Review Article

Formulation and Evaluation of Floating Dosage Forms: An Overview

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ABSTRACT

Floating dosage forms are emerging as a promising novel dosage forms. Floating dosage forms can be prepared as tablets, capsules by incorporating suitable excipients as well by adding certain gas-generating agents, which in turn give the buoyancy to the dosage form in gastrointestinal fluids. The various excipients such as poloxamer 188, carbopol 934P, hydroxypropylmethylcellulose, polyethylene glycol 6000, beta-cyclodextrin, polyvinyl acetate, purified shellac, Eudragit RS, or polymethyl methacrylate, alginate beads and casein-gelatin beads in combination provide buoyancy to the dosage form. The degree of drug embedded in dosage form determines its release. The hydrated layer slowly releases the drug from the dosage form by diffusion. Due to the hydrated gel layer, floating dosage forms can remain afloat in stomach for 6-8 h and release the active pharmaceutical ingredients for extended period of time in gastric environment. These systems have more flexibility in dosage design than conventional dosage form. For the optimization of the drug release pattern *in vivo*, floating devices such as InteliSite capsule can be used as it provides noninvasive determination of drug absorption and bioavailability at specific sites by gamma scintigraphy. This review summarizes various techniques adopted in the development of floating dosage forms, *in vitro* and *in vivo* studies to evaluate the performance and application of floating dosage forms.

Introduction

Drug delivery systems are used for maximizing therapeutic index of the drug and reduction in side effects due to site-specific drug delivery. With the recent developments and advances in pharmaceuticals, frequently taken medicaments are incorporated in a single unit dosage form. This reduces the frequency of administration of medicament to the patient. The real challenge in the development of a controlled drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form in the stomach or the upper small intestine until all the drug is completely released in the desired period of time.[1,2] The residence of a drug delivery system in the upper part of the gastrointestinal tract (GIT) can be accomplished by several drug delivery systems, such as intragastric floating systems,[3] swelling and expandable systems,[4] bioadhesive systems,[5] modified shape systems,[6] high-density systems,[7] delayed gastric-emptying systems[8] and low-density super porous systems.[9] This review deals with floating dosage forms, an oral novel drug delivery system.

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In general, the drug release is governed by various polymers, which are used in the formulation. These polymers entrap the drug material in the matrix form or form a membranous sheath around the drug. The polymer in either case controls the release rate of drug by diffusion or by erosion method. Such drug delivery systems are termed as controlled drug delivery systems, which release the drug(s) with a predictable kinetics. Other approaches and materials that have been reported are highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC) and floating systems based on ion-exchange resin technology.[10] Excipients used most commonly in these systems include HPMC, polyacrylate polymers, polyvinyl acetate, polyethylene glycol (PEG)-6000, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. Drugs used in the formulation of floating dosage forms and some of the marketed preparations are given in Tables 1 and 2.

The oral dosage forms taken orally are very much affected by the gastric physiology. As it is the gastric residence time (GRT), which decides the retention time of oral dosage form in GIT, the gastric emptying (GE) of liquids in the fasted state is a function of

Table 1: Drugs reported to be used in the formulation of floating dosage forms

Dosage forms	Drugs
Floating microspheres	Aspirin, Griseofulvin, p-Nitroaniline, Ibuprofen, Terfinadine and Tranilast
Floating granules	Diclofenac sodium, Indomethacin and Prednisolone
Films	Cinnarizine
Floating capsules	Chlordiazepoxide hydrogen chloride, Diazepam, Furosemide, Misoprostol, L-DOPA, Benserazide, Ursodeoxycholic acid and Pepstatin
Floating tablets and pills	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Diltiazem, Fluorouracil, Isosorbide mononitrate, p-aminobenzoic acid, Piretanide, Theophylline and Verapamil hydrochloride

the volume administered. The normal GE $t_{1/2}$ is 46.5 ± 5.5 min.[11-14] This sets an approximately 10 h limit for the delivery of drugs absorbed solely from the small intestine region. The various factors affecting GE include age, diseased state and diet. Normal aging is associated with various changes in gastrointestinal motility. The important factor is the impact of various age-related diseases on gastrointestinal motility in elderly patients; for example, long-standing diabetes mellitus may reduce GE in about 50%, depression significantly prolongs whole gut transit time, hypothyroidism may prolong orocecal transit time and chronic renal failure is associated with impaired GE. (Gastro intestinal transit time Figure 1) In addition, various frequently used drugs in an elderly patients cause disordered gastrointestinal motility. These drugs include anticholinergics, especially antidepressants with an anticholinergic effect, opioid analgesics and calcium antagonists.[15] Delayed GE or gastrointestinal symptoms occur in 30%-50% of patients with diabetes[16] as well as in chronic liver diseases.[17] High electrolyte content tends to decrease GE.[18] Glucose supplementation accelerates GE of glucose,[19] viscous polysaccharides show delayed GE and slow transit through the small bowel.[20] The GE is significantly slow during dehydration[21] and at times the GE is very rapid as with liquid diet, emotional stress and exercise. Thus, oral controlled release drug delivery systems have

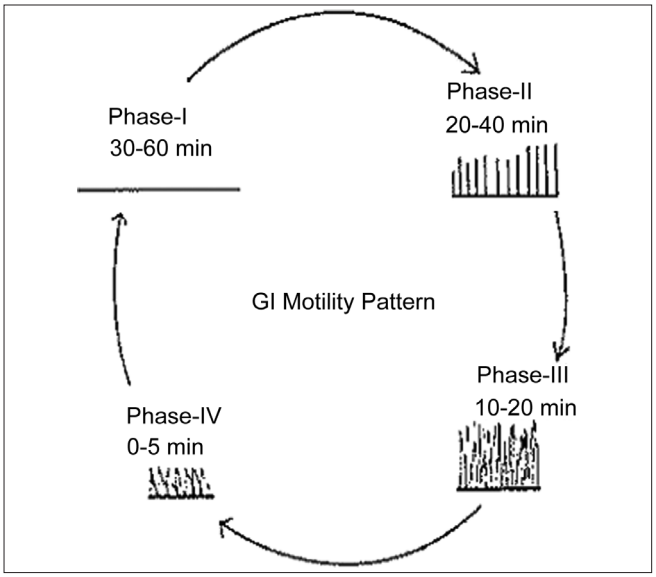

Figure 1: Gastrointestinal motility pattern

Table 2: Marketed preparation

Drug	Brand name
Diazepam Floating capsule	Valrelease
Benserazide and L-DOPA	Madopar
Aluminum-Magnesium antacid	Topalkan
Antacid preparation	Almagate Flot-Coat

limited use in the gastrointestinal controlled administration of drugs if the system cannot remain in the vicinity of the absorption site for lifetime of the drug delivery. The transit time for the mouth to the anus varies with each individual. Oral delivery for 24 h is possible for many drugs; however, the substance must be adequately absorbed throughout the whole GIT. A significant obstacle may arise if there is a narrow window for drug absorption in the GIT or if a stability problem exists in GI fluids or the drug is poorly soluble in the intestine or acts locally in the stomach.

Taking these factors into consideration, investigators formulated a novel drug delivery system for controlled drug delivery at the stomach level, termed as floating tablets or Hydrodynamically Balanced Systems (HBS) or gastroretentive drug delivery systems to prolong the residence of the dosage forms in the stomach or somewhere in the upper small intestine until all the drug is released for the desired period. Gastroretentive systems can remain in the gastric region for several hours, and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestine. Gastroretention helps provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. Different techniques used for gastric retention are mentioned in Figure 2.

Hydrodynamically balanced systems[22]

Sheth and Tossounian[23] developed an HBS system containing a homogeneous mixture of drug and the hydrocolloid in a capsule, which upon contact with gastric fluid acquired and maintained a bulk density of less than 1, thereby being buoyant on the gastric contents of stomach until all the drug was released.

The HBS is the novel dosage form, which when in contact with gastric fluid and after dissolution of the outer exposed surface of the dosage form, forms a hydrated gel layer and maintains bulk density less than 1 g/cm^3. Thus, this system remains buoyant in the gastric fluid inside the stomach for 6 h. Conventional dosage form

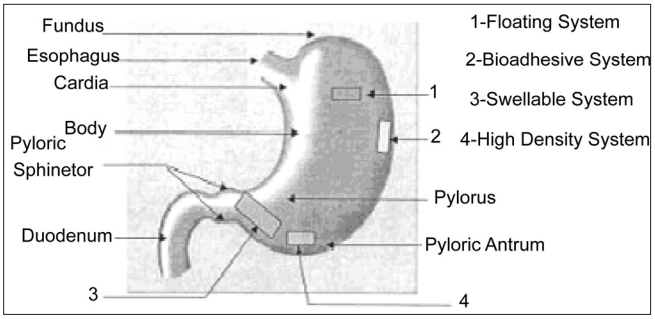

Figure 2: Physiology of gastrointestinal tract

disintegrate completely within 60 min and are emptied totally from the stomach shortly afterward. This dosage form releases the drug through the hydrated layer by diffusion principle. This system is valuable for drugs, which are soluble at lower pH and have absorption window in the upper GIT. By varying the composition of the excipient between 20% and 75% w/w of one or more gel-forming hydrocolloids such as hydroxyethylcellulose, hydroxypropylcellulose, HPMC and sodium carboxymethylcellulose, the granules are prepared and compressed into tablets or encapsulated into capsules, which results in the desired release rate of the drug. This hydrated gel controls the rate of solvent penetration into the device and the rate of drug release from the device.

In the early 70's, Michaels first introduced floating drug delivery device with self-activated mechanism for retaining the device in the stomach, which released the drug under controlled osmotic pressure. The device was found to consist of two chambers, one for the drug reservoir and the other for the osmogen. In the stomach the gastric fluid dissolves the osmogen, which creates pressure on the drug reservoir compartment. This pressure tends to reduce the total volume of drug reservoir compartment, thereby leading to the continuous release of the drug material from the device. In another attempt, Michaels sustained the release of drug in stomach by incorporation of liquid such as ether in an inflatable chamber. In the gastric fluid, the chamber inflates and retains the drug reservoir in stomach. The drug solutes are continuously released from the reservoir into the gastric fluid. Harrigan[24] formulated a drug delivery device with a chamber, which contained vacuum or filled with air or harmless gas. This made the dosage form to float in gastric fluids. The fluids enter the microporous aperture, dissolve the drug and carry the drug solutes out of the drug delivery system for absorption.

Later, Mao *et al*.[25] prepared oral controlled-release system of metoprolol (M-HBS) with first-order *in vitro* release kinetics. The gamma scintigraphy (GS) study indicates that after oral ingestion, M-HBS was retained in human stomach for longer time (5-6 h) than the conventional metoprolol tablet (1-1.5 h). The values of t_{max} and C_{max} were 5.247 h and 125.1 ng/ml, respectively. Moreover, the fraction of the dose absorbed from M-HBS *in vivo* is well correlated with dissolution rate *in vitro*.

Sawicki[26] formulated 40 mg verapamil floating tablet, which had a C_{max} of 28.27 ng/ml, t_{max} 3.75 h and AUC 364.65 ng/ml h, whereas the conventional tablets have 33.07 ng/ml, 1.21 h and 224.22 ng/ml h, respectively. Thus, the formulation had higher AUC and Ke, and therefore had a sustained release pattern.

A HBS-controlled drug delivery tablet of miocamycin was developed by Diao *et al*.[27] The GS study after oral ingestion showed that miocamycin HBS remained in human stomach for more than 7 h, which is much longer than the conventional tablet (3-4 h). The *in vitro* release characteristics showed first-order kinetics. The serum concentration time course of miocamycin HBS exhibited typical sustained release characteristics.

Krogel *et al*.[28] investigated the release behavior of the different devices as a function of HPMC viscosity grade, HPMC content, type of drug (chlorpheniramine maleate or ibuprofen), matrix weight, position of the matrix within the polymeric cylinder, addition of various fillers (lactose, dibasic calcium phosphate or microcrystalline cellulose) and agitation rate of the release medium. The drug release increased with a reduced HPMC viscosity grade, higher aqueous drug solubility, decreased HPMC content and increased surface area of the matrix. The release was fairly independent of the agitation rate, the position of the tablet within the polymeric cylinder and the length of the cylinder. With the pulsatile device, the lag time prior to the drug release could be controlled through the erosion rate of the matrix.

Wu *et al*.[29] prepared a solid dispersion of nimodipine with poloxamer 188 and added excipients (HPMC and PEG 6000) to formulate floating-sustained release tablet. Increasing the HPMC content and decreasing PEG 6000 content led to decrease in nimodipine release *in vitro*. The optimized formulation showed gastric residence time (GRT) of 5 h under fed condition, while GRT was only 3 h under fasting condition. GRT of nimodipine conventional tablet under fed and fasting conditions was 3 and 2 h, respectively. Relative bioavailability of nimodipine floating tablet was 391.46% and GRT over twice that of nimodipine conventional tablet, which appeared to have prolonged GRT and improved bioavailability. Similarly, captopril floating tablets were prepared by Nur *et al*.[30] using HPMC (4000 and 15,000 cps). With this the release profile of captopril from floating tablets could be apparently prolonged and as a result, a 24-h controlled-release dosage form of captopril could be achieved.

Furosemide (FR) is a weakly acidic drug and has a greater absorption window on the upper GIT. The bioavailability was enhanced by Ozdemir *et al*.[31] by preparing an inclusion complex of FR with beta-cyclodextrin (beta-CD) in a 1:1 proportion using the kneading method. After adding the excipients, floating tablets were prepared, which showed retention time of 6 h and AUC of about 1.8 times of the conventional dosage form. Similarly, Menon[32] observed around 15% increase in the bioavailability of FR by preparing monolithic modified release dosage form. Klausner *et al*.[33] reported the absorption phase of levodopa (narrow absorption window) was significantly prolonged following gastroretentive dosage forms (GRDF) administration in comparison with Sinemet CR, which was solely depended on size and rigidity of the novel GRDF.

For the treatment of *Helicobacter pylori*-associated peptic ulcers a floating device was formulated by Yang *et al*.[34] with triple drug regimen (tetracycline, metronidazole and bismuth salt). HPMC and poly (ethylene oxide) 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 could be included in one of the outer layers for instant release. Results demonstrated that sustained delivery of tetracycline and metronidazole over 6-8 h could be easily achieved while the tablet remained in floating state.

Eight healthy volunteers were observed in a pharmacokinetic and hemodynamic study by Hou *et al*.[35] of diltiazem floating tablet. Floating tablets showed that the $t_{1/2}$ (6.4 ± 4.4 h) and C_{max} (56 ± 23 ng/ml) were longer and lower than normal tablets as (2.3 ± 1.1 h and 96 ± 30 ng/ml, $P < 0.01$), respectively.

Streubel *et al*.[36] prepared floating microparticles consisting of (i) Polypropylene foam powder; (ii) verapamil HCl as model drug; and (iii) Eudragit RS, ethylcellulose (EC) or polymethyl methacrylate (PMMA) as polymers and were prepared with oil in water solvent evaporation method. The microparticles exhibited good *in vitro* floating behavior. The drug release rate increased with increasing drug loading and with decreasing polymer amounts.

Hydrodynamically balanced capsules

Apart from HBS tablets many investigators also formulated HBS capsules. The pharmacokinetics of the new drug delivery system named Madopar HBS was developed, which was characterized by lower and delayed plasma peak concentrations but a longer-lasting

concentration of L-DOPA and benserazide than standard Madopar. Therefore, this new controlled release system reduced the clinical fluctuations occurring in parkinsonian patients with "wearing-off" and "on-off" phenomena.[37-39] The drug is released and absorbed over a period of 4-5 h, thus maintaining substantial plasma concentrations for 6-8 h after dosing. The presence or absence of food in the stomach has no effect on the absorption of L-DOPA from Madopar HBS, but administration of antacids reduces the bioavailability. Thus, Madopar HBS showed improvement in the clinical condition by about 86% on average as compared with standard Madopar.[40]

Khar[41] formulated sustained-release floating capsules containing salbutamol sulfate, using different combinations of hydrocolloids of natural and semi-synthetic origin. The floating capsule formulated showed a Higuchian release profile, while the marketed product released only about 80% of the total dose in the stipulated 12 h in the dissolution medium. *In vivo* x-ray studies of the abdomen indicated a residence time up to 8-9 h in the stomach greater than for the non-floating capsule.

A bilayer floating dosage unit composed of HPMC was formulated by Oth *et al*.[42] to achieve local delivery of misoprostol (a prostaglandin E1 analog) at the gastric mucosa level. The use of a large capsule increases the GRT, as it impedes passage through the pylorus opening. GS studies revealed the average GRT was199 ± 69 min after a single meal (breakfast) and 618 ± 208 min after a succession of meals.

Hydrodynamically balanced systems with gas-generating agents

Buoyancy in tablets and capsules could be achieved by incorporating hydrophilic matrix or by incorporation of some inorganic salts that generate gas when in contact with the gastrointestinal fluids.

Baumgartner *et al*.[43] developed the floating matrix tablets with HPMC and by incorporating gas-generating agent together with microcrystalline cellulose in the formulation. The tablet composition and mechanical strength were retained and the floating characteristics as well the drug-release pattern were maintained by properly optimizing the formulation. The floating time was optimized with floating lag time of approximately 30 s and the duration of floating was more than 8 h. Radiological evidence suggests that, the formulated tablets did not adhere to the stomach mucus and that the mean GRT was 4 h.

Ichikawa *et al*.[44] developed an oral floating dosage system, which generated carbon dioxide gas. The system was composed of sustained release pills as seeds and double layers on the sustained release pills. The inner layer comprised an effervescent layer containing both sodium bicarbonate and tartaric acid separated by an inert layer. The outer layer was a swellable membrane layer containing mainly polyvinyl acetate 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. The reaction was due to carbon dioxide gas generated by neutralization in the effervescent layer with the diffusion of water through the swellable membrane layer. The buoyancy lag time was approximately 10 min and 80% remained floating over a period of 5 h irrespective of pH and viscosity of the test medium. The release rate of the drug from the system depends on the sustained release characteristics of the system.

Minitablets formulated by Rouge *et al*.[45] achieved buoyancy either by the swelling of the excipient or by incorporation of the gas-generating agent sodium bicarbonate. The buoyancy of the minitablets containing atenolol was greatly improved by adding gas-generating agent sodium bicarbonate to the floating layer as well as by a wet granulation. Atenolol minitablets containing 7% sodium bicarbonate and coated with Eudragit NE30D:RS 70:30 yielded satisfactory results regarding buoyancy and drug release rate for 6 h.

A bilayer floating tablet for gastric retention with cisapride as a model drug was developed by Wei *et al*.[46] Sodium bicarbonate was added to the floating layer. The tablet when immersed in simulated gastric fluid (SGF) expanded and rose to the surface and eventually the drug was found to release gradually. The *in vitro* drug release of this type of bilayer dosage was controlled by the amount of HPMC in the drug loading layer. Generally, more the HPMC, slower the drugs release. As cisapride has greater solubility in SGF than simulated intestinal fluid (SIF), its *in vitro* drug dissolution is faster as compared with SIF.

Frances *et al*.[47] formulated floating calcium alginate beads, designed to improve drug bioavailability from oral preparations compared with that from many commercially available and modified release products, have been investigated as a possible gastroretentive dosage form. They incorporated riboflavin as a model drug into the formula.

Bhise and Aloorkar[48] formulated floating capsules of theophylline using HBS approach.

In vitro evaluation method

Flow-through USP IV dissolution apparatus

The numerous tests developed for characterizing the biophar maceutical properties are generally based on two distinct methodologies, namely, closed system (beaker method) and an open system (flow-through method). The most common procedures to evaluate the drug release from the floating dosage forms are the paddle and basket methods. In dissolution testing, according to the U.S. Pharmacopoeia, a nonreactive stainless steel wire helix is typically used to sink dosage forms that would otherwise float. Depending on the type and shape, four classes of sinker shapes were defined, namely, longitudinal, lateral, screen enclosures and internal weights. Longitudinal sinkers contact the dosage form on the long axis. Lateral sinkers either wrap around or contact capsule dosage forms in the middle, such as the line where the top and bottom halves of a capsule shell come together. Screen enclosures are of two types, a wire cage that holds the entire capsule or a circular piece of wire screen placed on top of the capsule.[49]

An alternative method, the flow-through method, was also introduced into the pharmacopoeias. The advantages of the flow through method are evidenced from testing and assessing different types of dosage forms and active ingredients of very slight solubility. Also changes in testing fluids (e.g. change to the pH) can be easily performed during the test. Another advantage is seen in the positioning of the specimen. Capsules even when floating initially or pellets can be tested using the same equipment and requires no additional devices such as sinkers.[50] The USP IV assembly (Flow-through Cell) consists of a reservoir and a pump for the dissolution medium, a water bath that maintains the dissolution medium at 37 ± 0.5°C. The pump forces the dissolution medium upward via the flow-through cell. The pump has a delivery range of 240-960 ml/h with standard flow rates of 4, 8 and 16 ml/min. The volumetric flow

must be delivered at a constant rate that is independent of flow resistance in the filter device; the flow profile is sinusoidal with a pulsation of 120 ± 10 pulses/min. The flow-through cell is made of transparent and inert material and is mounted vertically with a filter system (specified in the individual monograph) that prevents the escape of undissolved particles from the top of the cell. standard cell diameters are 12 and 22.6 mm. The bottom cone is usually filled with small glass beads of diameter about 1 mm, with 1 bead of diameter about 5 mm positioned at the apex to protect the fluid entry tube. A tablet holder is available for positioning of special dosage form and the temperature is maintained at 37 ± 5 °C.

By modifying USP dissolution apparatus I and II, Durig *et al*.[51] evaluated floating and sticking extended-release delivery systems by preparing swellable hydrocolloid (guar) matrix tablets containing verapamil HCl. Two additional configurations were used, one with an additional single ring and another with mesh device or a double mesh device, which was located below the paddle in the dissolution vessel. Tablets were placed on top of the single mesh device or in the compartment formed between the two mesh surfaces of the double mesh device. In all cases, near linear ($n \geq 0.82$) release profiles were observed. By using apparatus I, it was observed that the highly swellable tablets were fully constricted by the basket within 5-7 h. This prevented further independent movement and unimpeded swelling and coincided with a departure from linear release and increased variability (SD ≤ 9.5%). By using apparatus I, two of three tablets adhered to the bottom of the dissolution vessel for the duration of the experiment. Consequently, their release profiles were found to differ markedly from those obtained under apparatus I conditions (similarity factor, $f(2) = 30.5$), with the release rate being approximately half of that obtained under apparatus I conditions. Adhesion to the dissolution vessel was also observed when paddle speed was doubled to 100 rpm, thus again resulting in large variability (SD ≤ 34%). Although the average single and double mesh configuration profiles were similar to the apparatus I profile ($f(2) = 57.36$ and 61.38, respectively), large variability (SD ≤ 11%) occurred with the single mesh configuration due to floating and random adhesion of tablets to the paddle or sampling tubes. When the tablets were located in the compartment formed by the double mesh device almost superimposable profiles were obtained (SD < 3%). Use of a double mesh device may therefore provide an alternative to current compendial dissolution methods when the reliable determination of the true release kinetics of floating and sticking delivery systems is desired.

In vivo evaluation method

Gamma scintigraphy

The study of residence in gastrointestinal transit time became necessary to evaluate the drug-release pattern at various levels of GIT by tracking the location of the dosage form. This provided the insight for formulation of a programmable drug dosage form, which would then release the drug at specific levels of the GIT. In earlier days for measurement of *in vivo* GRT, x-ray studies were used.[52] Radiographs of $BaSO_4$ were taken after ingestion of the dosage form, to locate the floating and non-floating (fabricated) dosage forms at various periodic time intervals.

Heidelberg capsule technique was introduced for monitoring GRT by radiotelemetry.[53-57] Ewe *et al*.[58] developed a new method for studying a large variety of physiological, pathophysiological and pharmacological questions concerning gastrointestinal transit by a metal sphere of 6 mm diameter, which can be located accurately in the body by a metal detector at a distance of 2-12 cm from the abdominal surface. This procedure had a correlation of $r = 0.99$, with pH-sensitive radiotelemetering Heidelberg capsule for recording gastric emptying.

Presently, *in vivo* evaluation of floating dosage forms is done by gamma scintigraphy (GS). GS is a technique, whereby the transit of a dosage form through its intended site of delivery can be noninvasively imaged *in vivo* via the judicious introduction of an appropriate short-lived gamma-emitting radioisotope. The observed transit of the dosage form can then be correlated with the rate and extent of drug absorption. Information such as the site of disintegration or dispersion can also be obtained.

Specific site delivery in the GIT can be done by using the InteliSite capsule. The InteliSite capsule is a radiofrequency-activated, non-disintegrating drug-delivery device. It is capable of noninvasive controlled delivery of drug formulations to the GIT for determining regional differences in drug absorption and bioavailability. Radiolabeling permits determination of the capsule location within a specific region of the GIT via GS. When the capsule reaches the desired location in the GIT, external activation opens a series of windows to the capsule drug reservoir. The release and degree of dispersion of the solution or powder contents from the capsule can be visualized. The transit of dosage form or the site of release of drug can be easily correlated with drug absorption. It facilitates neutron activation and standard radiolabeling techniques with regulatory compliance and expert consultation.

Success in formulation and development depends on defining the variables that affect the performance of a drug-delivery system. Often, *in vitro* testing methods are not predictive of *in vivo* results. For oral dosage forms, altered gastrointestinal transit due to individual variation in physiologic or pharmacologic factors or the presence of food may influence bioavailability. Disintegration, erosion or drug release may be premature or delayed *in vivo*. Similarly, altered deposition or clearance from other routes of administration such as nasal, ocular or inhalation may explain drug absorption anomalies. GS combined with knowledge of physiology and dosage form design helps to define these variables. The resulting insight can be used to accelerate the formulation development process and help ensure success in early clinical trials.

Standard radiolabeling techniques will incorporate the radioactive marker in a finished product shortly before dose administration. Alternatively, neutron activation is a technique in which a small amount of stable isotope is incorporated in the dosage form at the time of manufacture. The stable isotope is then converted to a radioactive isotope appropriate for GS by a short exposure to a neutron flux.[59] Hence, GS is a rapid and effective method for determining the rate and extent of drug absorption within specific regions of the GIT under pharmaceutically and physiologically relevant conditions and also it saves time and avoids wastage of resources during the drug-development process by defining formulation objectives.

The radionuclides are used because it is not possible to radiolabel drug molecules for GS. A radionuclide must therefore be used in a carrier or in the formulation, which is having radiation energy (Ideal about 150 KeV) with suitable half-life period. Also it should be easily available and should emit only pure gamma rays. Furthermore, it should be nontoxic and nonabsorbable (for nonparenteral routes).

The metal ion nuclides are most commonly used radionuclides [Table 3].[60-62] 99mTechnetium (99mTc) is the most popular nuclide due to

Table 3: The metal-ion nuclides

Radionucleotide	Radiation energy*	Half-life
^{99m}Tc[47-51]	140	6 h
111In[52]	171 and 245	68 h
113mIn[53]	390	104 min
153Samarium[54]	103	47 h
^{171}Er[55]		7.5 h

*KeV

its optimum energy, easy availability (through portable generator), versatile chemistry, low radiation dose and short half-life period.

Conclusion

Drug absorption in the GIT is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. Floating dosage forms promises to be a potential approach for gastric retention. These systems consisting of swelling and expanding systems, floating and inflating systems and bioadhesive 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. This review summarizes the various attempts, which have been made to develop a floating system, *in vitro* and *in vivo* evaluation studies and application of floating dosage forms.

References

1. Deshpande AA, Rhodes CT, Shah NH, Malick AW. Controlled-release drug delivery systems for prolonged gastric residence: An overview. Drug Dev Ind Pharm 1996;22:631-9.
2. Hwang SJ, Park H, Park K. Gastric retentive drug-delivery systems. Crit Rev Ther Drug Carrier Syst 1998;15:243-83.
3. Deshpande AA, Shah NH, Rhodes CT, Malick AW. Development of a novel controlled- release system for gastric retention. Pharm Res 1997;14:815-9.
4. Patel VF, Patel NM. Self correcting monolithic floating matrix tablets of dipyridamole: Influence of formulation variables. Indian J Pharm Sci 2007;69:219-25.
5. Li S, Lin S, Daggy BP, Mirchandani HL, Chein YW. Effect of HPMC and carbopol on the release and the floating properties of gastric floating drug delivery system using factorial design. Int J Pharm 2003;253:13-22.
6. Kedzierewicz F, Thouvenot P, Lemut J, Etienne A, Hoffman M. Evaluation of peroral silicone dosage forms in humans by gamma-scintigraphy. J Control Release 1999;58:195-205.
7. Davis SS, Stockwell AF, Taylor MJ, Hardy JG, Whalley DR, Wilson CG, *et al*. The effect of density on the gastric emptying of single and multiple-unit dosage forms. Pharm Res 1986;3:208-13.
8. Groning R, Heun G. Dosage forms with controlled gastrointestinal passage-studies on the absorption of nitrofurantoin. Int J Pharm 1989;56:111-6.
9. Streubel A, Siepmann J, Bodmeier R. Floating matrix tablets based on low density foam powder: Effects of formulation and processing parameters on drug release. Eur J Pharm Sci 2003;18:370-45.
10. Yeole PG, Khan S, Patel VF. Floating drug delivery systems: Need and development. Indian J Pharm Sci 2005;67:265-72.
11. Petrakis IE, Kogerakis N, Vrachassotakis N, Stiakakis I, Zacharioudakis G, Chalkiadakis G. Hyperglycemia attenuate erythromycin-induced acceleration of solid-phase gastric emptying in healthy subjects. Abdom Imaging 2002;27:309-14.
12. Degen LP, Peng F, Collet A, Rossi L, Ketterer S, Serrano Y, *et al*. Blockade of GRP receptors inhibits gastric emptying and gallbladder contraction but accelerates small intestinal transit. Gastroenterology 2001;120:361-8.
13. Silang R, Regalado M, Cheng TH, Wesson DE. Prokinetic agents increase plasma albumin in hypoalbuminemic chronic dialysis patients with delayed gastric emptying. Am J Kidney Dis 2001;37:287-93.
14. Kydoneius A. Controlled Release Technologies. 2nd ed. New York: Marcel Dekker; 1991. p. 109-24.
15. Mahony D, Leary P, Quigley EM. Aging and intestinal motility: A review of factors that affect intestinal motility in the aged. Drugs Aging 2002;19:515-27.
16. De Block CE, De Leeuw IH, Pelckmans PA, Callens D, Maday E, Van Gaal LF. Delayed gastric emptying and gastric autoimmunity in type 1 diabetes. Diabetes Care 2002;25:912-7.
17. Ishizu H, Shiomi S, Kawamura E, Iwata Y, Nishiguchi S, Kawabe J, *et al*. Gastric emptying in patients with chronic liver diseases. Ann Nucl Med 2002;16:177-84.
18. Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: A randomised controlled trial. Lancet 2002;359:1792-93.
19. Beckoff K, MacIntosh CG, Chapman IM, Wishart JM, Morris HA, Horowitz M, *et al*. Effects of glucose supplementation on gastric emptying, blood glucose homeostasis, and appetite in the elderly. Amer J Physiol Regul Integr Comp Physiol 2001;280:R570-6.
20. Blackwood AD, Salter J, Dettmar PW, Chaplin MF. Dietary fibre, physicochemical properties and their relationship to health. J R Soc Health 2000;120:242-7.
21. Van Nieuwenhoven MA, Vriens BE, Brummer RJ, Brouns F. Effect of dehydration on gastrointestinal function at rest and during exercise in humans. Eur J Appl Physiol 2000;83:578-84.
22. Chien YM. Novel drug delivery system. 3 ed. Vol. 1. New York: Marcel Dekker; 1992. p. 139.
23. Sheth PR, Tossounian JL. Sustained release pharmaceutical capsules. US patent 4,126,672. November 21, 1978.
24. Harrigan BM. Drug delivery device for preventing contact of undissolved drug with the stomach lining. 1977. US Patent 4055 178.
25. Li SL, Tu XD, Mao FF. Development and pharmacokinetic study of metoprolol tartrate controlled-release tablet remaining-floating in stomach. Yao Xue Xue Bao 1989;25:381-6.
26. Sawicki W. Pharmacokinetics of verapamil and norverapamil from controlled release floating pellets in humans. Eur J Pharm Biopharm 2002;53:29-35.
27. Diao Y, Tu X. Development and pharmacokinetic study of miocamycin sustained release tablet remaining floating in stomach. Yao Xue Xue Bao 1991;26:695-700.
28. Krogel I, Bodmeier R. Development of a multifunctional matrix drug delivery system surrounded by an impermeable cylinder. J Control Release 1999;61:43-50.
29. Wu W, Zhou Q, Zhang HB, Ma GD, Fu CD. Studies on nimodipine sustained release tablet capable of floating on gastric fluid with prolonged gastric resident time. Yao Xue Xue Bao 1997;32:786-90.
30. Nur AO, Zhang JS. Captopril floating and/or bioadhesive tablets: Design and release kinetics. Drug Dev Ind Pharm 2000;26:965-9.
31. Ozdemir N, Ordu S, Ozkan Y. Studies of floating dosage forms of furosemide: *In vitro* and *in vivo* evaluations of bilayer tablet formulations. Drug Dev Ind Pharm 2000;26:857-66.
32. Menon A, Ritschel WA, Sakr A. Development and evaluation of a monolithic floating dosage form for furosemide. J Pharm Sci 1994;83:239-45.
33. Klausner EA, Lavy E, Barta M, Cserepes E, Friedman M, Hoffman A. Novel gastroretentive dosage forms: Evaluation of gastroretentivity and its effect on levodopa absorption in humans. Pharm Res 2003;20:1466-73.
34. Yang L, Eshraghi J, Fassihi R. A new intragastric delivery system for the treatment of *Helicobacter pylori* associated gastric ulcer: *In vitro* evaluation. J Control Release 1999;57:215-22.
35. Gu TH, Chen SX, Zhu JB, Song DJ, Guo JZ, Hou HM. Pharmacokinetics and pharmacodynamics of diltiazem floating tablets. Yao Li Xue Bao 1992;13:527-31.
36. Streubel A, Siepmann J, Bodmeier R. Floating microparticles based on low density foam powder. Int J Pharm 2002;241:279-92.
37. Da Prada M, Kettler R, Zurcher G, Schaffner R, Haefely WE. Inhibition of decarboxylase and levels of dopa and 3-O-methyldopa: A comparative study of benserazide versus carbidopa in rodents and of Madopar

standard versus Madopar HBS in volunteers. Eur Neurol 1987;27:9-20.
38. Erni W, Held K. The hydrodynamically balanced system: A novel principle of controlled drug release. Eur Neurol 1987;27:21-7.
39. Malcolm SL, Allen G, Bird H, Quinn NP, Marion MH, Marsden CD, *et al*. Single-dose pharmacokinetics of Madopar HBS in patients and effect of food and antacid on the absorption of Madopar HBS in volunteers. Eur Neurol 1987;27:28-35.
40. Nordera GP, Lorizio A, Lion P, Durisotti C, D'Andrea G, Ferro-Milone F. Treatment of parkinsonian conditions with a controlled-release form of levodopa--preliminary study. Eur Neurol 1987;27:76-80.
41. Babu VB, Khar RK. *In vitro* and *in vivo* studies of sustained-release floating dosage forms containing salbutamol sulfate. Pharmazie 1990;45:268-70.
42. Oth M, Franz M, Timmermans J, Moes A. The bilayer floating capsule: A stomach-directed drug delivery system for misoprostol. Pharm Res 1992;9:298-302.
43. Baumgartner S, Kristl J, Vrecer F, Vodopivec P, Zorko B. Optimisation of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm 2000;195:125-35.
44. Ichikawa M, Watanabe S, Miyake Y. A new multiple-unit oral floating dosage system, I: Preparation and *in vitro* evaluation of floating and sustained release characteristics. J Pharm Sci 1991;80:1062-6.
45. Rouge N, Cole, ET, Doelker E, Buri P. Buoyancy and drug release patterns of floating minitablets containing piretanide and atenolol as model drugs. Pharm Dev Technol 1998;3:73-84.
46. Wei Z, Yu Z, Bi D. Design and evaluation of a two-layer floating tablet for gastric retention using cisapride as a model drug. Drug Dev Ind Pharm 2001;27:469-74.
47. Frances S, John TF, John HC, Luigi GM. Floating dosage forms to prolong gastro-retention-The characterisation of calcium alginate beads. Int J Pharm 2008;350:301-31.
48. Bhise SB, Aloorkar NH. Formulation and *in vitro* evaluation of floating capsules of theophylene. Indian J Pharm Sci 2008;70:224-7.
49. Soltero RA, Hoover JM, Jones TF, Standish M. Effects of sinker shapes on dissolution profiles. J Pharm Sci 1989;78:35-9.
50. Moller H, Wirbitzki E. Regulatory aspects of modified release dosage forms: Special cases of dissolution testing using the flow-through system. Boll Chim Farm 1993;132:105-15.
51. Durig T, Fassihi R. Evaluation of floating and sticking extended release delivery systems: An unconventional dissolution test. J Control Release 2000;67:37-44.
52. Casteel SW, Brown LD, Latti, Dunsmore M. Fasting and feeding effects on gastric emptying time in juvenile swine. Contemp Top Lab Anim Sci 1998;37:106-8.
53. Kosoglou T, Kazierad D, Schentag JJ, Patrick JE, Heimark L, Radwanski E, *et al*. Effect of food on the oral bioavailability of isosorbide-5-mononitrate administered as an extended-release tablet. J Clin Pharmacol 1995;35:151-8.
54. ZimmermannT, Yeates RA, Laufen H, Pfaff G, Wildfeuer A. Influence of concomitant food intake on the oral absorption of two triazole antifungal agents itraconazole and fluconazole. Eur J Clin Pharmacol 1994;46:147-50.
55. Alioth C, Blum RA, D'Andrea DT, Kochak GM, Teng L, Ziehmer BA, *et al*. Application of dual radiotelemetric technique in studying drug-drug interaction between diclofenac sodium and ranitidine HCl in volunteers. Pharm Res 1993;10:1688-92.
56. Mojaverian P, Reynolds JC, Ouyang A, Wirth F, Kellner PE, Vlasses PH. Mechanism of gastric emptying of a nondisintegrating radiotelemetry capsule in man. Pharm Res 1991;8:97-100.
57. Chan KK, Mojaverian P, Ziehmer BA, John VA. Application of radiotelemetric technique in evaluating diclofenac sodium absorption after oral administration of various dosage forms in healthy volunteers. Pharm Res 1990;7:1026-32.
58. Ewe K, Press AG, Dederer W. Gastrointestinal transit of undigestible solids measured by metal detector EAS II. Eur J Clin Invest 1989;19:291-7.
59. Borin MT, Khare S, Beihn RM, Jay M. The effect of food on gastrointestinal (GI) transit of sustained-release ibuprofen tablets as evaluated by gamma scintigraphy. Pharm Res 1990;7:304-7.
60. Wang X, Zhong YX, Zhang ZY, Lu J, Lan M, Miao JY, *et al*. Effect of L-NAME on nitric oxide and gastrointestinal motility alterations in cirrhotic rats. World J Gastroenterol 2002;8:328-32.
61. Viramontes BE, Kim DY, Camilleri M, Lee JS, Stephens D, Burton DD, *et al*. Validation of a stable isotope gastric emptying test for normal, accelerated or delayed gastric emptying. Neurogastroenterol Motil 2001;13:567-74.
62. Lappin G, Temple S. Radiotracers in drug development. 1st ed. London: CRC Press; 2006. p. 273.

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