Pharmaceutical Formulation and development of Floating and Swellable sustained drug delivery systems: a review

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Abstract

The purpose of this review on floating and swellable drug delivery systems is to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. The review also aims to discuss various parameters affecting the behavior of floating and swelling multiparticulate in oral dosage form summarizes the in vitro techniques, in vivo studies to evaluate the performance and application of floating and swellable systems, and applications of these systems. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form. From the formulation and technological point of view, the floating and swellable drug delivery systems are considerably easy and logical approach. An attempt has been made in this review article to introduce the scientists to the current technological developments in floating and swellable drug delivery system.

Key words: Floating dosage form, swelling delivery systems, Controlled release drug delivery systems

Intoduction

One would always like to have an ideal drug delivery system that will possess two main properties:

a) It will be a single dose for the whole duration of treatment.
b) It will deliver the active drug directly at the site of action.

Scientists try to develop systems that can be as close to an ideal system as possible. An attempt to develop a single dose therapy for the whole duration of treatment has focused attention on controlled or sustained delivery systems. Sustained delivery describes a drug delivery system with delayed and/or prolonged release of drug.[1,2]. The main purpose for developing these systems is to enhance the safety of a product to extend its duration of action. There are many disadvantages of these systems such as longer time to achieve therapeutic blood levels, more variation in bioavailability, enhanced first pass effect, and dose dumping. These systems are usually more expensive than the conventional systems[3]. Since these products are made for the population at large, and not for an individual, they may result in higher or lower steady state drug level in different individuals. If the therapeutic range of drug is broad enough, it may not cause any problem[4]. In spite of their disadvantages, research is continued in this area, as there is much scope to further improve currently available systems.

Controlled release drug delivery systems that can be retained in the stomach for a long time have many advantages over sustained release formulations. Such retention

systems are important for the drugs that are degraded in intestine or for drugs like antacids or certain enzymes that should act locally in the stomach. If the drugs are poorly soluble in intestine due to alkaline pH, gastric retention may increase solubility before they are emptied, resulting in improved bioavailability. Such systems are advantages in improving gastrointestinal absorption of a drug with narrow absorption windows as well as for controlling release of a drug having site-specific absorption limitations. Such systems are useful in case of absorption of albuterol where drug is best absorbed in stomach[5]. Retention of drug delivery systems in the stomach prolongs overall gastrointestinal transit time, thereby resulting in improved bioavailability for some drugs. For levodopa, gastric emptying controls its delivery at the site of action, which is proximal small intestine. In this case it will be useful if gastric emptying can be controlled to achieve maximum effect of the drug[6]. B-lactam antibiotics when administered in conventional forms are absorbed rapidly to produce transient peaks in serum blood levels. For such antibiotics, gastric retention systems would be useful as they would be useful, as they would delay gastric emptying and release drug at a slower and constant rate[7].
Such systems cannot be used in the case of drugs like aspirin and other nonsteroidal anti-inflammatory drugs like aspirin and other nonsteroidal anti-inflammatory drugs that induce gastric lesions or for drugs that are unstable in the acidic environment of stomach. Many times it is difficult to incorporate a drug in such gastric retention systems. The retention of these systems depends on many factors such as gastric motility, pH, and presence of food. It is not easy to design and fabricate a system that can overcome all these difficulties.

Discussion

G. Floating and swellable sustained drug delivery systems

Various approaches have been worked out to improve the retention of oral dosage form in the stomach, e.g. floating systems, swelling and expanding systems, bioadhesive systems, high density systems. Floating systems 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 gastro-retention time and reduces fluctuation in plasma drug concentration**,** Swelling delivery systems are capable of swelling to a size that prevents their passage through the pylorus; as a result, the dosage form is retained in the stomach for a longer period of time. Upon coming in contact with gastric fluid, the polymer imbibes water and swells[57,58]

G.1. Stomach

The main function of the stomach is to store food temporarily, grind it, and then release it slowly in to the duodenum. The stomach is an important site of enzyme production. Due to its small surface area, very little absorption takes place from the stomach. It provides a barrier to the delivery of drugs to the small intestine[8,9].
The stomach is located below the diaphragm. Various factors such as volume ingested, posture and skeletal build affect the exact position of the stomach. Anatomically it can be divided into four regions, namely, fundus, body, antrum and pylorus. The main function of funds and body is storage, whereas that of antrum is mixing and grinding. The fundus adjusts to the increased volume during eating by relaxation of fundal muscle fibers. The fundus also exerts a study pressure on the gastric contents, pressing them towards the distal stomach. To pass through the pyloric valve into the small intestine, particles should be of the order of 1-2mm. The antrum does this grinding[141].

G.2. Physiology

Factors such as pH, nature and volume of gastric secretions, and gastric mucosa play an important role in drug release and absorption. Environmental pH affects the performance of orally administered drugs. The pH of stomach in fasted condition is about 1.5 to 2, and in fed condition usually it is 2 to 6[9]. A study conducted in male and female subjects in the Netherlands obtained surprising results. It was found that many subjects in this study had basal pH higher than 6 and many values were between 7 and 9[10]. A large volume of water administered with an oral dosage form changes the pH of stomach to the pH of water initially. This change occurs because the stomach does not have enough time to produce a sufficient quantity of acid before emptying of liquid from the stomach. Thus it does not improve dissolution of basic drugs. Basic drugs will have a better chance to dissolve in a fed condition rather than in fasted conditions[11].

G.3. Volume

The resting volume of the stomach is about 25-50ml[9]. Gastric volume is important for dissolution of dosage forms in vivo.

G.4. Gastric Mucosa

Simple columnar epithelial cell lining is present in the entire mucosal surface of the stomach. Mucus, parietal, and peptic cells are present in the body of stomach. These cells are associated with different functions. The parietal cells secrete acid whereas the peptic cells secrete mucus and bicarbonate. They protect the stomach from digestion by pepsin and from adverse effects of hydrochloric acid. As mucus has a lubricating effect, it allows chime to move freely through the digestive system[8].

G.5. Gastric secretion

Acid, pepsins, gastrin, mucus, and some other enzymes are the secretion of the stomach. Normal adults produce a basal secretion up to 60ml with approximately 4mmol of hydrogen ions every hour. The volume of this secretion can go beyond 200ml and 15 to 50mmol of hydrogen ions, when stimulated. Pure parietal secretion is a mixture of hydrochloric acid and potassium chloride. Histamine stimulated acid secretion through the H_2 receptors located on gastric mucosa. Another potent stimulator of gastric acid is the hormone gastrin. The absorption of vitamin B_{12} from the ileum requires the intrinsic factor, which is continuously secreted by the stomach. The mean thickness of mucus in human stomach is 140μm. it is continuously digested from the surface. Generally it takes 4 to 5 hours for mucus turnover. It protects the gastric mucosa from pepsin and acid in the stomach[8].

G.6. Effect of food on gastric secretion

On average the daily intake of normal adult is 3 to 4 kg of food and drink. In response to this stimulus, the gut secretes an additional 5 liters of fluids. The volume produced within the first hour of eating can be twice of the meals. A distinct pH gradient exists in the stomach after a meal. Then contents of the body of stomach are neutralized and the antrum remains relatively acidic in nature. Thus ingestion of food is the major stimulus to acid secretion of stomach. This effect is more pronounced if the meal has high protein content. It is interesting to know that the protein content of meal has the maximum buffering capacity. Meals can increase the pH to 3 to 5 and feeds such as milk can raise it to over pH 6[8].

G.7. Gastric motility

The stomach produces coordinated movements of the gastric contents due to three layers of smooth muscles. These layers are outer longitudinal muscle layer, inner circular muscle layer, and an oblique layer[8].

It is difficult to control the environment of a dosage form in the gastrointestinal tract at all times following ingestion. The existing motility pattern at the time of administration affects the performance of oral dosage forms. The motility patterns are different in digestive or fasted and interdigestive or fed condition[9].

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There are four phased of stomach movement in the fasted condition. During the digestive phase, motility results in constant emptying of chime from the stomach into the duodenum. This movement occurs similar to a wave. The interdigestive myoelectric cycle, or migration myoelectric complex (MMC), is an electrical activity observed during fasting phase. It is divided into four phases. In phase 1 (basal phase), there is no contraction or secretion. It lasts for about 40 to 60mins. In phase 2 (Perburst phase), there are irregular contractions and bile secretion. During this phase the pressure rises to about 5 to 40mm of Hg during contractions. It lasts for about 20 to 40 min. mucus discharge takes place in phase 3 (burst phase). During this phase, the frequency and amplitude of contraction is at the peak. This a short phase that lasts for about 4 to 6min. during this phase, the baseline pressure increased substantially. The fourth phase is short transitional period of 0 to 5 min between phase 3 and 1 [8,9].

This phase activity moves along the oesophagus, stomach, antrum, duodenum, jejunum, ileum, and cecum. It takes about 2 hr for this phase to move from stomach to ileocecal junction. This phase acts as a cleaning phase, and thus it is also called the "housekeeper wave"[8,9]. In fed conditions, only one phase is present. This phase is present as long as there is food in the stomach. It consists of regular and frequent contractions. These contractions are not as severe as those in the third phase of fasted motility pattern[9].

G.8. Gastric emptying

Particle size[12-14] and feeding state[15, 16] strongly affect the residence time of the particles in stomach. Some other factors affecting gastric emptying are as fallows: type of meal and its caloric content, volume, viscosity, and co administered drugs. The rate of gastric emptying primarily depends on the caloric contents of the ingested meal [17.] It does not differ for proteins, fats, carbohydrates as long as their caloric content is the same. Generally an increase in acidity, osmolarity, and caloric value slows down gastric emptying [18]. Stress increases gastric emptying rate where as depression slows it down[19]. Generally females have a slower gastric emptying rate than males. Age and obesity also affect gastric emptying. Gastric emptying of dosage forms is different in fasted and fed conditions.

G.9. Liqids and fasted fed conditions

Volumes of liquids affect gastric emptying of liquids. Liquids empty exponentially; that is, larger the volume the faster the emptying. Gastric emptying of small volumes like 100 ml or less is governed by the MCC cycle whereas large volumes of liquids like 200ml or more are emptied out immediately after administration[9]. Fluids at body temperature leave the stomach more rapidly than either warmer or colder fluids. Local

or systemic effects of various drugs and physical orientation of the body affect gastric emptying.

G.10. Solids in fasted and fed conditions

Tablets or capsules do not have any significant caloric value. Therefore the stomach treats them as an indigestible material. The gastric residence time of such units is highly variable in fasted condition. Gastric emptying of such units is depending on MMC. It was shown that gastric emptying of tablets was not affected by the physical properties of the tablets [20]. It is known that particle smaller than 2mm in size are emptied from the stomach quickly.

In the fed conditions, the stomach handles particles of different sizes in different ways. In the case of large, nondisintigrating units, gastric emptying becomes more predictable when they are administered after light meal[21]. It was shown that spheres empty from the stomach filled with food as a function of their diameter[22, 23]. They have also shown that this relationship ends when the diameter drops below 1 mm. In case of pellets, it was found that on an empty stomach, the typical emptying time $t_{50\%}$ was 50 to 80 min. In the case of fed stomach, gastric emptying time was 188min. Pellets were emptied from the stomach in 119 and 285 min when administered after a light and a heavy breakfast, respectively[24, 26].

G.11. Dosage forms

The design of controlled release dosage forms should take into account three important criteria, viz., drug, delivery, and destination. Preformulation studies help in studying the physiochemical properties of drugs. These properties include pKa, pH, solubility, and incompatibility[26]. The solubility of a compound affects the choice of a controlled drug delivery system. If the compound has very low solubility (i.e. less than 0.01mg/ml), it is inherently sustained. A drug has to cross a variety of biological membrances in order to produce a therapeutic effect when it is administered to the gastrointestinal tract. Thus a partition coefficient of a drug is important in determining penetration of these membrane barriers by the drug. Compounds with very low partition coefficients will not easily penetrate these membranes, resulting in poor bioavailability. Acid-base hydrolysis and enzymatic degradation attack orally administered drugs. Compounds such as propantheline are unstable in small intestine. This results in decrease bioavailability when administered in controlled release delivery form[27].

Today, a wide range of gastrointestinal controlled delivery systems is available in the market. Generally the nature of delivery depends on the physiochemical properties and dose of the drug, the purpose for controlling drug release, and constraining physiological and pathological factors[26].

In case of oral drug delivery systems, the first destination is the gastrointestinal tract. From here the drug is absorbed and is taken to the site of action. Thus physiology of the gastrointestinal tract has a direct effect on the design of controlled release delivery systems. In addition, effects of disease conditions and co-administered drugs also affect the design[26].

It is noteworthy that there is a relatively paucity of controlled drug delivery systems of proven value for use by the oral route. Though much research has been conducted to develop controlled release delivery systems, very few systems, which retained in the stomach for a long time, have been developed so far. These systems mainly consist of swelling and expanding systems, floating and inflating systems and bioadhesive systems.

G.12. Swelling and expanding systems

One way to retain a dosage form in the stomach is increasing the size. The stomach discharges its content through its pylorus into intestine. If the dosage form can attain size larger than that of the pylorus, it can be retained in the stomach for a long time. Of course, it is not possible to swallow dosage form of such a large size. Thus it should attain this a large size once it is in the stomach. This large size should be achieved fairly quickly; otherwise the dosage form will be emptied through the pylorus. In addition this enlarged form should not block the pylorus. Such a dosage form should also be strong enough to be able to withstand the powerful waves from the stomach.

Various patents are available for these swelling forms. Johnson et al.[27] have a patent on swelling tablets or capsules. These tablets or capsules contain a reaction product of gelatin and N-acetyl-homocystein thiolactone as a component. After swallowing these products swell to an extent that prevents their exit from stomach through the pylorus. Mamajek and Moyer[28] used an expandable envelope containing a drug and an agent. This agent expands when gastric fluid permeates through the envelope. Thus this device enlarges and remains in the stomach for a long time. Theeuwes and Urquhart[29] describe a device containing a hydrogel. This device swells 2 to 50 fold in the stomach. Small pills containing drugs are released from these devices, which disintegrate or are emptied from the stomach.

Caldwell et al.[30-32] have described gastric retention devices in shape of solid stick figure, a ring figure, and a particular figure. These devices are made up with at least one erodible polymer. They are erodible in the presence of gastric juices so that they loose their enlarged forms after a predetermined time. Examples of erodible polymers that can be used practically are cellulosics such as klucel, polyarcylates such as Eudragit E, polyactones, and polyanhydrides. Examples of non erodible polymers are polyolefins, polyamides, and polyurethanes. A drug can be dispersed within an erodible matrix. It can also be fastened to the retention device in the form of controlled drug module. An example of such module is a miniature constant flow pump. The inventors administered these devices to dogs in gelatin capsules. So far, these devices have not been converted for human use.

Cargill et al. tried a different approach to delay gastric emptying of drugs[33]. They carried out the studies in dogs. They studied the importance of physical characteristics such as size, shape, and flexibility on gastric emptying. They molded cloverleaf, disk, string and pellet shapes from silastic elastomers. They fabricated tetrahedron and rigid ring shapes from blends of polyethylene or ethylene, vinylacetate. These were loaded in capsules and administered to dogs with 15-50ml of water. It was observed that the tetrahedron made with low density polyethylene remained in the stomach for longer periods than other shapes of similar size. Gastric retention of rigid rings was affected by their size. Disk and cloverleaf shapes showed poor gastric retention. The stomach eliminated strings and pellets rapidly. Though this study does not give the final solution to the problem of gastric retention, it is definitely thought provaking. More work can be done in this area to develop gastric retention systems[33].

G.13. Floating systems

A floating dosage unit is useful for drugs acting loacally in the proximal gastrointestinal tract. These systems are also useful for drugs, which are poorly soluble or unstable in intestinal fluids. The floating properties of these systems help in retaining these systems in the stomach for a long time. Various attempts have been made to develop a floating system. This system will float on gastric contents for the desired time period. During this time period drug will be released from this system.

After the release of the drug, the remnant of the system will be emptied from t5he stomach. Watanabe et al.[34] developed a floating system. They used empty globular shells with a lower density than that of gastrointestinal fluid. This enabled the shell to float on the gastric fluid and thus achieved prolonged residence in stomach. They used polymers such as polystyrene. Though this system was able to float on gastric fluid, it was difficult to incorporate drugs into such a system. Mitra [35] described a system containing multilayered polymer films. This system contained a drug in matrix along with sealed air pockets. Sheth and Tossounian[36] developed a system of drug and hydrocolloid mixture. This mixture swells and forms a soft gelatinous mass, which floats on the top of the gastrointestinal fluid when it comes in contact with it.
Bolton and Desai[37] developed another floating system with a gel type matrix. They incorporated light oil with drug in this system. Cook et al. [38] increased the efficacy and reduced the side effects with a hydro dynamically balanced capsule containing iron salts. Khattar et al [39] used this system for delivery of propanolol hydrochloride.
Oth et al. [40] developed a bilayer floating capsules for misoprolol. There were two layers in a capsule: a release layer and a floating layer. The floating layer cinsisted of Methocel K4M, lactose, aerosol 200, and magnesium state. The release layer consisted of various combinations of Methocel K4M, K100, drug, HPMC and pharmacoat 606 and 603. Dissolution and χ-scintigraphic studies were conducted on these capsules. Large quantities of high viscosity polymers were incorporated to form a strong viscous layer. This helped in maintaining the integrity of floating layer for a long time. The drug release layer consisted of a gelling agent. This helped avoiding disintegration and prevented delivery of large particles containing drug in to small intestine, thus reducing side effects. There was complete erosion of the release layer during dissolution. The mean gastric residence time was 199±69 min after a light breakfast. After meals, gastric residence time was found to be 618±208min. the study indicated that the two layers did not separate during drug release. This study has shown that a bilayer-floating capsule of sufficient size is a viable system for delivery of drugs at the proximal gastrointestinal tract level[41].
Thanoo et al. developed a floating polycarbonate sphere[42]. They used aspirin as a sample drug. In order to reduce the side effects of aspirin, especially in high dosage therapy such as is needed in arthritis, scientist have tried to develop a system that can overcome these problems. Low dosages for a long time can help in reducing gastrointestinal irritation. They prepared a hollow drug loaded polycarbonate microspheres using a solvent evaporation process. In vitro release studies were conducted in simulated gastric and intestinal fluids. Drug entrapment efficiency of the microspheres depends on initial drug loading. Initial drug loading also affected the particle size distribution of the microspheres. Increased loading of the drug resulted in increased release rate. Particle size affected the release patterns. Initially faster release was observed from the smaller particles, and from the larger particles in the later stages. These scientists have shown that polymers such as polycarbonate can be used to form hollow microspheres that can float on gastric fluids and release drug a long time to reduce the side effects of drugs like aspirin[42].
Mazer et al.[43] investigated the cause for slow absorption kinetics of a floating capsule of isradipine is calcium channel blocker. They also investigated effect of food on intragastric behavior of these floating capsules. Davis et a[44] have shown that gastric residence time of floating and non-floating dosage forms is longer under fed conditions than under fasted conditions. Muller-Lissner et al.[45] concluded that presence of food is the most important factor affecting gastric residence time. Thus these authors studied isrdipine showed that floating capsules remained intact and

floating during the 8hr run. Only 56% of drug was released from these capsules at the end of 8hr. slow erosion of the hydrocolloid matrix was the rate limiting factor for the drug release in vitro. Under fasted conditions there was a transient rise and fall in drug levels. Floating capsules exhibited much lower peak gastric juice drug levels than the normal capsules. Floating capsules displayed sustained released plasma levels. A high fat breakfast strongly influenced gastric juice drug levels from the floating capsules. Under fed conditions both gastric juice drug levels and plasma levels exhibited lag times. Under fed conditions there was a close relationship between the intragastric behavior and the plasma levels. In vitro data showed an excellent correlation with vivo absorption kinetics under fasted conditions. This showed that slow erosion from the capsule surface was responsible for slow drug release, and not the floating characteristics of the capsule. These scientists have shown that floating does not invariably increase gastric residence time[45].

Agyilirah et al. studied the effect of fasted and fed conditions on gastric retention of balloon dosage forms[5]. They compared the gastric emptying time of the balloon dosage forms and the uncoated nondisintegrating tablets. In 0.1M hydrochloric acid at 37^{o}C, the coating from the tablets separated from the core. It formed a balloon around the core. As a result, the entire tablet started floating. This floatation occurred within 15min dropping the tablet into the medium. The balloon tablet three to six times larger than the original one. These tablets released 88% of drug over 8hr during in vitro dissolution studies. The drug release occurred through diffusion. Under fasted conditions the balloon type and the nondisintegrating types of tablets were emptied from stomach quite quickly. Under fed conditions, the balloon tablets remained in the stomach for a longer time than the nondisintegrating tablets. The balloon tablets floated more quickly in fasted conditions than in fed condition. This could be due to presence of high viscosity gastric contents during fed condition.

All these floating types of devices function on the basis of buoyancy whereas inflating balloon type devices achieve enlarged size by converting part of the device into gaseous form.

G.14. Biadhesives systems

Another approach to increase gastric residence time of the dosage forms is to bind them to gastric mucosa or epithelial cell surfaces. Park et al. [46] studied a broad spectrum of polymers for their bioadhesive properties. They concluded that anionic polymers have better binding capacity than neutral or cationic polymers. Longer et al. showed that performance of a drug such as chlorothiazide improved when it was formulated in a bioadhesive dosage form[47]. Chlorothiazide is an antihypertensive drug. It is slightly soluble in water. It is a good candidate for development of a bioadhesive dosage form due to its physicochemical and biological properties. Polycarbohil-albumin beads containing the drug were prepared. In vitro dissolution studies and in vivo studies on rat were conducted. Albumin beads released the drug slowly over period of 8hr. Polycarbophil did not affect the drug release. In vivo studies showed that 90% of the polycarbophil-albumin beads administrated remained in the stomach even after 6hr. autopsy showed that bulk of the polymer was binding to the surface closely. Rinsing could not easily remove it. The polycarbophil-albumin beads improved the bioavailability of the drug by 1.95 times. It is not easy to relate this study to human beings.

In case of bioadhesive systems, the mechanism of adhesion is thought to be the formation of electrostatic and hydrogen bonding at the mucus-polymer boundary. The adhesion is favored by rapid hydration. These bioadhesive systems do not seem to be a

very feasible solution as this bond formation is prevented by the acidic environment and thick mucus present in the stomach. High turnover of mucus adds to the difficulties in retaining a bioadhesive system at the site.
All the above systems claim to increase gastric residence time of the drugs. All of them have some drawbacks and most of them show reliable retention for only few hours.

G.15. In vitro and in vivo evaluation

The various parameters that need to be evaluated for their effects on GRT of buoyant formulations can mainly be categorized into following different classes.

1. Galenic parameters: diametral size(cut-off size), flexibility and density of matrices.
2. Control parameters: floating time, dissolution, specific gravity, content uniformity, hardness and friability (if tablet).
3. Geometric parameters: shape
4. Physiological parameters: age, sex, posture, food, and bioadhesion.

The test for buosyancy and in vitro drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 37^{o}C. In practice, floating time is determined by using the USP dissolution apparatus containing 900ml of 0.1 HCl as a testing medium maintained at 37^{o}C. The time required to float the HBS dosage form is noted as floating (or floatation) time.
Dissolution tests are performed using the USP dissolution apparatus. Samples are withdrawn periodically from the dissolution medium, replenished with the same volume of fresh medium each time, and then analyzed for their drug contents after an appropriate dilution. Recent methodology as described in USP XXIII states that the dosage unit is allowed to sink to the bottom of the vessel before rotation of blade is started. A small, loose piece of non reactive material such as not more than a few turns of wire helix may be attached to the dosage units that would otherwise float. However, standard dissolution methods based on the USP or British Pharmacopoeia (BP) have been shown to be poor predictors of in vitro performance for floating dosage forms [48,49]. Illay and Fassihi [47] investigated the application of the helical awire sinker to the swellable floating systems containing theophylline (a sparingly water soluble drug). They observed that the procedure tends to inhibit the three dimensional swelling process of the dosage form and consequently drug release from the formulation was suppressed. Based on their observations, the authors proposed an alternative method in which the floatable delivery system was fully submerged under a ring/mesh assembly. The results showed a significant increase in drug release (>20%). In addition, the proposed method was found to provide reproducible hydrodynamic conditions and consistent release profiles. However, in the case of swellable floating systems, which contain diltiazem (a highly water soluble drug) the authors did not find any difference in release between the proposed method and the USP method. These finding led to the conclusion that drug release from swellable floating systems depends on full surface exposure, unhindered swelling and the drug solubility in water.
Another method to modify official dissolution methods were made by Burns et al.[50] who developed and validated an in vitro dissolution method for a floating dosage form which had both rapid release and SR properties. The method, although based on the standard BP (1993)/ USP (1990) apparatus 2 method, was modified such that naddle blades were positioned at the surface of the dissolution medium. The results obtained with this modified paddle method showed reproducible biphasic release profiles when paddle speeds were increased from 70 to 100 rpm and the dissolution medium pH was

varied from 6.0 to 8.0. The dissolution profile was also unaltered when the bile acid concentration in the dissolution medium was increased from 7 to 14mM. In contrast, the standard paddle or basket method, as described in the BP (1993) was unable to provide either sufficient mixing of the dissolution medium to disperse oily rapid release material or sufficient mechanical erosion of the SR component of the formulation.
In additional studies[49], the authors modified a standard dissolution vessel for more reliable assessment of the performance of the floating dosage forms, particularly those which rely on an erosion mechanism for drug release. The result showed a more reproducible dissolution profile while eliminating the need for the positioning of the paddle blades at the surface of the dissolution medium, thereby simplifying sampling procedures and preventing the adhesion of dosage forms to the paddle blades. Nevertheless, the method retained its ability to differentiate between acceptable and unacceptable dissolution performance.

The specific gravity of floating drug delivery system (FDDS) can be determined by the displacement method using analytical grade benzene as a displacing medium[181]. Timmermans and Moes [50] recommended that the initial (dry state) bulk density of the dosage form and changes in the floating strength with time should be characterized prior to in vivo comparison between floating and non floating units. Further, the optimization of floating formulations should be realized in terms of stability and durability of the floating capability that might occur during in vivo studies. These investigators have also described a method for determining the buoyant capabilities of floating forms and sinking capabilities of the non floating forms [51,52]. The method involves the use of a specially designed apparatus for measuring the total force acting vertically on an object immersed in a liquid. The technical details of the apparatus for measuring the total force acting vertically on an object immersed in a liquid have been described elsewhere[51,52]. The in vivo gastric receptivity of floating dosage forms are usually determined by γ-scintigraphy[54]. Studies are done both on fasted and fed conditions using floating and non floating dosage forms. It is also important that both dosage forms are nondisintegrating units[54, 55, 56].

Conclusion

Though much research has been conducted to develop controlled release delivery systems, very few systems, which retained in the stomach for a long time, have been developed so far. These systems mainly consist of swelling and expanding systems, floating and inflating systems and bioadhesive systems. Floating dosage unit is useful for drugs acting loatable in the proximal gastrointestinal tract. These systems are also useful for drugs, which are poorly soluble or unstable in intestinal fluids. The floating properties of these systems help in retaining these systems in the stomach for a long time. Various attempts have been made to develop a floating system. Large number of pharmaceutical and biotech companies is focusing toward commercializing these techniques and still needs further developments for the sustainable development of pharmaceutical industry.

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