Polymers for Floating Drug Delivery System

Prajapati ST, Patel LD¹, Patel CN

Department of Pharmaceutics and Pharmaceutical Technology, Shri Sarvajanik Pharmacy College, Mehsana, ¹Department of Pharmaceutics and Pharmaceutical Technology, C. U. Shah College of Pharmacy, Wadhvan, Gujarat, India

Introduction

Oral controlled release (CR) dosage forms (DFs) have been developed for the past three decades due to their considerable therapeutic advantages. However, this approach has not been suitable for a variety of important drugs, characterized by a narrow absorption window in the upper part of the gastrointestinal (GI) tract i.e., stomach and small intestine. This is due to the relatively short transit time of the DF in these anatomical segments. Thus, after only a short period of less than 6 h, the CR-DF has already left the upper GI tract and the drug is released in nonabsorbing distal segments of the GI tract. This results in a short absorption phase that is often accompanied by less bioavailability. Therefore, under certain circumstances prolonging the gastric retention of a delivery system is desirable for achieving greater therapeutic benefit of the drug substance. For example, drugs that are absorbed in the proximal part of the GI tract,[2] and drugs that are less soluble in or are degraded by the alkaline pH may benefit from prolonged gastric retention.[3,4]

In addition, for local and sustained drug delivery to the stomach and proximal small intestine to treat certain conditions, prolonged gastric retention of the therapeutic moiety may offer numerous advantages including improved bioavailability and therapeutic efficacy and possible reduction of dose size.[5-7]

Several approaches have been attempted in the preparation of gastroretentive drug delivery systems. These include floating systems,[8,9] swellable and expandable systems,[10-12] high-density systems,[13] bioadhesive systems,[14-16] altered shape systems,[17-20] gel-forming solution or suspension systems[21] and sachet systems.[22]

Floating drug delivery formulations and the polymers used in these systems have become much more sophisticated, with the ability to do more than simply extend the effective release period for a particular drug. While much of work is still in its early stages, to develop newer polymers and optimization of different polymer combination for development of FDDSs.

From review of literature related on FDD it is suggested that future research work in the FDDSs should be aimed at discovering means to accurately control the drug input rate into the GI tract for the optimization of the pharmacokinetic and toxicological profiles of medicinal agents by selecting proper polymers.
Methods used for development of floating drug delivery

Floating systems, first described by Davis in 1968, are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased GRT and reduces fluctuation in plasma drug concentration. Floating systems can be classified as effervescent and noneffervescent systems.

**Effervescent systems.** Flotation 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 an organic solvent (e.g., ether or cyclopentane) or by the CO2 produced as a result of an effervescent reaction between organic acids and carbonate–bicarbonate salts. These devices contain a hollow deformable unit that converts from a collapsed to an expanded position and returns to the collapsed position after predetermined amount of time to permit the spontaneous ejection of the inflatable system from the stomach.

**Noneffervescent systems.** Noneffervescent systems incorporate a high level (20–75% w/w) of one or more gel-forming, highly swellable, cellulosic hydrocolloids (e.g., hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC) and sodium carboxymethylcellulose (NaCMC)), polysaccharides or matrix-forming polymers (e.g., poly(glycolic acid), polylactide-co-glycolide) into tablets or capsules. Upon coming into contact with gastric fluid, these gel formers, polysaccharides and polymers hydrate and form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the DF dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density of and confers buoyancy to the DF. On other hand microspheres, beads, microballoon and micro/nanoparticles which are having lower density than gastric fluid also capable to float in stomach.

![Figure 1: Schematic presentation of working of a triple-layer system. (A) Initial configuration of triple-layer tablet. (B) On contact with the dissolution medium the bismuth layer rapidly dissolves and matrix starts swelling. (C) Tablet swells and erodes. (D) and (E) transition front and erodible gel layer](image)

**Use of various polymers in floating drug delivery system**

**Polymers used for floating tablets**

**Cellulosic hydrocolloids**

Yang et al. developed a swellable asymmetric triple-layer tablet with floating ability to prolong the gastric residence time of triple drug regimen (tetracycline, metronidazole and clarithromycin) in Helicobacter pylori-associated peptic ulcers using HPMC and PEO as the rate-controlling polymeric membrane excipients. List of polymer used in floating drug delivery systems are shown in Table 1. The design of the delivery system was based on the swellable asymmetric triple-layer tablet approach. HPMC and PEO were the major rate-controlling polymeric excipients. Tetracycline and metronidazole were incorporated into the core layer of the triple-layer matrix for controlled delivery, while bismuth salt was included in one of the outer layers for instant release. The floatation was accomplished by incorporating a gas-generating layer consisting of sodium bicarbonate-calcium carbonate (1:2 ratios) along with the polymers. Ozdemir et al. developed floating bilayer tablets with CR for furosemide. The low solubility of the drug could be enhanced by using the kneading method, preparing a solid dispersion with β-cyclodextrin mixed in a 1:1 ratio. One layer contained the polymers HPMC 4000, HPMC 100 and CMC (for the control of the drug delivery) and the drug. The second layer contained the effervescent mixture of sodium bicarbonate and citric acid. The in vitro floating studies revealed that the lesser the compression force the shorter is the time of onset of floating, i.e., when the tablets were compressed at 15 MPa, these could begin to float at 20 minutes whereas at a force of 32 MPa the time was prolonged to 45 minutes. Radiographical studies on six healthy male volunteers revealed that floating tablets were retained in stomach for 6 hours and further blood analysis studies showed that bioavailability of these tablets was 1.8 times that of the conventional tablets.

Wu et al. developed floating sustained release tablets of nimodipine by using HPMC and PEG 6000. Prior to formulation of floating tablets, nimodipine was incorporated into poloxamer-188...
solid dispersion after which it was directly compressed into floating tablets. It was observed that by increasing the HPMC and decreasing the PEG 6000 content a decline in vitro release of nimodipine occurred.

Sheth and Tossounion[38,39] developed sustained release floating tablet that were hydrodynamically balanced in the stomach for an extended period of time until all the drug-loading dose was released. Tablets were comprised of an active ingredient, 0-80% by weight of an inert materials and 20-75% by weight of one or more hydrocolloids such as MC, HPC, HEC, HPMC and NaCMC, which upon contact with gastric fluid provide a water impermeable colloid gel barrier on the surface of tablets [Figures 2 and 3].

### Gel-forming hydrocolloids / Matrix formers

#### Carbopol

Nur and Zhang[40] developed floating tablets of captopril using HPMC (4000 and 15,000 cps) and carbopol 934P. In vitro buoyancy studies revealed that tablets of 2 kg/cm² hardness after immersion into the floating media floated immediately and tablets with hardness 4 kg/cm² sank for 3-4 minutes and then came to the surface. Tablets in both cases remained floating for 24 hours. The tablet with 8 kg/cm² hardness showed no floating capability. 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 the gastric fluids and the presence of internal voids in the center of the tablet (porosity). A prolonged release from these floating tablets was observed as compared with the conventional tablets and a 24-hour CR from the DF of captopril was achieved.

Admixtures containing Carbopols 940, 941 and NaCMC were assessed for bioadhesive delivery of metronidazole. The bioadhesive properties of the admixtures were estimated by using the adhesion of polymer coated glass beads on a biological tissue and the modified Lecomte Du Nouy tensiometer. The rheological behaviors of the polymers and their admixtures were studied as well. The bioadhesive, swelling and release characteristics of tablet compacts formulated with the polymers and their admixtures, which contained metronidazole, were also determined. Results obtained indicated that although all single polymers and their admixtures had high bioadhesive potentials, Carbopol 940 and 941 admixtures (2:1) showed the best performance and NaCMC/Carbopol 940 admixture (2:1) exhibited the least bioadhesive strength.

### Polyvinyl lactam and polyacrylate, polyvinyl acetate

Penners et al.,[41] developed an expandable tablet containing mixture of polyvinyl lactams and polyacrylates that swell rapidly in an aqueous environment and thus reside in stomach over an extended period of time. In addition to this, gas-forming agents were incorporated. As the gas formed, the density of the system was reduced and thus the system tended to float on the gastric contents.

### Alginites

Talwar et al.,[42] 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% xanthum gum, 13.7% sodium bicarbonate and 12.1% crosslinked polyvinyl pyrrolidine. The viscolysing agent initially and the gel-forming polymer later formed a hydrated gel matrix that entrapped the gas, causing the tablet to float and be retained in the stomach or

---

**Table 2: Commercially available floating formulation**

<table>
<thead>
<tr>
<th>Name of the product</th>
<th>Active ingredient</th>
<th>Category</th>
<th>Name of company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madopar® HBS Capsule</td>
<td>Levodopa (100mg) and Benserazide (25 mg)</td>
<td>Anti-parkinsonial</td>
<td>Roche, USA</td>
</tr>
<tr>
<td>Valrelease® Capsule</td>
<td>Diazepam (15 mg)</td>
<td>Anti-anxiety</td>
<td>Hoffman-La Roche, USA</td>
</tr>
<tr>
<td>Liquid Gaviscon</td>
<td>Al hydroxide (95 mg), Mg carbonate (358 mg)</td>
<td>Antacid (in reflux esophagitis)</td>
<td>Glaxo Smithkline, India</td>
</tr>
<tr>
<td>Topalkan®</td>
<td>Algic acid, aluminium and magnesium salts</td>
<td>Antacid</td>
<td>Pierre Fabre Drug, France</td>
</tr>
<tr>
<td>Almagate flotcoat</td>
<td>Al-Mg antacid</td>
<td>Antacid</td>
<td>Ranbaxy, India</td>
</tr>
<tr>
<td>Conviron</td>
<td>Ferrous sulfate</td>
<td>Antacid</td>
<td>Ranbaxy, India</td>
</tr>
<tr>
<td>Cifran OD</td>
<td>Ciprofloxacin (1 mg)</td>
<td>Antibiotic</td>
<td>Ranbaxy, India</td>
</tr>
<tr>
<td>Cytotec Bilayer capsule</td>
<td>Misoprostal (100 mcg/200 mcg)</td>
<td>Pharmacia, USA</td>
<td></td>
</tr>
</tbody>
</table>

---

**Figure 2:** Intragastric floating tablet (US Patent 4, 167, 558, September 11, 1979)

**Figure 3:** Intragastric floating bilayer tablet (US Patent 4, 140, 755, February 20, 1979)
upper part of the small intestine (spatial control). The hydrated gel matrix created a tortuous diffusion path for the drug, resulting in sustained release of the drug (temporal delivery). They concluded that minor change in the percentage of hydrophilic polymer (sodium alginate) from 0.71% w/w of the composition to 0.34% w/w of the composition resulted in a dramatic and unexpected improvement in the pharmacodynamic and pharmacokinetic parameters, which are important measures of therapeutic efficacy.

Raft-forming systems composed of a gel-forming solution (sodium alginate solution-containing carbonates or bicarbonates) swells and form a viscous cohesive gel containing entrapped CO₂ bubbles [Figure 4] on contact with gastric fluid. Formulations also typically contain antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastroesophageal reflux treatment[43-45] as with Liquid Gaviscon® (GlaxoSmithKline).

**Polymer used for floating capsule**

Ichikawa et al.,[47] developed floating capsules composed of a plurality of granules that have different residence times in the stomach and consist of an inner foamy layer of gas-generating agents. This layer was further divided into two sublayers, the outer containing sodium bicarbonate and the inner containing tartaric acid. This layer was surrounded by an expansive polymeric film (composed of PVA and shellac), which allowed gastric juice to pass through, and was found to swell by foam produced by the action between the gastric juices and the gas-generating agents. It was shown that the swellable membrane layer played an important role in maintaining the buoyancy of the pills for an extended period of time. Two parameters were evaluated: the time for the pills to be floating (TPF) and rate of pills floating at 5 hours (FP₅h). It was observed that both the TPF and FP₅h increased as the percentage of swellable membrane layer coated on pills having an effervescent layer increased. As the percentage of swellable layer was increased from 13 to 25% (w/w), the release rate was decreased and the lag time for dissolution also increased. The percentage of swellable layer was fixed at 13% w/w and the optimized system showed excellent floating ability in vitro (TPF ~10 minutes and FP₅h ~80%) independent of pH and viscosity of the medium.

Matharu et al.,[43] reported a simple method for the preparation of a floating capsule containing captopril. The formulation consists of simple blending of drug, HPMC (4000 and 15000 cps), lactose, microcrystalline cellulose and magnesium stearate and filling into capsules. The capsules were buoyant, but the floating time of the capsules was not reported.

Sheth et al.[49] developed a hydrodynamical balance system (HBS) formulation for sustained drug delivery. This is a capsule formulation consisting of active ingredient, highly swellable hydrocolloids (e.g., cellulose ethers and fatty excipients). When coming into contact with gastric juice, the capsule shell dissolves and the exposed hydrocolloids swell, resulting in the formation of a hydrated boundary on the surface, which gives floating property to the DF and facilitate the controlled diffusion of drug. The continuous erosion of hydrated surface allows for the hydration of inner layers, thereby maintaining the hydrated surface and floating ability of the system. The fatty excipients incorporated in the formulation aid in slow penetration of water, which otherwise would result in sinking of the DF. The authors have also developed sustained release HBS tablets for floating in the stomach for a longer time.[50,51] The tablets contain drug and one or more hydrocolloids such as HPMC, HEC, HPC and NaCMC which swell in gastric fluid and provide controlled drug release.

A CR powder formulation for a basic drug having poor solubility in the small intestine (verapamil hydrochloride) has been developed by Dennis et al.[52] The formulation consists of drug, pH dependent polymer (sodium or potassium salt of alginic acid), pH-independent swellable polymer (e.g., MC, HPC and HPMC) and a binding agent. Water present in the dissolution medium penetrates into the capsule, initiating the surface hydration of the swellable polymer resulting in a gel layer, and the trapped air in gel matrix aid in buoyancy of the capsule. Drug dissolves in the gel layer and diffuses out into the surrounding medium. The drug release of the capsule was comparable to that of the sustained release tablets.

Gerogiannis et al.[53] studied the floating and swelling characteristics of various hydrophilic polymers in deionised water (DIW) and simulated meal medium (SMM). The polymers were filled volumetrically into capsules and the floating measurements were done. The floating characteristics of the polymers were enhanced with increase in their molecular weight (decrease in the rates of hydration). The same phenomena were observed in HPMC and PEO. The floating behavior of all polymers was found enhanced in SMM than in DIW, leading to higher buoyancy for the same volume of the DF. The polymer of different viscosity grades showed significant differences in both the AUC (area under curve i.e., the area between resultant weight curve and the zero baseline) and maximum floating time values. The floating time of all HPMC K-series was found to be more than 8 h.

Stockwell et al.[54] performed in vitro evaluation of floating capsules containing a mixture of sodium alginate and sodium...
bicarbonate. When exposed to the acidic media, the capsules showed floating behavior because of the trapped CO$_2$ in the hydrated gel matrix.

**Polymer used for floating microspheres/bead/microparticles**

**Chitosan and sodium alginate**

Ishak RA and co-workers$^{[55]}$ prepared metronidazole (MZ), in chitosan-treated alginate beads by the ionotropic gelation method by using a (3×2×2) factorially designed in which three viscosity-imparting polymers namely, MC, carbopol 934P and κ-carrageenan, two concentrations (0.2 and 0.4% w/v) of chitosan as encapsulating polymer and two concentrations (2.5 and 5% w/v) of the low density magnesium stearate as a floating aid were tested. The in vivo tests were carried out by orally administering MZ floating alginate beads or MZ suspension, to *H. pylori*-infected mice under fed conditions as a single daily dose for 3 successive days in different doses 5, 10, 15 and 20 mg/kg. They found that histopathological examination showed that groups receiving MZ in the form of floating alginate beads at doses 10, 15 and 20 mg/kg were better than the corresponding suspension form, regarding eradication of *H. pylori* infection. The in vivo *H. pylori* clearance tests showed that MZ floating beads with a dose of 15 mg/kg provided 100% clearance rate whereas the MZ suspension with a dose of 20 mg/kg gave only 33.33%.

Yotsuyangi and co-workers$^{[56]}$ reported that alginate gel particles show a pH-sensitive swelling property, i.e., the particles remain unchanged in distilled water or acidic medium (pH 1.5 KCl-HCl) but swell rapidly in pH 7.0 phosphate buffers to a size greater than the original size. This property of alginate can be useful of drugs, which are acid-sensitive because they can be shielded from attack of gastric juices and can be released at desirable rates in the intestine because of reswelling of xerogels in the intestine.

Hwang and co-workers$^{[57]}$ incorporated ibuprofen in alginate beads. This offers the advantage that gastric irritation caused by ibuprofen can be avoided because the drug is not released much in acidic pH of stomach.

**Casein**

Bulgarelli *et al.*$^{[34]}$ studied the effect of matrix composition and process conditions on casein gelatin beads prepared by emulsification extraction method. Casein by virtue of its emulsifying properties causes incorporation of air bubbles and formation 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 efficiency of high porous matrices is lower than that of low porous matrices.

**Eudragit**

El-Kamel and co-workers$^{[59]}$ developed floating microparticulate drug delivery system. The system consists of microparticles containing drug prepared by the emulsion solvent diffusion technique using four different ratios of Eudragit S100 (ES) with Eudragit RL (ERL). The encapsulation efficiency was decreased with increase in ERL content. They demonstrate that formulation in a ratio of two polymers (1:1) gave the best floating ability in the three different media taken. This can be mainly due to its low bulk density obtained before and after tapping respectively.

**Polymer used in floating system**

Ikura and co-workers$^{[60]}$ reported sustained release floating granules containing tetracycline HCl. The granules are a mixture of drug granulates of two stages A and B, A containing 60 parts of HPMC, 40 parts of polycrylic acid and 20 parts of drug; and B containing 70 parts of sodium bicarbonate and 30 parts of tartaric acid. Sixty parts by weight of granules of stage A and 30 parts by weight of stage B are mixed along with a lubricant and filled into capsule. In dissolution profile, the capsule shell dissolves and liberates the granules, which showed a floating time of more than 8 hours and sustained drug release of 80% in about 6.5 hr.

Streubel *et al.*$^{[61]}$ developed floating microparticles composed of polypropylene foam, Eudragit S, EC and polymethyl methacrylate (PMMA) and were prepared by solvent evaporation technique. High encapsulation efficiencies were observed and were independent of the theoretical drug loading. Good floating behavior was observed as more than 83% of microparticles were floating for at least 8 hours. The in vitro drug release was dependent upon the type of polymer used. At similar drug loading the release rates increased in the following order PMMA < EC < Eudragit S. This could be attributed to the different permeabilities of the drug in these polymers and the drug distribution within the system.

**Gelucire**

Massik and co-workers$^{[62]}$ studied the suitability of different grades of Gelucires (G) to formulate carbamazepine (CBZ) extended release capsules by the application of semisolid matrix (SSM) filling capsule technology. The following results were obtained: a) Release data could not be correlated to the melting point of Gelucires used, pointing to relative lipophilicity of the base as a more important determinant of drug release. Among Gelucire grades having melting points higher than 37°C, the release rate proved to be highly dependent on the HLB value and matrix composition. b) CBZ release occurred by different mechanisms, including matrix disintegration, diffusion and or erosion depending on the vehicle employed. c) Zero-order release profiles of CBZ were obtained from SSM-based on G 50/13, G 53/10 and their blends in ratios higher than 1:1 and G 53/10 with croscarmellose sodium. d) The ageing study revealed that these latter formulations, except those based on Gelucire 50/13, also showed high dissolution stability during 1 yr.

Patel *et al.*$^{[63]}$ were developed controlled release multiunit floating system of a highly water-soluble drug, 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. EC, MC and HPMC were evaluated as release rate modifiers. They found that the moderate amount of Gelucire 43/01 and EC provides desired release of ranitidine hydrochloride from a floating system.

Paradkar *et al.*$^{[64]}$ prepared and evaluated single and multiunit floating matrices of risedronate sodium using Gelucire 43/01 by melt solidification and melt granulation technique, respectively. Multiunit system obtained has shown initial burst release, which was suppressed in single unit system. Both single- as well as multiunit systems showed increase in rate of drug release on aging due to changes in the properties of the Gelucire 43/01. Multiunit matrices obtained by melt granulation were relatively easier for scale-up and advantageous if the initial burst release does not cause any significant clinical adversity.
Ion exchange resin

Lee and co-workers[8] prepared floating microsphere based on acrylic resin with an internal hollow structure using a solvent diffusion and evaporation method. They found that mixing ratio of components in the organic phase affected the size and the yield of microsphere and the optimum result were obtained at the volume ratio of ethanol:propanol:dichloromethane (8:2:5) at rotation speed and temperature of 250 rpm and 25°C, respectively. The release profiles were significantly different depending on the solubility of a drug in the release medium and the physicochemical properties of an encapsulated drug.

Ayabi and co-workers[60] developed a floating system using ion exchange resin that was loaded with bicarbonate by mixing the beads with 1 M sodium bicarbonate solution. The loaded beads were then surrounded by a semipermeable membrane to avoid sudden loss of CO₂. Upon coming in contact with gastric contents an exchange of chloride and bicarbonate ions took place that resulted in CO₂ generation thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads [Figure 5]. The in vivo behavior of the coated and uncoated beads was monitored using a single channel analyzing study in 12 healthy human volunteers by gamma radio scintigraphy. Studies showed that the gastric residence time was prolonged considerably (24 hours) compared with uncoated beads (1-3 hours). List of commercial floating drug delivery systems are shown in Table 2.

**Conclusions**

The currently available polymer-mediated non-effervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be an effective and rational approach to the modulation of controlled oral drug delivery. This is evident from the number of commercial products and a myriad of patents issued in this field. The FDDS become an additional advantage for drugs that are absorbed primarily in the upper segments of GI tract, i.e., the stomach, duodenum and jejunum. Some of the unresolved, critical issues related to the rational development of FDDS include (1) the quantitative efficiency of FDDSs in the fasted and fed states; (2) the role of buoyancy in enhancing GRT of FDDS; and (3) the correlation between prolonged GRT and SR/PK characteristics. Finally, with an increasing understanding of polymer behavior and the role of the biological factors mentioned above, it is suggested that future research work in the FDDSs should be aimed at discovering means to accurately control the drug input rate into the GI tract for the optimization of the pharmacokinetic and toxicological profiles of medicinal agents.

**References**

15. Lehr CM, Bouwstra JA, Kok W, de Boer AG, Tukker JL, Verhoeof JC.


Source of Support: None. Conflict of Interest: None declared.