

REVIEW ARTICLE

Gastroretentive Dosage Forms: An Approach to Oral Controlled Drug Delivery Systems

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ABSTRACT

Gastric retentive dosage forms have been developed to provide controlled release therapy for drugs with reduced absorption in the lower gastrointestinal (GI) tract or for local treatment of diseases of the upper GI tract. Gastric retentive dosage forms depends on natural GI physiology such as floating or large tablets that depend on delayed emptying from the fed stomach or the dosage forms that are designed to fight the physiology and avoid emptying in the fasted state through dosage forms of even larger sizes with or without flotation or bioadhesion. Floating systems have been considered as one of the important categories of drug delivery systems with gastric retentive behavior. Floating matrix tablets have been developed to prolong gastric residence time leading to an increase in drug bioavailability. The review article explains the various floating drug delivery systems that are formulated in order to enhance the drug bioavailability. Moreover, the identification of key factors influencing the variability of gastric retention has been discussed.

Key Words: Gastroretentive, Drug delivery system, Floating systems

INTRODUCTION

The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery process depends upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs [1-2]. 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 profiles, 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 [3-4]. 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 to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site to show local action in the stomach requires a specialized delivery system. A significant approach for showing local action and for the treatment of gastric disorders can be achieved by floating drug delivery systems (FDDS) [5-6]. A number of FDDS involving various technologies have been developed such as single and multiple unit hydro dynamically balanced systems (HBS), single and multiple unit gas generating systems, hollow microspheres and raft forming systems [7-8]. The present review article summarizes various approaches towards prolonging the gastric emptying time and delivering drugs in higher concentrations to the absorption site in order to show enhanced duration of action of the dosage form. Moreover, many FDDS developed that are found to increase the bioavailability of the dosage forms have been delineated.

GASTRORETENTIVE FLOATING DRUG DELIVERY SYSTEM: REVIEW FROM PREVIOUS STUDIES

Previous studies reported on the FDDS include tablets (single layer and double layer), floating capsule, balloon tablets, multiparticulate systems, hollow microspheres and floating beads^[9-12]. The reports that are available are briefly reviewed as follows.

Kumar et al.^[13] 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 along with 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.^[14] 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.^[15] 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.^[16] 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.^[17] 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.^[18] 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 Pawar^[19] 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.^[20] 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. [21] 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. [22] reported optimization of bilayer floating tablet containing metoprolol tartrate as a model drug for gastric retention. They employed a 2^3 factorial design in formulating the GFDDS with total polymer content-to-drug ratio (X_1), polymer-to-polymer ratio (X_2), and different viscosity grades of HPMC (X_3) as independent variables. The results indicate that X_1 and X_2 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. [23] 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 6 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. [24] 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 quasiemulsion 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. [25] 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 greater 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. [26] 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, Guar gum (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. [27] 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. [28] 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 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 favor sustained release of ranitidine HCl from a gastroretentive formulation.

Streubel et al. [29] 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. [30] 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 2x3 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. [31] 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. [32] 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. [33] 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. [34] 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. [35] 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. [36] 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

The identification of new diseases and the resistance shown towards the existing drugs felt the need 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 GIT and others have absorption windows in the upper part of the small intestine. The drugs that are required for local action in the GIT require a specialized delivery system which has been achieved by FDDS. A number of FDDS have been developed such as single and multiple unit HBS, single and multiple unit gas generating systems, hollow microspheres and raft forming systems. Development of sustained release formulations is advantageous in providing prolonged gastric retention and increased efficacy of the dosage forms. The floating behavior of the low density drug delivery systems could successfully be combined with accurate control of the drug release patterns in order to boast accurate bioavailability. Hence further studies are needed in this regard in order to encompass effective drug delivery systems.

REFERENCES

1. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery systems. *Expert Opin Drug Deliv* 2006; 3:217-33.
2. Bardonnet PL, Faivre V, Pugh WJ, Piffaretti JC, Falson F. Gastroretentive dosage forms: overview and special case of *Helicobacter pylori*. *J Control Release* 2006; 111:1-18.
3. Rouge N, Buri P, Doelker E. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. *Int J Pharm* 1996; 136:117-39.
4. Murphy CS, Pillay V, Choonara YE, du Toit LC. Gastroretentive drug delivery systems: current developments in novel system design and evaluation. *Curr Drug Deliv* 2009; 6:451-60.
5. Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage forms. *J Control Release* 2003; 90:143-62.
6. Kiss D, Zelko R. Gastroretentive dosage forms. *Acta Pharm Hung* 2005; 75:169-76.
7. Reddy L, Murthy R. Floating dosage systems in drug delivery. *Crit Rev Ther Drug Carrier Syst* 2002; 19:553-85.
8. Hou SY, Cowles VE, Berner B. Gastric retentive dosage forms: a review. *Crit Rev Ther Drug Carrier Syst* 2003; 20:459-97.
9. Chungi VS, Dittert LW, Smith RB. Gastrointestinal sites of furosemide absorption in rats. *Int J Pharm* 1979; 4:27-38.
10. Sheth PR, Tossounian J. The hydrodynamically balanced system (HBSTM): a novel drug delivery system for oral use. *Drug Dev Ind Pharm* 1984; 10:313-39.
11. Gutierrez-Rocca J, Omidian H, Shah K. Progress in Gastroretentive drug delivery systems. *Business Briefing Pharmatech* 2003; 52:6.
12. Kale RD, Tayade PT. A Multiple Unit Drug Delivery System of Pyroxicam Using Eudragit Polymer. *Indian J Pharm Sci* 2007; 69:120-3.
13. Kumar R, Philip A. Gastroretentive Dosage forms for prolonging gastric residence time. *Int J Pharm Med* 2007; 21:157-71.
14. El-Kamel AH, Sokar MS, Al Gamal SS, Naggat VF. Preparation and Evaluation of Ketoprofen Floating Oral Delivery System. *Int J Pharmaceutics* 2001; 220:13-21.
15. Ali J, Arora S, Ahuja A, Babbar AK, Sharma RK, Khar RK, et al. Formulation and development of hydrodynamically balanced system for metformin: In vitro and in vivo evaluation. *Eur J Pharmaceutics Biopharm* 2007; 67:196-201.
16. Patel DM, Patel NM, Patel VF, Bhatt DA. Floating Granules of Ranitidine Hydrochloride-Gelucir 43/01: Formulation Optimization Using Factorial Design. *AAPS Pharm Sci Tech* 2007; 8:2.
17. Sahoo SK, Mohapatra S, Dhal SK, Behera BC, Barik BB. Formulation of Floating Microspheres of Ciprofloxacin Hydrochloride by Crosslinking Technique. *The Ind Pharmacist* 2007; 65:8.
18. Choia BY, Park HJ, Hwangb SJ, Parkc JB. Preparation of Alginate Beads for Floating Drug Delivery System: Effects of CO₂ Gas-Forming Agents. *Int J Pharmaceutics* 2002.

19. Sharma S, Pawar A. Low Density Multiparticulate System for Pulsatile Release of Meloxicam. *Curr Drug Delivery* 2006; 3:87-96.
20. Jamini M, Rana AC, Tanwar YS. Formulation and Evaluation of Famotidine Floating Tablets. *Curr Drug Delivery* 2007; 4:51-5.
21. Dave BS, Amin AF, Patel MM. Gastroretentive Drug Delivery System of Ranitidine Hydrochloride: Formulation and In Vitro Evaluation. *AAPS Pharm Sci Tech* 2004; 5: Article 34.
22. Narendra C, Srinath MS, Babu G. Optimization of Bilayer Floating Tablet Containing Metoprolol Tartrate as a Model Drug for Gastric Retention. *AAPS Pharm Sci Tech* 2006; 7: Article 34.
23. Sunil KJ, Govind PA, Narendra KJ. Evaluation of Porous Carrier –Based Floating Orlistate Microspheres For Gastric Delivery. *AAPS Pharm Sci Tech* 2006;7:Article 90
24. Umamaheswari RB, Jain S, Tripathi PK, Agrawal GP, Jain NK. Floating-Bioadhesive Microspheres Containing Acetohydroxamic Acid for Clearance of Helicobacter Pylori. *Drug Delivery* 2002; 9:223-31.
25. Patel VF, Patel NM, Yeole PG. Studies on formulation and evaluation of ranitidine floating tablets. *Ind J Pharm Sci* 2005; 67:703-9.
26. Srivastava AK, Wadhwa S, Ridhurkar D, Mishra B. Oral sustained delivery of atenolol from floating matrix tablets-formulation and in vitro evaluation. *Drug Dev Ind Pharm* 2005; 31:367-74.
27. Gohel MC, Mehta PR, Dave RK, Bariya NH. A more relevant dissolution method for evaluation of floating drug delivery system. *Diss Tech* 2004; 22:5.
28. Amin AF, Dave BS, Patel MM. Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and in vitro evaluation. *AAPS Pharm Sci Tech* 2004; 26:7.
29. Streubel A, Siepmann J, Bodmeier R. Floating matrix tablets based on low density foam powder: effect of formulation and processing parameters on drug release. *Eur J Pharm Sci* 2003; 18:37-45.
30. Li S, Lin S, Daggy BP, Mirchandani, HL, Chien, TW. Effect of formulation variables on the floating properties of gastric floating drug delivery system. *Drug Dev Ind Pharm* 2002; 28:783-93.
31. Sangekar S, Vadino WA, Chaudry I, Parr A, Beihn R, Digenis G. Evaluation of the effect of food and specific gravity of tablets on gastric retention time. *Int J Pharm* 1987; 35:187-91.
32. Xiaoqiang X, Minjie S, Feng Z, Yiqiao H. Floating matrix dosage form for phenoprolamine hydrochloride based on gas forming agent: In vitro and in vivo evaluation in healthy volunteers. *Int J Pharm* 2006; 310:139-45.
33. Rahman Z, Mushir A, Khar RK. Design and evaluation of bilayer floating tablets of captopril. *Acta Pharm* 2006; 56:49-57.
34. Bomma R, Swamy Naidu RA, Yamsani MR, Veerabrahma K. Development and evolution of gastro retentive norfloxacin tablets *Acta Pharma* 2009;59:211-21.
35. Thakkar VT, Shah PA, Soni TG, Parmar MY, Gohel MC, Gandhi TR. Fabrication and evaluation of levofloxacin hemihydrate floating tablets. *Res Pharm Sci* 2008; 3:1-8.
36. Rao BP, Kottan NA, Snehith VS, Ramesh C. Development of Gastro retentive drug delivery system of cephalixin by using factorial design. *ARS Pharmaceutica* 2009; 50:8-24.