosan at varying concentrations were used for release controlling properties, sodium bicarbonate acts as an effervescent agent, aerosol, magnesium stearate and lactose is used as diluent. The tablets were prepared by direct compression technique. The Floating tablets exhibits prolonged gastric residence time up to 12 hours with controlled drug release and good bioadhesive strength which improved its bioavailability. Ciprofloxacin HCl is synthetic chemotherapeutic antibiotic.\[62\]

ii) Floating tablets of Tinidazole using two different grades of HPMC K4M and HPMC E15M, PVP K30, and other excipients like magnesium stearate, ethanol and chloroform in different concentrations by effervescent granulation technique and sodium bicarbonate used as an gas-generating agent. Floating tablets exhibited prolonged drug release up to 8 hours
which improves its gastric residence time and enhanced bioavailability. Tinidazole is an antiamoebic, antiprotozoal, antibacterial and antibiotic type of drug. 

3. Treatment of diabetes: Floating and bioadhesive tablets of Glipizide were prepared which possess a unique combination of floatation and bioadhesion properties. The tablets were prepared by using HPMC K4M, HPMC K15M, and HPMC K100M as hydrophilic polymers and carbopol 974P as bioadhesive polymer along with other excipients like sodium bicarbonate, microcrystalline cellulose, talc and magnesium stearate by direct compression method. Controlled drug release was obtained upto 24 hrs which improved its bioavailability and prolonged residence in the stomach as compared to conventional stomach specific dosage form. Glipizide is a second generation sulfonylurea drug which is typically prescribed to treat type II diabetes (non insulin dependent diabetes mellitus).

3. Treatment of ulcer: Bilayer floating bioadhesive tablets of Famotidine using HPMC (K15M, K100M), microcrystalline cellulose, and other excipients like starch 1500, talc, magnesium stearate, sodium bicarbonate and HCl. Thus, floating bioadhesive system exhibited independent regulation of buoyancy ad drug release upto 12 hours and showed good antiulcer efficacy confirming potential floating bioadhesive tablets as drug delivery system for prolonging gastric residence time and enhancing local effect of Famotidine.

REFERENCES


