

GASTRORETENTIVE DOSAGE FORMS: REVIEW ON FLOATING DRUG DELIVERY SYSTEMS

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ABSTRACT

Gastroretentive drug delivery system has been a significant approach over the past few years that have been noted to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal (GI) tract for local or systemic effects. The present study has been investigated to compile the recent as well as past literature with special focus on various gastroretentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery. Floating systems have been considered as one of the imperative categories of drug delivery systems with gastric retentive behavior. The review article explains the various floating drug delivery systems that are formulated in order to enhance the drug bioavailability. Moreover, various gastroretentive approaches designed and developed such as high density, floating, bioadhesive, super porous hydrogel and magnetic systems have been clearly discussed in the article.

KEY WORDS: Gastroretentive, Drug delivery system, Floating systems

INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the systemic circulation as it provides improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulations. The effective oral drug delivery practice depends upon various factors like gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs¹. It has been frequently observed that the drugs that are easily absorbed from GI tract have short half-lives and are eliminated quickly from the systemic circulation which leads to incomplete absorption of drugs from the upper part of the small intestine. The recurrent dosing of the drugs is obligatory to achieve appropriate therapeutic activity and to avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the GI tract that helps to maintain an effective drug concentration in the systemic circulation for a prolonged period of time^{1,2}. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner so that the drug could be supplied continuously to its absorption sites. Hence, an advantageous drug delivery system to control and prolong the gastric emptying time

and to deliver drugs in higher concentrations to the absorption site necessitates a specialized delivery system. A significant approach in this regard can be achieved by floating drug delivery systems (FDDS)^{3,4}. A large number of FDDS involving various technologies have been developed such as single and multiple unit hydrodynamically balanced systems (HBS), single and multiple unit gas generating systems, hollow microspheres and raft forming systems^{5,6}. The present review article deals with various gastroretentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery systems. Moreover, many approaches towards the development of FDDS to increase the bioavailability of the dosage forms have been delineated.

FLOATING SYSTEMS: THE SUPERLATIVE APPROACH

Floating systems are one of the important categories of drug delivery systems with gastric retentive behavior. Drugs that could take advantage of gastric retention include: furosemide, cyclosporine, allopurinol, ciprofloxacin and metformin. Drugs whose solubility is less in the higher pH of the small intestine than the stomach (e.g. chlorthalidone and cinnarizine, the drugs prone for degradation in the intestinal pH (e.g.

captopril), and the drugs for local action in the stomach (e.g. misoprostol) can be delivered in the form of dosage forms with gastric retention. Antibiotics, catecholamines, sedative, analgesics, anticonvulsants, muscle relaxants, antihypertensive and vitamins can be administered in HBS dosage form^{7,8,9,10}.

Drugs that have been reported to be used in the formulation of floating dosage forms include floating microspheres (aspirin, griseofulvin, p-nitroaniline, ibuprofen, terfenadine and tranilast), floating granules (diclofenac sodium, indomethacin and prednisolone), films (cinnarizine), floating capsules (chlordiazepoxide hydrogen chloride, diazepam, furosemide, misoprostol, L-Dopa, benserazide, ursodeoxycholic acid and pepstatin) and floating tablets and pills like acetaminophen, acetylsalicylic acid, ampicillin, amoxicillin trihydrate, atenolol, diltiazem, fluorouracil, isosorbide mononitrate, para aminobenzoic acid, piritamide, theophylline and verapamil hydrochloride^{7,10,11-12}.

GASTRORETENTIVE DRUG DELIVERY SYSTEM

The Prominent Proposal

Most of the orally administered dosage forms have several physiological limitations such as GI transit time, incomplete drug release from devices and too short residence time of the pharmaceutical dosage forms in the absorption region of GI tract. This leads to lower the bioavailability of sustained release dosage forms and even if slow release of drug is attained, the drug released after passing the absorption site is not utilized, thus lowering the efficacy of the drug¹³. The gastrointestinal transit time is one of several physiological limitations that must be controlled in the development of peroral sustained release dosage forms.

Drug absorption from GI tract is complex procedure and is subject to many variables. It has been reported that the extent of GI tract drug absorption is related to contact time with the small intestinal mucosa. Rapid GI transit can result incomplete drug release from a device above the absorption zone, leading to diminished efficacy of the administered dose^{13,14}.

The oral controlled release dosage forms have been developed for the past three decades due to their advantages. The design of oral controlled drug delivery system is primarily aimed at achieving more predictable and increased bioavailability, thereby obtaining a maximum therapeutic effect. However, some of these systems do not work as planned due to several physiological difficulties, such as inability to restrain and localize the drug delivery system within desired region of GIT and highly variable nature of gastric emptying

process¹⁵. It can be anticipated that, depending upon the physiological state of subject and the design of pharmaceutical formulation, the emptying process can last from a few minutes to 12 hours. Rapid GI transit can prevent complete drug release in the absorption zone and reduce the efficacy of administered dose since the majority of drugs are absorbed in stomach or upper part of small intestine. Thus, placement of drug delivery system in a specific region of the GI tract offers a numerous advantages especially to the drug having narrow absorption window, stability problem in intestine, poor solubility in alkaline pH, local activity in stomach and property to degrade in column^{15,16,17}. Therefore the design of a sustained release preparation requires both prolongation of GI transit of dosage form as well as controlled drug release.

To overcome these limitations, several controlled oral drug delivery systems with prolonged gastric residence times have been reported recently. Gastro retentive drug delivery system is an approach to prolong gastric residence time, thereby targeting site-specific drug release in upper gastro intestinal tract. The gastro retentive drug delivery system can be retained in the stomach and assist in a improving the oral sustained delivery of drug that have an absorption window in a particular region of the gastrointestinal tract^{15,18,19}. The systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability.

APPROACHES TO ACHIEVE GASTRIC RETENTION

Literature from Previous Studies

Previously published data have significantly reported on the FDDS including tablets (single layer and double layer), floating capsule, balloon tablets, multiparticulate systems, hollow microspheres and floating beads^{20,21,22,23}. The reports that are available are briefly reviewed as follows (Figure 1).

Kumar et al.²⁴ demonstrated works on the gastroretentive dosage forms for prolonging gastric residence time. In the study, the concepts of gastric emptying and absorption windows and current technological developments in gastroretentive drug delivery systems were discussed including their advantages and disadvantages alongwith various evaluation techniques and marketed products for gastroretentive drug delivery. According to the authors, the bioadhesive superporous hydrogel, floating and expanding systems showed the most promising potential for achieving the goal of gastroretention.

El-Kamal et al.²⁵ prepared and evaluated ketoprofen floating oral delivery system. They designed sustained

release system for ketoprofen to increase its residence time in the stomach without contact with the mucosa which was achieved through the preparation of floating microparticles by the emulsion-solvent diffusion technique. They used four different ratios of Eudragit S100 with Eudragit RL to form the floating microparticles. It was found that release rates were generally low in 0.1 N HCl especially in presence of high content of Eudragit S100 while in phosphate buffer pH 6.8, high amounts of Eudragit S100 tended to give a higher release rate.

Ali et al.²⁶ formulated hydrodynamically-balanced system for metformin as a single unit-floating capsule. The formulation was optimized on the basis of in vitro buoyancy and in vitro release in simulated fed state gastric fluid. Effect of various release modifiers was studied to ensure the delivery of drug from the HBS capsules over a prolonged period. Capsules prepared with HPMC K4M and ethyl cellulose gave the best in vitro percentage release and were taken as the optimized formulation.

Patel et al.²⁷ developed and optimized a controlled-release multiunit floating system of ranitidine HCl using Compritol, gelucire 50/13 and gelucire 43/01 as lipid carriers. Ranitidine HCl lipid granules were prepared by the melt granulation technique and evaluated for in vitro floating and drug release. Ethyl cellulose, methylcellulose and hydroxypropyl methylcellulose were evaluated as release rate modifiers. They concluded that the hydrophobic lipid Gelucire 43/01 could be considered an effective carrier for design of a multiunit floating drug delivery system for highly water-soluble drugs such as ranitidine HCl.

Sahoo et al.²⁸ formulated floating microspheres of Ciprofloxacin HCl by cross-linking technique. A polymeric mixture of sodium alginate and hydroxy propyl methyl cellulose (HPMC) was used. Sodium bicarbonate was used as gas forming agent. The solution was dropped to 1% calcium chloride solution containing 10% acetic acid for carbon dioxide release and gel formation. The prepared floating microspheres were evaluated with respect to particle size distribution, floating behavior, drug content, entrapped morphology and in vitro release study. Effect of sodium bicarbonate on the above mentioned parameters were evaluated and it was found that sodium bicarbonate had a pronounced effect on various parameters.

Choia et al.²⁹ reported preparation of alginate beads for floating drug delivery system and studied the effects of CO₂ gas forming agents. Floating beads were prepared from a sodium alginate solution containing CaCO₃ or NaHCO₃ as gas-forming agents. They studied the release

characteristics of riboflavin as a model drug. Release rate of riboflavin increased proportionally with addition of NaHCO₃. The results of these studies indicate that CaCO₃ is superior to NaHCO₃ as gas forming agent in alginate bead preparations.

Sharma and Pawar³⁰ developed low-density multi particulate system for pulsatile release of meloxicam for which they combined the principles of floating and pulsatile drug delivery system. They prepared multi particulate floating pulsatile drug delivery system using porous calcium silicate and sodium alginate for time and site-specific drug release of Meloxicam.

Jaimini et al.³¹ formulated and evaluated Famotidine floating tablets. They used Methocel K100 and Methocel K 15 M with effervescent mixture. It was observed that decrease in the citric acid level increased the floating lag time but tablets floated for longer duration. A combination of sodium bicarbonate (130 mg) and citric acid (10mg) was found to achieve optimum in vitro buoyancy. They reported that tablets prepared with k 100 had longer floating time compared with formulations containing Methocel K15 M.

Dave et al.³² reported a gastroretentive drug delivery system of ranitidine hydrochloride. Guar gum, xanthan gum, and hydroxy propyl methylcellulose were evaluated for gel forming properties. Sodium bicarbonate was incorporated as a gas-generating agent. They investigated the effect of citric acid and stearic acid on drug release profile and floating properties. They concluded that the proper balance between a release rate retardant and a release rate enhancer could produce a drug dissolution profile similar to a theoretical dissolution profile.

Narendra et al.³³ reported optimization of bilayer floating tablet containing metoprolol tartrate as a model drug for gastric retention. They employed a 2³ factorial design in formulating the GFDDS with total polymer content-to-drug ratio (X₁), polymer-to-polymer ratio (X₂), and different viscosity grades of HPMC (X₃) as independent variables. The results indicate that X₁ and X₂ significantly affected the floating time and release properties but the effect of different viscosity grades of HPMC (K4M and K10M) was non-significant.

Sunil et al.³⁴ prepared floating microspheres consisting of calcium silicate as porous carrier and Eudragit S as polymer by solvent evaporation method and evaluated their gastroretentive and controlled release properties. They studied the effect of various formulation and process variables on the particle morphology, micromeritic properties, in vitro percentage drug entrapment and in vitro drug release. Prolonged gastric residence time of over six hours was achieved in rabbits for calcium silicate based floating microspheres of

orlistate. The enhanced elimination half-life observed after pharmacokinetic investigation is due to the floating nature of the designed formulations.

Umamaheswari et al.³⁵ prepared floating-bioadhesive microspheres containing acetohydroxamic acid for clearance of *Helicobacter Pylori*. They explored a synergism between a floating and a bioadhesive system. Floating microspheres containing the antiurease drug acetohydroxamic acid were prepared by a novel quasi emulsion solvent diffusion method. The microballons were coated with 2% w/v solution of polycarbophil by the air suspension coating method. The results suggested that AHA-loaded floating microspheres were superior as potent urease inhibitor whereas urease plays an important role in the colonization of *H. Pylori*.

Patel et al.³⁶ developed ranitidine floating tablets; in which they optimized types of filler, different viscosity grades of HPMC and its concentration. Two fillers namely Avicel pH 102 and Tablettose 80 were used. Study revealed that type of filler had significant effect on release of drug from hydrophilic matrix tablets (f_2 value 41.30) and floating properties. Three different viscosity grades of HPMC namely K100 LV, K4M and K15M were used. Viscosity had a major influence on drug release from hydrophilic matrices as well as on floating properties. The drug release from hydrophilic matrices occurred via diffusion mechanisms following square root of time profile. Hardness of tablets had grater influence on floating lag time which might be due to decreased porosity whereas the position of paddle and types of dissolution medium had no significant effect on drug release.

Srivastava et al.³⁷ prepared floating matrix tablets of atenolol to prolong gastric residence time and increase drug bioavailability. The tablets were prepared by direct compression technique, using polymers such as HPMC K15M, K4M, Guargum (GG), and sodium carboxy methylcellulose (SCMC), alone or in combination and other standard excipients. Tablets were evaluated for physical characteristics like hardness, swelling index, floating capacity, thickness and weight variation. The effect of effervescent on buoyancy and drug release pattern was also studied. In vitro release mechanism was evaluated by linear regression analysis. GG- and SCMC-based matrix tablets showed significantly greater swelling indices compared with other batches. The tablets exhibited controlled and prolonged drug release profiles while floating over the dissolution medium.

Gohel et al.³⁸ developed a more relevant in vitro dissolution method to evaluate a carbamazepine floating drug delivery systems. The glass beaker was modified by adding a side arm at the bottom of the beaker so that the

beaker can hold 70 ml of 0.1 N HCl dissolution mediums and allow collection of samples. The tablet did not stick to the agitating device in the proposed dissolution method. The drug release followed zero order kinetics in the proposed method. The proposed test may show good in vitro in vivo correlation (IVIVC) since an attempt is made to mimic the in vivo conditions.

Amin et al.³⁹ developed a gastroretentive drug delivery system of ranitidine hydrochloride which was designed 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. The addition of stearic acid reduces the drug dissolution due to its hydrophobic nature. A 3^2 full factorial design was applied to systemically optimize the drug release profile and the results showed that a low amount of citric acid and a high amount of stearic acid favor sustained release of ranitidine HCl from a gastroretentive formulation.

Streubel et al.⁴⁰ prepared single-unit floating tablets based on polypropylene foam powder and matrix-forming polymer. Incorporation of highly porous foam powder in matrix tablets provided density much lower than the density of the release medium. A 17% w/w foam powder was achieved in vitro for at least 8 hours. It was concluded that varying the ratios of matrix-forming polymers and the foam powder could alter the drug release patterns effectively.

Li et al.⁴¹ evaluated the contribution of formulation variables on the floating properties of a gastro floating drug delivery system using a continuous floating monitoring device and statistical experimental design. The formulation was conceived using 2×3 full factorial designs for calcium delivery. HPMC was used as a low-density polymer and citric acid was incorporated for gas generation. Analysis of variance (ANOVA) test on the results from these experimental designs demonstrated that the hydrophobic agent magnesium stearate could significantly improve the floating capacity of the delivery system. High-viscosity polymers had good effect on floating properties. The residual floating force values of the different grades of HPMC were in the order K4 M~ E4 M~K100 LV> E5 LV but different polymers with same viscosity, i.e., HPMC K4M, HPMC E4M did not show any significant effect on floating property. Better floating was achieved at a higher HPMC/carbopol ratio and this result demonstrated that carbopol has a negative effect on the floating behavior.

Sangekar et al.⁴² studied the effect of food and specific gravity on the gastric retention time of floating (spec. grav. 0.96) and non-floating (spec. grav. 1.59) tablet formulations was investigated using gamma scintigraphy

in humans. The results obtained indicate that the presence of food in the stomach appears to significantly prolong gastric retention of both the floating and non-floating tablets while specific gravity does not seem to play an important role in the residency time of the tablets in the stomach.

Xiaoqiang et al.⁴³ developed hydrodynamically balanced sustained release tablets containing drug and hydrophilic hydrocolloids which on contact with gastric fluids at body temperature formed a soft gelatinous mass on the surface of the tablet and provided a water-impermeable colloid gel barrier on the surface of the tablets. The drug slowly released from the surface of the gelatinous mass that remained buoyant on gastric fluids.

Rahman et al.⁴⁴ developed a bilayer-floating tablet (BFT) for captopril using direct compression technology. HPMC, K-grade and effervescent mixture of citric acid and sodium bicarbonate formed the floating layer. The release layer contained captopril and various polymers such as HPMC-K15M, PVP-K30 and Carbopol 934p, alone or in combination with the drug. The floating behavior and in vitro dissolution studies were carried out in a USP 23 apparatus 2 in simulated gastric fluid (without enzyme, pH 1.2). Final formulation released approximately 95% drug in 24 h in vitro, while the floating lag time was 10 min and the tablet remained floatable throughout all studies. Final formulation followed the Higuchi release model and showed no significant change in physical appearance, drug content, floatability or in vitro dissolution pattern after storage at 45 °C/75% RH for three months.

Bomma et al.⁴⁵ prepared floating matrix tablets of norfloxacin which were developed to prolong gastric residence time leading to an increase in drug bioavailability by using wet granulation technique using polymers such as HPMCK4M, HPMCK100M and Xanthan gum. The tablets exhibited controlled and prolonged drug release profile while floating over dissolution medium was confirmed as drug release mechanism from these tablets.

Thakkar et al.⁴⁶ formulated and evaluated the levofloxacin hemihydrate floating tablets that were prepared by direct compression method using gelucire 43/01 and HPMC polymers in different ratio. The in vitro release study revealed the fact that the release rate of drug was decreased by increasing the proportions of gelucire 43/01 by 5 to 40% matrix tablets containing 25% HPMCK4M and 15% gelucire 43/01.

Rao et al.⁴⁷ formulated and optimized the floating drug delivery system of cephalexin. Tablets were prepared by direct compression method incorporating HPMCK4M, xanthan gum, guar gum, sodium bicarbonate and tartaric

acid as gas generating agent. The diffusion exponent of krosmeier peppas for optimized formulation was found to be 0.635 which significantly indicated the mechanism of drug release.

CONCLUSION

Based on the previous studies reported, it may be concluded that gastroretentive drug delivery recommends various potential advantages for drugs with poor bioavailability as their absorption is restricted to the upper GI tract. Moreover, they can be delivered efficiently thereby capitalizing on their absorption and enhancing absolute bioavailability. In addition, the identification of new diseases and the resistance shown towards the existing drugs considered the need for the introducing new therapeutic molecules. In response, wide arrays of chemical entities have been introduced that have absorption all over the GI tract and. The drugs that are requisite for showing local action in absorption sites require a specialized delivery system which has been achieved by FDDS. Numerous FDDS approaches have been developed such as single and multiple unit HBS, single and multiple unit gas generating systems, hollow microspheres and raft forming systems. All these gastroretentive drug delivery systems are interesting and presenting their own advantages and disadvantages due to which a lot of work is in a row to develop different types of gastroretentive delivery systems of various drugs. Moreover, further studies are expected in the future that would ultimately lead to improved efficiencies of various types of pharmacotherapies.

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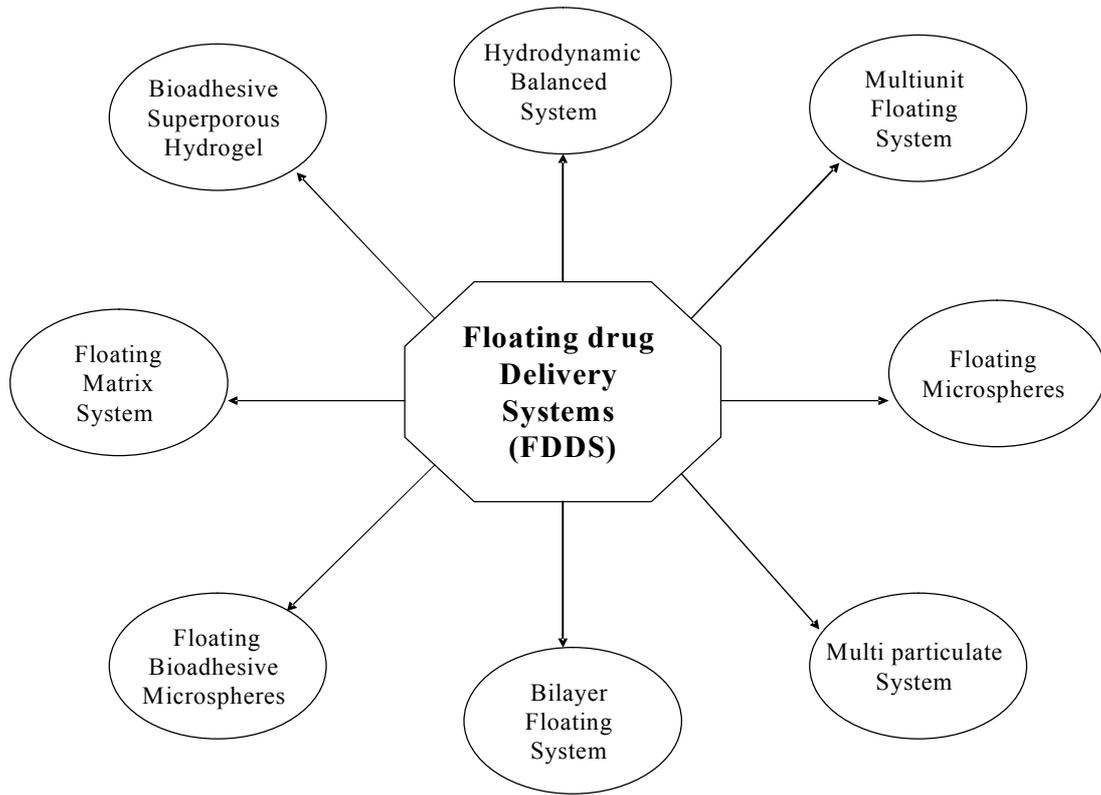


Figure 1. Diagram showing various approaches of floating drug delivery systems