REVIEW ARTICLE

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Floating Drug Delivery Systems: Need and Development

P. G. YEOLE*, SHAGUFTA KHAN, AND V. F. PATEL[1]
Institute of Pharmaceutical Education and Research, Wardha-442 001
[1]B. M. Shah College of Pharmaceutical Education and Research, Modasa-383 315

Recent scientific and patent literature shows increased interest in academics and industrial research groups regarding the novel dosage forms that can be retained in the stomach for a prolonged and predictable period of time. One of the most feasible approaches for achieving a prolonged and predictable dug delivery profiles in the gastrointestinal tract is to control the gastric residence time, using gastroretentive dosage forms that will provide us with new and important therapeutic options. From the formulation and technological point of view, the floating drug delivery system is considerably easy and logical approach. An attempt has been made in this review article to introduce the readers to the current technological developments in floating drug delivery system.

Oral controlled release dosage forms (CRDFs) are being developed for the past three decades[1] due to their advantages[2]. The design of oral controlled drug delivery systems (CDDS) should primarily be aimed at achieving more predictable and increased bioavailability of drugs. However, the developmental process is precluded by several physiological difficulties, such as inability to restrain and locate the CDDS within desired regions of gastrointestinal (GI) tract due to the variable gastric emptying and motility. It can be anticipated that, depending upon the physiological state of the subject and the design of pharmaceutical formulation, the emptying process can last from a few minutes to 12 h. This variability may lead to unpredictable time for peak plasma levels and bioavailibility[3]. Therefore, the CRDFs approaches has not been suitable for a variety of important drugs, characterized by a narrow absorption window in the upper part of the GI tract i.e. stomach and small intestine, which is due to relatively short transit time of the DFs in these anatomical segments. Thus within a short period (less than 6 h), the CRDFs of such drugs leave the upper part of GI tract and reaches to the non- absorbing distal segment, eventually resulting in a short absorption phase accompanied with lesser bioavailability[4].

Furthermore, the relatively brief Gastric emptying time (GET) in humans, which normally averages 2-3 h through the major absorption zone (stomach or upper part of the intestine), can result in incomplete drug release from the DDS leading to diminished efficacy of the administered dose. Thus, placement of the DDS in a specific region of the GI tract offers numerous advantages, especially to the drugs having narrow absorption window in GI tract[3-6], primary absorption in the stomach, stability problem in intestine, poor solubility at alkaline pH, local activity in stomach, and property to degrade in colon[7,8]. It has been suggested that compounding the drugs with narrow absorption window in a unique pharmaceutical dosage form, which prolongs the gastric residence time would enable an extended absorption phase of these drugs[4,9].

Recent scientific and patent literature shows increased interest in academics and industrial research groups regarding the novel dosage forms that can be retained in the stomach for a prolonged and predictable period of time[10,11]. One of the most feasible approaches for achieving a prolonged and predictable dug delivery profiles in the GI tract is to control the gastric residence time (GRT), using gastroretentive dosage forms (GRDFs) that will provide us

*For correspondence
dr_yeole@rediffmail.com

with new and important therapeutic options[10]. Gastroretentive dosage forms (GRDFs) are designed on the basis of one of the several approaches like, formulating low density dosage form that remain buoyant above gastric fluid (floating dosage form)[3,12] or high density dosage form that is retained at the bottom of the stomach[13], imparting bioadhesion to the stomach mucosa[14], reducing motility of the GI tract by concomitant administration of drugs or pharmaceutical exicipients[10], expanding the dosage form by swelling or unfolding to a large size which limits emptying of the dosage form through the pyloric sphincter[4], utilizing ion-exchange resin which adheres to mucosa[15], or using modified shape sysytem[16].

From the formulation and technological point of view, the floating drug delivery system (FDDS) is considerably easy and logical approach in the development of GRDFs. Hence, this review article focuses on the current technological development in FDDS with special emphasis on its potential for oral controlled drug delivery.

BIOLOGICAL ASPECTS OF GRDFs

Physiology of the stomach:

To comprehend the consideration taken in the design of the GRDFs and to evaluate their performance, the relevant anatomy and physiology of the GI tract must be fully understood[4]. The GI tract is essentially a tube about 9 m long that runs from the mouth to the anus and includes the throat (pharynx), esophagus, stomach, small intestine and large intestine. The wall of the GI tract has the same general structure through most of its length from the esophagus to the anus, with some local variation for each region[6]. The stomach is a J-shaped dilated portion of the alimentary tract situated in the epigastric, umbilical and left hypochondriac regions of the abdominal cavity. Its size varies with the amount of food it contains. The volume is 1.5 l or more in adult[17] and after food has emptied a 'collapsed' state is obtained with a resting volume of only 25-30 ml[18]. The stomach is composed of the fundus (above the opening of the esophagus into the stomach), the body (central part) and the antrum. The pylorus is an anatomical sphincter situated between the most terminal antrum and the duodenum[19]. The fundus and the body store food temporarily, secrete digestive juices, and propels chime, a milky mixture of food with gastric juices, to the antrum. The antrum grinds and triturates food particles and regulates the secretion of the hydrochloric acid as well as the emptying of food[20].

Gastric emptying of content from the stomach:

The process of gastric emptying occurs both during fasting and fed states, however, the pattern of motility differ markedly in the two states. In the fasted state, it is characterized by an interdigestive cycle both through the stomach and small intestine every 2-3 h. This activity is called the interdigestive myoelectric cycle or migrating myoelectric complex (MMC)[3], the interdigestive state is composed of fours phases[4]. Initially, the alimentary canal is quiescent (45-60 min), then, irregular contractions (30-45 min) of intermediate amplitude involving bile secretions followed by regular contractions with high amplitude, also termed as housekeeper waves (5-15 min), which push any residual contents distally and finally, irregular contractions with descending amplitude (0-5 min) ultimately reaching to the basal phase. In the fed state, the gastric emptying rate is slowed since the onset of MMC is delayed[21,22]. In other words, feeding results in a lag time prior to the onset of gastric emptying.

Factors affecting gastric retention:

There are several factors that can affect gastric emptying (and hence GRT) of an oral dosage form. The factors that affect gastric retention time include density[23], size and shape of the dosage form[24], concommitant intake of food[25], and drugs[26] like anticholinergic agents (atropine, propantheline), opiates (codeine) and prokinetic agents (metoclopramide, mosapiride). Other factors such as gender, posture, age, body mass index, and disease state (diabetes, Crohn's disease) also affect gastric retention[3,4,27]. Most of these factors and relevant works have been described here in the context of FDDS.

FDDS remains in the stomach or upper part of GI tract for a prolonged period of time due to their floating capabilities. To make the system float in the stomach, the density of dosage form should be less than gastric content i.e. 1.0 g/cm^3. However, the bulk density of a dosage form is not a sole measure to describe its buoyant capabilities[28], because the magnitude of floating strength may also vary as a function of time and gradually decreases after immersion of the dosage form into the fluid as a result of the development of its hydrodynamic equilibrium[23].

There are several findings related to the effect of specific gravity and food on GRT of FDDS. Several studies[29-31] on the effect of food on performance of FDDS demonstrated that there is a significant effect of food on the gastric residence time of FDDS. It has been suggested that when the

gastroretentive properties of a floating dosage form is independent of meal size, the dosage form will be suitable for patients with a wide range of eating habits[31]. Mazer *et al.*[32], demonstrated that release and absorption kinetic of a lipophillic drug from a floating modified release capsule might be affected by intragastric interaction with the lipid phase of a high fat meal, which indicate that the performance of FDDS also depend on the type of meals.

Most of the studies related to the effect of food on GRT of FDDS share a common view point that food[22] intake is the main determinant of GRT, while specific gravity has only a minor effect on emptying process[32,33]. Thus, it may be concluded from foregoing discussion that although FDDS possess an inherent ability for gastric retention, they rely more on the presence of meal to retard their emptying. The prolongation of GRT by food is expected to maximize drug absorption from a FDDS. This may be rationalized in terms of increased dissolution of drug and longer residence at the most favorable site of absorption[3]. The role of food in the prolongation of the GRT also highlights other determinants of gastric retention. For instance, some studies have shown that the GRT of a dosage form in the fed state can also be influenced by its size[29].

Apart from the food and buoyancy effects, there are other biological factors that can influence the GRT. Thairs *et al.*[34] concluded that the increase in retention time of dosage form may also be due to mucoadhesion by mechanism of charged based attraction by ion exchange resin. Another morphological parameter apart from size, that is shape, also has major influence on gastric emptying and ultimately GRT of dosage form. Berner and Louie-Helm[35] found in their study that the swellable controlled release oral dosage form upon ingestion swell within 30 min in shape having two orthogonal axes of different lengths, the longer axis being at most 3.0 cm in length, and shorter axis being long enough to achieve a length at least 1.2 cm., retained in stomach for prolonged period of time.

Mojavarian *et al.*[36] investigated the effect of gender, posture, and age on the GRT of an indigestible food, the Hiedelberg capsule and found that the mean ambulatory GRT in the male was significantly faster than in their age (±3 years) and race-matched female counterparts (3.4±0.6 vs. 4.6±1.2 h, $p<0.01$). Further, the data indicated that women emptied their stomach at a lower rate than men, regardless of weight, height, body surface area and even when the hormonal changes due to the menstrual cycle were normalized. The mean GRT for volunteers in the supine state was not statistically significant from that in the upright, ambulatory state (3.4±0.8 vs. 3.5±0.7h, $p>0.05$). In the case of elderly, the GRT was prolonged, especially in subjects more than 70 years old (mean GRT-5.8 h; n=3). Another confounding factor is the variability of a transit within and between individuals. Coupe *et al.*[37] revealed that variability in gastric emptying of single and multiple unit systems was large compared to that in small intestinal transit times, however, the intrasubject variation was less than intersubject for both gastric and small intestinal transit times.

Timmermans and Moes[23] carried out a comparative evaluation of gastric transit of floating (F) and non-floating (NF) matrix dosage forms and found that mean GRTs of the NF forms were much more variable and highly dependent on their size, which were in the order of small<medium<large units ($P<0.05$). Moreover, in supine subjects, size influenced GRT of both the F and NF forms ($P<0.05$).

PRACTICAL APPROACHES IN THE DEVELOPMENT OF FDDS

The concept of FDDS was first described in the literature as early as 1968[38], when Davis disclosed a method for overcoming the difficulty experienced by some persons of gagging or choking while swallowing medicinal pills. The author suggested that such difficulty could be overcome by providing pill having a density of less than 1.0 g/cm^3, so that pill will float on water surface. Since then several approaches have been used to develop an ideal floating drug delivery system. Various buoyant preparations include hollow microspheres (micro balloons), microparticles, granules, powders, capsules, tablets (pills), and cylinder. Kawashima *et al.*[39] suggest that most of the floating systems reported in literature are single unit systems such as hydrodynamically balance systems (HBS) and floating tablets, which are unreliable and irreproducible in prolonging GRT in the stomach when orally administered, owing to their fortuitous (all or nothing) emptying process. Some authors[40,41] showed that multiple unit floating dosage forms distributes uniformly within the gastric content and gradually emptied from the stomach, possibly resulting in long lasting effects and reduced variability in absorption with lower probability of dose-dumping. Based on the mechanism of buoyancy, two distinctly different technologies, i.e. non effervescent and effervescent system has been utilized in the development of FDDS[4]. Various approaches used in their formulation and mechanism of buoyancy are discussed in the following subsections.

Effervescent FDDS:

The most commonly used excipients utilized in the development of effervescent FDDS are swellable polymers such as Methocel® [13], polysaccharides e.g. chitosan[42], sodium alginates, and effervescent mixtures, e.g. sodium bicarbonate or calcium carbonate and citric or tartaric acid[43] or matrices containing chambers of liquid that gasify at body temperature[44,45]. The matrices are so prepared that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloid, which creates an upward motion of the dosage form and maintain its buoyancy. The carbon dioxide generating components may be intimately mixed within the tablets matrix containing hydrophilic swellable polymer like HPMC alone or in combination, in each case a single layer tablet may be produced or a bilayer tablet may be compressed, which contains the gas generating layer in the hydrocolloid containing layer and the drug in the other layer formulated for a sustained release effect[46]. Li *et al.*[47] formulated floating capsule by incorporating citric acid into the drug delivery system which contained HPMC of K-100 LV grade having viscosity of 100 cps. It was reported that when this floating capsule comes in contact with aqueous medium, the later penetrates into the calcium containing gastric floating drug delivery system (GFDDS). It was suggested that citric acid reacts with calcium carbonate and generates carbon dioxide, which after entrapment in the polymeric system helps in the floating of the delivery system.

A multiparticulate floating reservoir type of delivery system was developed[48]. The system was based on the expansion of the core, which lead to floating due to a low density. Core expansion caused rupturing of the coating allowing rapid drug release in a pulsatile manner, which solved the intention of formulation. The similar approach was also utilized[49] in the development of floating or pulsatile drug delivery system based on coated effervescent core. The system consisting of sustained release core of HPMC with the effervescent component along with the drug was formulated. The effervescent components were sodium bicarbonate and citric acid in a ratio of 1: 0.7 in a concentration of 30-50 %w/w of the core. The PEG 4000 in a concentration of 4% w/w and lactose or microcrystalline cellulose as filler was added. In presence of aqueous medium, the carbon dioxide so generated get entrapped within the polymeric matrix enabling it to float. They observed that inclusion of 10-20 % w/w HPMC significantly retard the drug release as compared to the dosage form without HPMC. As a part of the same study, it was reported that the release rate of the drug was slightly slower in presence of effervescent component, as later might have formed an additional diffusion barrier for the drug to be released.

Yang *et al.*[50] prepared triple layer tablet with swellable gas generating layer composed of polyox (mw=7×10^6), HPMC K4M, calcium carbonate and sodium carbonate in concentrations of 60% w/w, 10% w/w, 20% w/w and 10% w/w of total weight of parent layer as the first layer. The second layer consisted of polyox (mw:1×10^6), Tetracycline HCl, metronidazole and lactose in a concentration of 15% w/w, 0-5% w/w, 0.25% w/w and 10-60% w/w of total weight of parent layer and was termed as swellable/sustainable drug(s) containing layer. The third layer, a rapidly dissolving drug layer composed of lactose, bismuth salts, Ac-Di-501 and polyox (mw:1×10^6) in a concentration range of 38–78% w/w, 0-60% w/w, 2% w/w, and 0-20% w/w of total weight of parent layer. They evaluated the triple layer tablets for floating properties and release characteristics. It was also observed that all the tablets ascended to the upper one third of the dissolution vessels within short time, and remained floated until the completion of release studies.

Choi *et al.*[51] prepared alginate beads consisting of gas generating agents. The system consisted of sodium alginate and HPMC solution admixed with gas generating agent in a concentration range of 0-1% w/w of 3% w/w of alginate solution and the resultant solution was injected in a $CaCl_2$ solution containing 10%w/w of acetic acid. The resultant suspended beads were stirred with a magnetic stir bar for 10 min and separated after completion of reaction to produce gas. They evaluated the effect of CO_2 producing agents, sodium bicarbonate and calcium carbonate on morphological and floating properties. It was observed that the kind and amount of gas forming agent had a profound effect on size, floating ability, pore structure, morphology, release rate and mechanical strength of floating beads. In general, $CaCO_3$ formed smaller and stronger floating beads than $NaHCO_3$. Consequently, beads formed with $CaCO_3$ significantly extended drug release.

Atyabi *et al.*[15] developed a floating system utilizing ion exchange resins. The system consisted of resin beads, which were loaded with bicarbonate and a negatively charged drug that was bound to the resin. The resultant beads were then encapsulated in a semipermeable membrane to overcome rapid loss of CO_2 upon arrival in the acidic environment of stomach, an exchange of chloride and bicarbonate ions took place, as was expected. As a

result of this reaction, CO_2 was released and trapped in the membrane, thereby carrying beads towards the top of gastric contents and producing a floating layer of resin beads. In contrast, the uncoated beads sank quickly. Radioactivity measurement by scintigraphy showed that gastric residence was substantially prolonged, compared with a control, when the system was given after a light, mainly liquid meal. Furthermore, the system was capable of slow release of drug, a property that widens the scope of such floating system for SR preparation of drugs possessing negative charge since they can be easily bound to the resin in combination with bicarbonate ions.

Ichikawa *et al.*[52] developed multiple unit type of oral floating dosage system, floating pills, which generate CO_2 gas. The system was composed of sustained release pills as seeds surrounded by double layers. The inner layer was an effervescent layer containing both sodium bicarbonate and tartaric acid. The outer layer was a swellable membrane layer containing mainly polyvinylacetate and purified shellac. When the system was immersed in water, it formed swollen pills, like balloons, with a density much lower than 1.0 g/cm^3. They found that system was floating completely within approximately 10 minute and approximately 80% remained floating over a period of 5 hours irrespective of pH and viscosity of the test medium.

Non-effervescent FDDS:

The non-effervescent FDDS are based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as chitosan and carbopol. One of the approaches to the formulation of such floating dosage form involves intimate mixing of drug with a gel forming hydrocolloids, which swell in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier[53]. The air trapped by the swollen polymer confers buoyancy to these dosage forms. In addition, the gel structure acts as the reservoir for sustained drug release since the drug is slowly released by a controlled diffusion through the gelatinous barrier. Sheth and Tossounian[54] postulated that when such dosage form comes in contact with an aqueous medium, the hydrocolloid starts to hydrate by first forming a gel at the surface of 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 in to the solution, the gel layer is maintained by the immediate adjacent hydrocolloid layer becoming hydrated, as a result, the drug dissolves in and diffuses out with the diffusing solvent, creating a 'receding boundary' within the gel structure.

Sheth and Tossounian[55] developed a HBS capsule containing a mixture of a drug and hydrocolloids. Upon contact with gastric fluid the capsule shell dissolved with subsequent swelling, forming a gelatinous barrier, which remained buoyant in the gastric juice for an extended period of time.

Streubel *et al.*[56] developed a floating matrix tablet based on low-density foam powder. The tablet consisted of polypropylene foam powder (Accurel MP 1002, MP 1000), matrix forming materials (HPMC, carbopol, sodium alginate, corn starch, Noveon AA1, carrageenan, gum guar, gum Arabic) and fillers like lactose, microcrystalline cellulose and dibasic calcium phosphate. The system was found to float in the dissolution medium due to highly porous foam powder in the matrix tablets, which provided lower density (0.69-0.98 g/cm^3) than the density of the release medium (1g/cm^3). They found that 17% w/w of foam powder was sufficient to achieve proper *in vitro* floating behavior for at least 8 hours. Extended floating times was suggested to be achieved due to the air entrapment within the foam powder particles, which was found to escape slowly from the system upon contact with the dissolution medium. Bolton and Desai[57] developed controlled release floating tablets of theophylline using agar and light mineral oil. Tablets were made by dispersing a drug/mineral oil mixture in a warm agar gel solution and pouring the resultant mixture into tablet moulds, which on cooling and air-drying formed floatable controlled release tablets. The air entrapped in the tablet gel network reduced the density and enabled the dosage form to float.

Krogel and Bodmeir[43] developed a multifunctional matrix drug delivery system surrounded by an impermeable cylinder. They prepared three different types of configurational cylinders in which layer 2 was composed of an impermeable cylinder with two matrix tablets fixed within the two orifices of the cylinder. The air filled space between the two tablets resulted in a low density floating system. The device remained buoyant until at least one matrix tablet got eroded/dissolved.

Mitra[58] described a multilayer, flexible, sheet like medi-

cament device that was buoyant in the gastric juice of the stomach and had sustained release characteristics. The device consisted of at least one dry, self-supporting carrier film made up of a 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 to entrap a plurality of small air pockets, which brought about the buoyancy to the laminated films.

Thanoo *et al.*[59] developed drug loaded polycarbonate microsphere using a solvent evaporation technique, which endured high drug loading (7.5%). Further increasing the drug to polymer ratio in the microsphere increased their mean particle size and the release rate of the drugs. In another study, authors[60] developed hollow microsphere based on polycarbonate using a solvent evaporation technique containing piroxicam as active moiety. A higher drug loading was achieved (95%). *In vitro* release study demonstrated that the system had released the drug up to 24 h.

Choi *et al.*[61] 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 results were obtained at the volume ratio of ethanol: propanol: dichloromethane (8:2:5) at rotation speed and temperature of 250 rpm and 25°, respectively. Several different drugs with various physicochemical properties were used as model drugs for encapsulation and release tests. When a drug had low solubility in dichloromethane and high solubility in both water and a mixture of ethanol/isopropanol, the loading efficiency was the lowest. 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.

Iannuccelli *et al.*[64] developed air compartments multiple unit system for prolonged gastric residence. The system consisted of a coated bead composed of calcium alginate core separated by an air compartment from a calcium alginate or calcium alginate/polyvinyl alcohol membrane. The floating ability depended on the presence of the air compartment and on membrane porosity. The porous structure generated by the leaching of polyvinyl alcohol, employed as a water-soluble additive in the coating composition, increased the membrane permeability preventing air compartment shrinkage. The floating ability increased with the increase in polyvinyl alcohol concentration and molecular weight and it was found to be excellent when using polyvinyl alcohol 1 00 000 at a concentration of at least 5%. The presence of the air compartment provided units with apparent density value less than unity, which made the units to float immediately on immersion in water. The units showed lasting (more than 24 h) and excellent (100% floating ability) buoyancy. The water penetrated into the compartment but did not fill it completely thus not impairing floating ability.

Murata *et al.*[62] prepared floating alginate gel beads for stomach specific drug delivery. They prepared two types of alginate gel beads: The first, alginate gel beads containing vegetable oil (ALGO), held in the alginate gel matrix. The model drug was released gradually into artificial gastric juice, the release rate being inversely related to the percentage of oil. The second alginate gel beads containing chitosan (ALCS) was dried gel beads with dispersed chitosan in the matrix. The drug release profile was not affected by the kind of chitosan contained in ALCS. When ALCS containing drug was administered orally to guinea pigs, it floated in the gastric juice and released the drug in stomach. Furthermore, the concentration of drug in the gastric mucosa after administration of ALCS was higher than that in the solution, though the drug serum concentration was the same irrespective of the type of gel administered.

El-Kamel *et al.*[63] developed floating microparticulate drug delivery system. The system consisted 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 the increase in ERL content. They demonstrated 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. Moreover, its high packing density plus its high packing factor mean that intervoid space is relatively low.

Bodmeier *et al.*[41] developed floating microparticulate system beads on low-density foam powder. The system consisted of polypropylene foam powder, a drug, and Eudragit RS, ethyl cellulose (EC) or polymethylmethacrylate (PMMA) as polymers were prepared with an o/w solvent evaporation method. The encapsulation efficiency close to 100% was achieved. The release rate increased with increasing the drug loading and with decreasing polymer amounts.

They reported that more than 83% of the particles kept floating for at least 8 h *in vitro*, which was due to low apparent density of the microparticles. The foam powders as well as polymer have a highly porous internal and external structure, which when exposed to the aqueous media enabled the extended floating properties due to air entrapment into the polymeric structure.

A synergism between a bioadhesive system and a floating system has also been explored. Nur and Zhang[14] developed floating and/or bioadhesive tablets using HPMC (4 000 cps and 1 500 cps) and carbopol 934 P. They reported that the system released the drug over 24 h *in vitro* and followed the Higuchi model as well as Korsmeyer and Peppas equation[64]. They also reported that tablet hardness was found to be a determining factor with regard to the buoyancy of the tablets. It was noteworthy that release kinetics for effervescent floating systems significantly deviated from the classical Higuchi model and approached zero order kinetics systems[52,65]. This deviation in drug release behavior has been attributed to the air entrapment in the matrix, which was considered as a barrier to diffusion, and matrix relaxation[42]. In contrast, noneffervecent-floating system obeyed the Higuchi model, indicating drug release via a diffusion mechanism[63,66].

Improvements in all aspects of this delivery system are required if efficient systems are to emerge. Since interest in this area has dramatically increased in the past few years it is likely that all the techniques being developed will eventually lead to the development of the successful dosage form especially for drugs with narrow absorption window.

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