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# Floating Drug Delivery Systems

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With the recent advances in the field of drug delivery, there had been increased interest in improving the efficacy of therapeutic agents through controlled oral drug delivery system, which are retained in the stomach for a prolonged and predictable period of time. Several approaches are currently used in the prolongation of gastroretentive drug delivery system (GRT). From the formulation and technical point of view, several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems and other delayed gastric emptying devices. Floating drug delivery systems is considerably easy and logical approach for drugs which are poorly soluble at an alkaline pH, having narrow window of absorption, absorbed readily from gastrointestinal tract (GIT) and that are degrade in the colon. This review discusses the biological, pharmacokinetic and pharmacodynamic aspects of gastroretentive drug delivery system, various techniques, evaluation and *in vitro-in vivo* correlation of FDDS.

**Key Words: Floating, Drug delivery systems.**

## INTRODUCTION

In the last decades, considerable efforts have been made to develop new pharmaceutically viable and therapeutically effective controlled drug delivery systems[1,2]. Attention has been focused particularly on orally administered controlled drug delivery systems because of the ease of administration, economy and ease of manufacture of oral dosage forms such as tablets and capsules. Drugs that are easily absorbed from the gastrointestinal tract (GIT) and having a short half-life are eliminated quickly from the blood circulation. To avoid this problem, the oral controlled release formulations have been developed, as these will release the drug slowly in to the GIT and maintain a constant drug concentration in the serum for a longer period of time[3,4]. One of the most feasible approaches to control is the gastric residence time.

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Gastro retentive dosage forms significantly extend the period of time over which drugs may be released, prolong dosing intervals and increase patient compliance. Such retention systems are much important for drugs that are degraded in intestine or for drugs like antacids or certain antibiotics, enzymes that act locally in the stomach Such systems are more advantageous in improving GI absorption of drugs with narrow absorption windows as well as for controlling release of the drugs having site-specific absorption limitation. Retention of drug delivery systems in the stomach prolongs overall GI transit time, thereby resulting in improved bioavailability for some drugs. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, floatation, sedimentation, expansion, modified shape systems or by the simultaneous administration of pharmacological agents that delay gastric emptying. Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability.

An important requisite for the successful performance of oral controlled drug delivery system is that the drug should have good absorption through out gastrointestinal tract (GIT), to ensure the continuous absorption of the released drug.

Drugs having site specific absorption are difficult to design as oral CDDS because only the drug released in the region preceding and enclose vicinity to the absorption window is available for absorption. Moreover the therapeutic window of many drugs is limited due to their short circulating half-life and absorption. Such pharmacokinetic limitation leads to frequent dosing of these medicaments to achieve a required therapeutic effect. This results in pill burden and consequently decreases the patient compliance. The phenomenon of absorption *via* a limited part of GIT has been termed as narrow absorption window. Once the dosage form crosses the absorption windows the drug will be neither bioavailable nor effective[10].

A rational approach to enhance bioavailability and improve pharmacokinetic and pharmacodynamic profiles is to retain the drug reservoir above its absorption area, *i.e.* in the stomach and to release the drug in a controlled manner, so as to achieve zero order kinetics for a prolonged period of time. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile is to control the gastric residence time in GIT[11,12].

**Gastroretentive approaches:** The main approaches used to increase the gastric residence time of pharmaceutical dosage forms include: Floating systems[13]: effervescent system, non-effervescent system; bio/mucoadhesive system[14,15]: hydration-mediate adhesion, bonding mediated adhesion; swelling system[16,17]; expanding systems[18,19]; high density system[20,21]; raft system; modified shaped system[22].

**Floating system:** It is low-density system, which is having a sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric content, the drug is released slowly at the desired rate. It results in increased gastro retentive time and reduces fluctuation in the plasma drug concentration[23].

**Effervescent system:** Floatation of a drug delivery system in the stomach can be achieved by incorporating a floating chamber filled with vacuum, air or an inert gas. Gas can be introduced into the floating chamber by the volatilization of the organic solvent or by the carbon dioxide produced as a result of an effervescent reaction between organic acid and carbonate-bicarbonate salts. The air trapped by the swollen polymer lowers the density and confers the buoyancy to the dosage form. The mechanism of floating effervescent system can be explained as: an osmotically controlled floating system, the device comprised of a hollow deformable unit that was convertible from a collapsed to an expanded position and returnable to a collapsed position after an extended period of time. Although this type of sophisticated dosage form might be used to administer a drug at a controlled rate for a prolonged period of time, it could not be recommended for smokers because of safety reasons[24].

Ozdemir *et al.*[25] prepared controlled release floating bilayer tablets of furosemide with β-cyclodextrin as one layer of the tablet contained the drug, polymers-HPMC 4000, HPMC 100 and CMC and the second layer contained the effervescent mixture of sodium bicarbonate and citric acid. Evaluation of the tablets showed that floating tablets were retained in stomach for 6 h and bioavailability of these tablets was 1.8 times that of conventional tablets.

Choi *et al.*[26] prepared floating alginate beads using gas forming agents (calcium carbonate and sodium bicarbonate) and studied the effect of carbon dioxide generation on the physical properties, morphology and release rates. *In vitro* floating studies revealed that the beads free of gas generating agents in proportions ranging from 5:1 to 1:1 demonstrated excellent floating.

*In vitro* dissolution of metronidazole from sustained release floating tablets was studied with varied proportions of sodium bicarbonate and Pharmatose DCL 11. Two polymers with different hydration characteristics, methocel K4M and carbopol 971P NF, were used to formulate the matrices. The variables studied include the matrices' release profile, hydration volume and floating behaviour. All methocel matrices floated more than 8 h with sodium bicarbonate proportions up to 24 %, while carbopol matrices floated more than 8 h with sodium bicarbonate proportions only up to 12 %[27].

Talwar *et al.*[28] developed a once daily formulation for oral administration of ciprofloxacin. The formulation was composed of 69.9 % ciprofloxacin base, 0.34 % sodium alginate, 1.03 % xanthan gum, 13.7 % sodium bicarbonate and 12.1 % cross-linked polyvinyl pyrollidine. The hydrated gel matrix created a tortuous diffusion path for the drug, resulting in sustained release of the drug.

Baumgartner[29] prepared a matrix floating tablet containing 54.7 % of the drug, HPMC K4M, avicel PH101 and a gas-generating agent. *In vitro* experiments with fested state beagle dogs revealed prolonged gastric residence time. The comparison of gastric motility and stomach emptying between human and dogs showed no much difference and therefore it was speculated that the experimentally proven increased gastric residence time in beagle dogs could be compared with the known literature for human.

Moursy *et al.*[30] developed sustained release floating capsules of nicardipin hydrochloride. For floating, hydrocolloids of high viscosity grade were used and to aid in buoyancy sodium bicarbonate was added to allow the release of carbon dioxide. *In vitro* analysis of a commercially available 20 mg capsule of nicardipine hydrochloride (MISCARD) was performed for comparison. Results showed an increase in floating with increase in proportion of hydrocolloid.

A gastro retentive drug delivery system of ranitidine hydrochloride was designed using guargum, xanthan gum and hydroxy methyl propyl cellulose and sodium bicarbonate as a gas-generating agent. The effect of citric acid and stearic acid on drug release profile and floating properties was investigated using 32 full factorial design. Result showed that a low amount of citric acid and a high amount of stearic acid favour sustained release of ranitidine hydrochloride from a gastro retentive formulation[31].

**Non-effervescent floating dosage forms:** When such dosage forms come in contact with an aqueous medium, the hydrocolloid starts to hydrate by first forming a gel at the surface of the dosage form. The resultant gel structure then controls the rate of diffusion of solvent in and drug out of the dosage form. As the exterior surface of the dosage form goes into solution, the gel layer becomes hydrated. As a result of this, the drug dissolves in and diffuses out with the diffusing solvent, creating a receding boundary within the gel structure[32]. Sheth and Tossounian[33] developed a hydrodynamically balanced system capsule containing a mixture of a drug and hydrocolloids. Upon contact with gastric fluid, the capsule shell dissolves resulting the mixture swells and forms a gelatinous barrier thereby remaining buoyant in the gastric juice for an extended period of time.

Mitra[34] described a multilayered, flexible sheet-like medicament device that was buoyant in the gastric juice of the stomach and had SR characteristics. The device consisted of at least one dry, self-supporting carrier film made up of water-insoluble polymer matrix having a drug dispersed or dissolved therein and a barrier film overlaying the carrier film. The barrier film consisted of one water-insoluble and a water- and drug-permeable polymer or copolymer. Both barrier and carrier films were sealed together along their periphery, in such a way as to entrap a plurality of small air pockets, which brought about the buoyancy of laminated films. A patent assigned to Eisai Co. Ltd.[35,36] of Japan described a floatable-coated shell, which consisted essentially of a hollow globular shell made from polystyrene. The external surface of the shell was coated with cellulose acetate phthalate followed by a final coating containing ethyl cellulose and HPMC in combination with an effective. Iannuccelli and co-workers[37] described a multiple-unit system that contained an air compartment. The units forming the system were composed of a calcium alginate core separated by an air compartment from a membrane of calcium alginate or calcium alginate, PVA. The porous structure generated by leaching of the PVA, which was employed as a water- soluble additive in the coating composition, was found to increase the membrane permeability, preventing the collapse of the air

compartment. The *in vitro* results suggested that the floating ability increased with an increase in PVA concentration and molecular weight.

Streubel *et al.*[38] prepared single unit floating tablets based on polypropylene foam powder, matrix forming polymer(s), drug and an optional filler. It was concluded that varying the ratios of matrix forming polymers and the foam powder could alter the drug release pattern effectively.

Floating alginate beads of amoxycillin were developed by drop wise addition of alginate into calcium chloride solution, followed by removal of gel beads and freeze-drying. The beads containing the dissolved drug remained buoyant for 20 h and high drug loading levels were achieved[39].

Bulgarelli *et al.*[40] studied the effect of matrix composition and process conditions on casein by virtue of its emulsifying properties causes incorporation of air bubbles and formulation of large holes in the beads that act as air reservoirs in floating systems and serve as a simple and inexpensive material used in controlled oral drug delivery systems. It was observed that the percentage of casein in matrix increases the drug loading of both low and high porous matrices, although the loading efficiencies of high porous matrices is lower than that of low porous matrices.

Nur and Zhang[41] developed floating tablets of captopril using HPMC (4000-15000 cps) and carbopol 934 P. It was concluded that the buoyancy of the tablet is governed by both the swelling of the hydrocolloid particles on the tablet surface when it contacts with the gastric fluids and the presence of internal voids in the center of the tablet (porosity).

Floating microparticles composed of polypropylene foam, eudragit S, ethyl cellulose and polymethylmethacrylate were prepared by solvent evaporation techniques. High encapsulation efficiencies were observed and were independent of the theoretical drug loading. Good floating behaviour was observed as more than 83 % microparticles were floating for at least 8 h[42].

Chauhan and coworkers[43] prepared risedronate sodium and gelucire floating matrices using melt solidification with a view that incorporation of bisphosphates in the lipid reduces gastric irritation. Only gastric retention with sustained release allows the drug to reach the duodenum and jejunum and improves the availability of bisphosphates. The sustained release floating metrices were evaluated for and *in vivo* floating ability and *in vitro* drug release. A new emulsion-gelatin method to prepare oil-entrapped calcium pectinate beads was designed[44]. The gel beads containing edible oil were prepared by gentle mixing or homogenizing an oily phase and a water phase containing pectin and then extruded into calcium chloride solution with gentle agitation at room temperature. The gel beads formed were then separated, washed with distilled water and dried. The effect of selected factors, such as type of oil, percentage of oil and type of pectin on morphology and floating properties were investigated. The type and percentage of oil play an important role in controlling the floating of oil entrapped CaPG beads. The result suggested that oil entrapped CaPG beads were promising as a carrier for intragastric floating drug delivery.

Floating microcapsules of melatonin were prepared by ionic interaction of chitosan and a surfactant, sodium dioctyl sulfosceinate that is negatively charged the dissolution studies of the floating microcapsules showed zero order release kinetics in simulated gastric fluid[45]. The release of drug from the floating microcapsules was greatly retarded with release lasting for several hours as compared with non-floating microspheres where drug release was almost instantaneous. Most of the hollow microcapsules developed showed floating over simulated gastric fluid for more than 12 h.

Sato and Kawashima[46] developed microballoons of riboflavin by emulsion solvent technique. To assess the usefulness of the intragastric floating property of the developed microballoons of riboflavin were administered to three volunteers. The pharmacokinetics was assessed by urinary excretion data. Total urinary excretion of riboflavin from the floating microballoons was lower than that of riboflavin powder. Shimpi *et al.*[47] reported that gelucire 43/01 can be considered as an effective carrier for design of a multi unit FDDS of highly water-soluble drugs such as diltiazem hydrochloride. The granules were prepared by melt-granular technique and evaluated for *in vitro-in vivo* floating ability, surface topography and *in vitro* drug release. *In vivo* floating ability was studied by γ-scintigraphy in 6 healthy humen volunteers and the result showed that the formulation remained in the stomach for 6 h. The hydrodynamically balanced capsules were prepared by physical mixing of various grades of HPMC and poly(ethylene oxide) (PEO) alone as well as in combinations. The *in vitro* release of the floating capsules and microspheres was found to be 96.02 and 95.83 % in 12 h, respectively. Both the dosage forms follow Higuchi model for release from formulations[48]. The oral delivery of the anti-psychotic agent carbamazepine was facilitated by preparing a non-disintegrating floating dosage form which can increase its absorption in the stomach by increasing the drug's gastric residence time. The polymers used were HPMC (low and high viscosity), guar gum and carbopol, along with sodium bicarbonate as the gas-generating agent. The prepared tablets were evaluated for their physicochemical properties and drug release. *In vitro* release studies indicated that the carbamazepine release from the floating dosage forms was uniform and followed a zero-order release[49]. Jain *et al.*[50] prepared floating microspheres consisting of (1) calcium silicate as porous carrier; (2) orlistat, an oral anti-obesity agent and (3) Eudragit S as polymer, by solvent evaporation method and to evaluate their gastro-retentive and controlled-release properties. Release pattern of orlistat in simulated gastric fluid from all floating microspheres followed Higuchi matrix model and Peppas-Korsmeyer model[50].

**Properties of drugs having therapeutic interest to prolong the gastric residence time of pharmaceutical dosage form:** (a) They are locally active in the stomach (*e.g.*, misoprostol[51], antacids[52] and antibiotics against *Helicobacter pylori*[53-55]; (b) They have an absorption window in the stomach or in the upper small intestine (*e.g.*, L-DOPA[56,57], *p*-aminobenzoic acid[58], furosemide[59] and riboflavin[60,61]; (c) They are unstable in the intestinal or colonic environment (*e.g.*, captopril[62]); or (d) They

exhibit low solubility at high pH values (*e.g.*, diazepam, chlordiazepoxide[63] and verapamil HCl[64-66].

**Suitable drug candidates for GRDDS:** Acyclovir[67,68], alendronate[69], atenolol[70], captopril[71], ciprofloxacin[72], cisapride[73], furosemide[74-77], verapamil[75], ketoprofen[76], levodopa[77], melatonin[78], misoprostol[79], minocyclin[80], metformin[81], riboflavin[82], sotalol[83], tetracyclin[84], verapamil[85].

## Conclusion

Gastro retentive drug delivery systems have shown very promising results in improving the efficacy of therapeutic agents, which are confirmed by *in vitro* and *in vivo* performance of formulations. They seem to hold a lot of potential and if suitably harnessed, they can be useful in improving the bioavailability of many drugs and such formulations may improve patient compliance and also be helpful in reducing the overall cost of therapy. The focus will probably be on multiple unit systems, as they permit the reduction of the risk of all-or-nothing effects related with single-unit dosage forms.

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