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FLOATING MULTIPARTICULATE DRUG DELIVERY SYSTEMS: AN OVERVIEW

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ABSTRACT

In recent scientific and technological advancement have been made in the research and development of rate controlled oral drug delivery systems overcoming physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). Furthermore, absorption windows in the proximal gut can limit the bioavailability of orally administered compounds and can be a major obstacle to the development of controlled release formulations for important drugs. Methods to increase the residence of drug formulations at or above the absorption window are discussed in this review[1]. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery system (FDDS), also known as hydro dynamically balanced systems (HBS), swelling and expanding systems, modified shape systems and high density system. In this review, the current status of floating multiparticulate drug delivery systems including hollow microspheres (micro balloons), low density floating micro pellets and floating micro beads (acrylic resin based), microcapsules etc, their evaluation parameter, advantages, application, limitation and future potential for oral control drug delivery are discussed.

KEYWORDS

Intragastric floating system; micro balloons, microcapsules, micro beads, micro pellets, granules.

INTRODUCTION

Oral drug administration is by far the most preferable route for taking medications. However, their short circulating half-life and restricted absorption via a defined segment of intestine limits the therapeutic potential of many drugs. Such a pharmacokinetic limitation leads in many cases to frequent dosing of the medication to achieve therapeutic effect. This results in pill burden and consequently, patient complains. The phenomenon of absorption via a limited part of the GIT has been termed the narrow absorption window; once this dosage form passes the absorption window the drug will be neither bioavailable nor effective. In extreme cases drugs that are insufficiently absorbed due to narrow absorption window cannot be delivered entirely and are either given by the parenteral route or the development of such medication, which is otherwise safe.

A rational approach to enhance bioavailability and improve pharmacokinetic and pharmacodynamic profile is to retain the drug reserve above its absorption region in GIT, i.e. in the stomach and to

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release the drug in controlled manner so as to achieve a zero order release kinetics (i.e. oral infusion) for prolonged period of time.[2, 3]

The main approach used to increase the gastric residence time of pharmaceutical dosage forms include:

1. Bioadhesive delivery systems, which adhere to mucosal surfaces[4]
2. Delivery systems that rapidly increase in size once they are in the stomach to slow the passage through the pylorus[5]
3. Density controlled delivery system, which either float or sink in gastric fluids[6, 7]

FACTORS AFFECTING THE GASTRIC EMPTYING

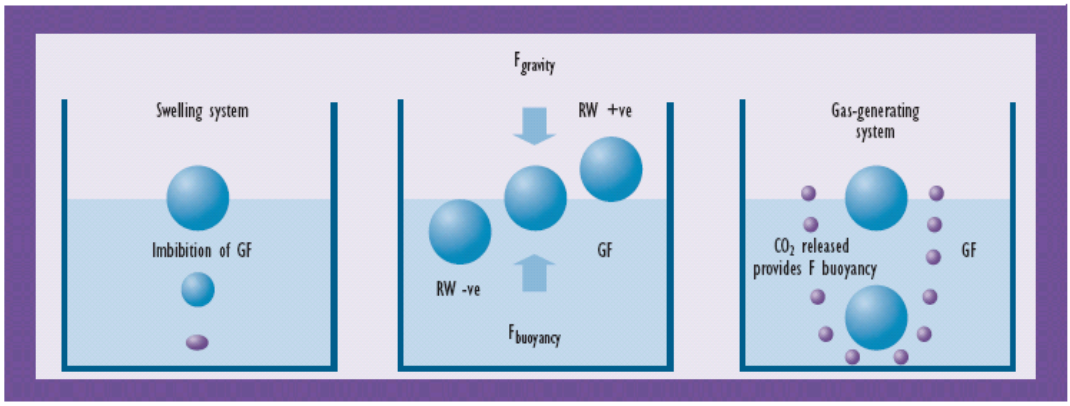
1. Density, size and shape of the dosage form. [8-11]
2. Concomitant ingestion of the food and its nature, caloric content and frequency of intake.[12-18]
3. (Simultaneous) administration of drugs acting as anticholinergic agents (e.g. atropine, propentheline), opoides (e.g. codeine) and prokinetic agents (e.g.metoclopromide, isapride) [19.]
4. Biological factor, such as gender, posture, age, sleep, body weight, physical activity and disease states (e.g. diabetes, crohn's disease) [20-23]

MULTIPARTICULATE DRUG DELIVERY SYSTEMS

In recent years, multiparticulate dosage form such as matrix or coated pellets or micro particles have gained popularity for variety of reasons. Considerable research efforts have been taken on oral sustained or controlled release multiparticulate drug delivery system due to its advantages over monolithic dosage form[24]

Currently more emphasis is given on floating concept of multiparticulate reservoir type delivery system. Floating multiparticulate oral sustained release drug delivery system includes- hollow microspheres (micro balloons), low density floating micro pellets, floating micro beads (acrylic resin based) etc. Reports have been published on the development of both non-effervescent and effervescent multiple unit systems. Much research has been focused and the scientists are still exploring the field of hollow microspheres [25-26], capable of floating on the gastric fluid and having improved gastric retention properties. (**Fig. 1**)

Figure1
The Mechanism of Floating Systems.



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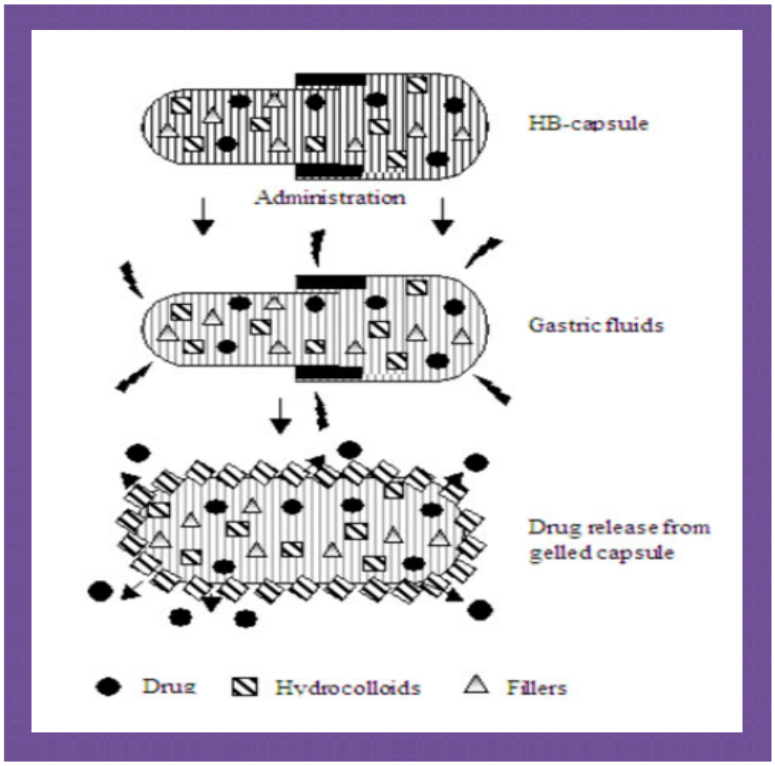
1. NON-EFFERVESCENT SYSTEMS:

Hollow microspheres are considered as one of the most promising buoyant systems[25-27.] They possess the unique advantages of multiple unit systems as well as better floating properties, because of central hollow space inside the microspheres. The general techniques involved in their preparation include simple solvent evaporation and solvent diffusion and evaporation. The drug release and better floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers such as polycarbonate, eudragit® S, cellulose acetate butyrate, ethyl cellulose (EC), poly methyl methacrylate (PMMA) etc. were used in the preparation of hollow microspheres and the drug release can be modulated by optimizing the polymer quantity and the polymer-plasticizer ratio. [32,45,46,48] Hydro dynamically balanced sustained release floating microspheres using polycarbonate were developed by Thanoo et al[28], employing solvent evaporation technique and using Aspirin, griseofulvin and p-nitro aniline as model drugs. The authors also tried the possibility of preparing the hollow spheres using polymers like polymethyl methacrylate and polystyrene, but could only get hard and solid spheres (**Fig. 2**).

Figure 2
Working principle of hydro dynamically balanced system



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El-Gibaly et al[29] developed floating (F) microcapsules containing melatonin (MT), prepared by the ionic interaction of chitosan and a negatively charged surfactant, sodium dioctyl sulfosuccinate (DOS). The characteristics of the floating microcapsules generated compared with the conventional non-floating (NF) microspheres manufactured from chitosan and sodium tripolyphosphate (TPP) were also investigated.Talukder, R. et al[30] developed a floatable multiparticulate system with potential for intragastric sustained drug delivery. Cross-linked beads were made by using calcium and low methoxylated pectin (LMP), which is an anionic polysaccharide, calcium, LMP, and sodium alginate. Beads were dried separately in an air convection type oven at 40 ^{o} C for 6 hours and in a freeze dryer to evaluate the changes in bead characteristics due to process variability. Riboflavin (B-2), tetracycline (TCN), and methotrexate (MTX) were used as model drugs for encapsulation. Ionic and nonionic excipients were added to study their effects on the release profiles of the beads.

Kawashima et al [31] described hollow microspheres (micro balloons) with drug in their outer polymer shells, prepared by a novel emulsion solvent diffusion method. A solution of drug and enteric acrylic polymer (Eudragit® S) in a mixture of ethanol and dichloromethane was added to the aqueous phase containing polyvinyl alcohol (0.75% w/v) and stirred continuously to obtain o/w emulsion. The microspheres showed good flow and packing properties and floating time of more than 12 h in acidic medium containing surfactant.

A modified technique was used by Lee et al [32] in the preparation of hollow microspheres using propranolol hydrochloride, theophylline and cyclosporine as a model drugs. The authors investigated the effect of ethanol and isopropanol in microsphere formation.

Soppimath et al[33] prepared hollow microspheres of cellulose acetate containing cardiovascular drugs by novel solvent diffusion-evaporation method. The method involves organic solvents such as acetone and ethyl acetate. Because of solubility, the organic solvents diffuse into the aqueous phase; this process is responsible for the induction of interfacial polymer deposition resulting in the formation of hollow microspheres[34, 35]. Scanning electron microscopic studies indicated the hollowness and absence of drug crystals on the surface of microspheres suggesting uniform drug distribution, as the physical state of the drug influences the drug release kinetics[36]. The incorporation of hydrophilic substances such as polyethylene glycol[37] and sucrose[38] results in increased drug release from the microspheres and sometimes the lag phase associated with drug release can also be eliminated[39] According to the free volume theory[40], the diffusion occurs by localized activated jumps from the pre-existing cavities to the next cavity. Fell et al[41] prepared floating alginate beads incorporating amoxicillin. The beads were produced by drop wise addition of alginate into calcium chloride solution, followed by removal of gel beads and freeze-drying.

El-kamel et al[42] prepared floating microsphere of ketoprofen; by emulsion solvent diffusion technique. Four different ratios of Eudragit S100 with Eudragit RL were used.

Streubel et al [43] developed floating micro particles composed of polypropylene foam, eudragit S, ethyl cellulose (EC) and poly methyl methacrylate (PMMA) by solvent evaporation technique. At similar drug loading the release rates increased in the following order PMMA<EC<Eudragit S. This could be attributed to different permeability of the drugs in these polymers and the drug distribution within the system.Agrawal et al[44] developed floating micro particles of ripaglinide by the emulsion solvent diffusion technique consisting of

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calcium silicate (FLR) as porous carrier and eudragit S as polymer. .

Srivastava et al [45] prepared floating microspheres of cimetidine as a model drug by solvent evaporation method using polymers hydroxy propyl methylcellulose and ethyl cellulose. The effects of stirring rate during preparation, polymer concentration, and solvent composition on the size of microspheres was studied and the effect of dissolution medium on drug release was also observed.

2. EFFERVESCENT SYSTEMS (GAS-GENERATING SYSTEMS):

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, eg, sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

Ikura et al [46] reported sustained release floating granules containing tetracycline hydrochloride. The granules were mixture of drug granulates at two stages A and B. Stage A contained 60 parts of hydroxypropyl methylcellulose, 40 parts of polyacrylic acid and 20 parts of drug and stage B contained 70 parts of sodium bicarbonate and 30 parts of tartaric acid. Stage A and Stage B granules were mixed in 60:40 ratio by parts and along with a lubricant filled into capsules. In dissolution media, the capsule shell dissolved and liberated the granules, which showed a floating time of more than 8 h and sustained drug release of 80% in about 6.5 h.

Umezawa[47] has reported floating minicapsules of pepstatin having a diameter of 0.1-0.2 mm. These minicapsules contain a central core and a coating. The central core consists of a granule composed of sodium bicarbonate, lactose and a binder, which is coated with hydroxypropyl methylcellulose. Pepstatin is coated on the top of the hydroxypropyl methylcellulose layer. The system floats because of the CO_2 released in gastric fluid and the pepstatin resides in the stomach for prolonged period. Similar double layered coated systems, but in the form of granules have been developed by Ichikawa et al[48]. The granules are comprised of a central core containing drug and are coated with two layers. The immediate layer called the foamable layer is divided into an inner layer containing bicarbonate and outer layer containing an organic acid. The external layer is a polymeric film called the expandable layer. When the granules are placed in gastric fluid, the foamable layer causes foam production leading to expansion of the external expandable layer and result in floating of the granules. The same authors reported floating pills with similar construction as in case of granules[49]. Two layers, an inner effervescent layer and an outer swellable membrane containing polyvinyl alcohol and shellac surrounded the pills. When placed in buffer media, the pills swell like balloons attaining a density lower than 1.0 g/ml, and had a floating time of over 5 h. (**Fig. 3**)

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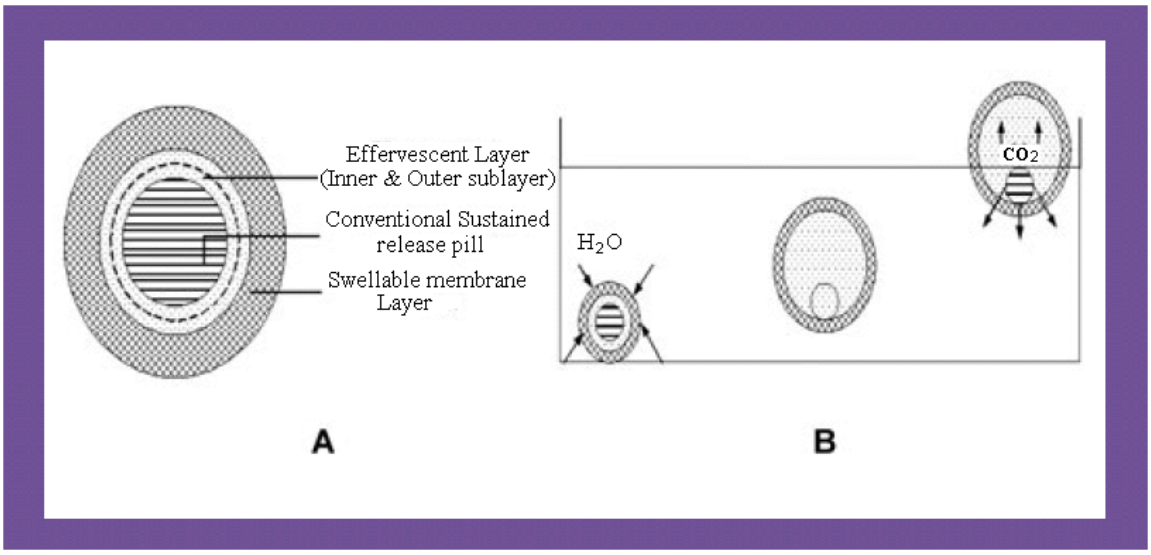
Figure 3

(A)Multiple-unit oral floating drug delivery system.
(B) Working principle of effervescent floating drug delivery system.



A novel method of preparation was utilized by Stithit et al[50] in the preparation of floating microspheres containing theophylline. A modified emulsion-solvent evaporation technique was used for the preparation of microspheres. The drug-polymer (cellulose acetate butyrate and Eudragit RL 100 (1:1)) dispersions were pressurized under CO_2 gas, resulting in the dissolution of the gas in dispersions. Upon release of the pressure, the bubbles were formed and got entrapped into the dispersed drug-polymer droplets, forming cavities inside the microspheres. Alginates have received much attention in the development of multiple unit systems. Alginates are non-toxic, biodegradable linear copolymers composed of L-glucuronic and L-mannuronic acid residues. They are widely used in food and pharmaceutical industries[51, 52, 53.] They may be directly incorporated as salts (e.g. calcium alginate) or in situ salt formation technique can be utilized. A multiple unit system prepared by Iannuccelli et al[54] comprised of calcium alginate core and calcium alginate/PVA membrane, both separated by an air compartment.Increase in molecular weight and concentration of PVA, resulted in enhancement of the floating properties of the system. Freeze-drying technique is also reported for the preparation of floating calcium alginate beads [55, 56]. The obtained beads are freeze-dried resulting in a porous structure, which aid in floating. The authors studied the behavior of radio labeled floating beads and compared with nonfloating beads in human volunteers using gamma scintigraphy[57, 58.]

Floating alginate beads can also be used for delivering the high concentration of drugs to gastric mucosa, taking advantage of both floating and mucoadhesive properties. Two types of floating alginate beads containing metronidazole

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are reported by Murata et al [59]. Choi et al[60] studied the effect of gas-forming agents such as calcium carbonate and sodium bicarbonate on the bead size and floating properties of the alginate floating beads.

The ion exchange property of resins when exposed to the gastric fluids could be utilized in the preparation of controlled release floating beads. Atyabi et al[61] described an ion exchange resin based novel gastro-retentive system. The method of preparation includes loading of resin particles with bicarbonate, and coating with a semi-permeable membrane (Eudragit® RS). In gastric fluid, the exchange of bicarbonate and chloride ions take place leading to the formation of CO_2, which gets entrapped in the membrane making the beads to float. Drug containing ion exchange resin beads were also prepared by using theophylline as a model drug[62], and drug loading of the beads was done by column flow through method [63]. The loaded beads were coated with Eudragit® RS by coacervation and phase separation method, which showed 90% drug release in 24 h. The rate controlling step in ion exchange is assessed by an equation suggested by Boyd et al[64]. From the experimental results, the plot of Bt vs. t[65] was found to be linear, indicating diffusion as the rate-limiting step. The gamma scintigraphic studies showed that the floating times of coated beads were longer compared to the uncoated control, when the volunteers were given a light liquid meal. Since the resin could incorporate both bicarbonate and technetium ions, it can be inferred that the anionic drugs can also be loaded into the resin[66]. A similar formulation, containing anion exchange resin (cholestyramine) has been described by Todd et al[67].S. Jain, et al.[68] prepared cellulose acetate butyrate (CAB)-coated cholestyramine microcapsules as a intragastric floating drug delivery system endowed with floating ability due to the carbon dioxide generation when exposed to the gastric fluid.

EVALUATION OF FLOATING MULTIPARTICULATE

Floating Multiparticulate is characterized by their micromeritics properties such as particle size, tapped density, compressibility index, true density and flow properties including angle of repose. The particle size is determined by optical microscopy; true density is determined by liquid displacement method; tapped density and compressibility index are calculated by measuring the change in volume using a bulk density apparatus; angle of repose is determined by fixed funnel method.[69, 70, 71.]

The surface morphology of the multiple unit systems can be studied by scanning electron microscopy. The determination of physical state of the drug in the multiple unit systems is important. There may be chances of change in crystallinity of the drug during the process, and such changes may influence the drug release properties. The crystallinity of drug can be studied by X-ray powder diffraction technique (XRD) and differential scanning colorimetry (DSC) [72].

Floating properties of the dosage form such as buoyancy lag time and floating time are to be evaluated, as they influence the dosage form behavior. The buoyancy lag time is determined in order to assess the time taken by the dosage form to float on the top of the dissolution medium, after placing the dosage form in the medium. This parameter can be measured as a part of dissolution test[73]. The floating ability of the system i.e. the time for which the system continuously floats on the dissolution media can also be evaluated as a part of dissolution test.

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Whitehead, L., J. T. Fell, et al[74] developed a freeze-dried calcium alginate multiple-unit Floating dosage forms and demonstrated favorable *in-vitro* floating characteristics. The aim of this study was to investigate the *in-vivo* behavior of this system compared to a multiple-unit non-floating dosage form manufactured from identical material. The study was performed in seven healthy volunteers, who swallowed the radiolabelled formulations after a standard breakfast. Transit was monitored by gamma-scintigraphy and subjects were maintained in the fed state. Prolonged GRTs of over 5.5 h were achieved in all subjects for the floating formulations, which remained high up in the stomach for the whole of the test period. In contrast, the non-floating beads displayed short GRTs, with a mean onset emptying time of 1 h. The results of this study suggest that, in the fed state, this floating drug formulation has potential for sustained drug delivery for either local or systemic purposes.

The general method of *in-vitro* testing involves the incorporation of dosage form into the simulated gastric fluid (in order to mimic the *in-vivo* conditions) contained in the dissolution vessel and performing the dissolution as per the standards of the pharmacopoeias. Most of the studies utilized USP dissolution methods, especially paddle type [75, 76, 77.] Various methods such as radiographic imaging techniques and gamma scintigraphy can be used to study the *in-vivo* behavior of the floating dosage forms.[78, 79.]

ADVANTAGES FLOATING MULTIPARTICULATE OVER MONOLITHIC DOSAGE FORM[30]

1. It has lower potential for dose dumping and it minimizes the risk of local irritation.
2. It results in shorter lag time for floating multiparticulate drug delivery System**.**
3. It avoids all or none emptying process.
4. It reduces patient-to-patient variability.
5. It provides greater flexibility to the formulators.
6. It distribute more uniformly in the GIT, thus resulting in more uniform drug absorption.
7. Finally, multiparticulate could be filled into hard gelatin capsules or be compressed into tablets.

APPLICATIONS FLOATING MULTIPARTICULATE DRUG DELIVERY SYSTEMS[33]

Floating multiparticulate drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

1) Sustained Drug Delivery:

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a low bulk density than that of GI fluid as a result of which they can float on the gastric fluid. These systems are relatively large in size and passing through the pyloric opening is prohibited. Hollow microspheres of non-steroidal anti inflammatory drugs are very effective for controlled release as well as it reduces the major side effect of gastric irritation; for example floating microspheres of Indomethacin are quiet beneficial for rheumatic patients

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2) Site-Specific Drug Delivery:

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, eg, riboflavin and furosemide. A bilayer-floating capsule was developed for local delivery of misoprostol, which is a synthetic analog of prostaglandin E1 used as a protectant of gastric ulcers caused by administration of NSAIDs.

3) Absorption Enhancement:

Drugs that have poor bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

LIMITATIONS OF FLOATING MULTIPARTICULATE DRUG DELIVERY SYSTEMS[30]:

1. The residence time in the stomach depends upon the digestive state. Hence, floating multiparticulate drug delivery systems should be administered after the meal.
2. The ability to float relies in the hydration state of the dosage form. In order to keep this microsphere floating i*n-vivo*, intermittent administration of water (a tumbler full, every 2 hours) is beneficial.
3. The ability of drug to remain in the stomach depends upon the subject being positioned upright.
4. Floating multiparticulate drug delivery systems are not suitable for the drugs that have solubility or stability problems in the gastric fluid.
5. Drug like Nifedipine, which is well absorbed along the entire GIT and which undergoes significant first pass metabolism, may not be a desirable candidate for floating multiparticulate drug delivery systems since the slow gastric emptying may lead to the reduced systemic bioavailability.

FUTURE SCOPE OF FLOATING MULTIPARTICULATE DRUG DELIVERY SYSTEMS

Floating multiparticles can greatly improve the pharmacotherapy of the stomach through local drug release, used to eradicate *Helicobacter pylori* from the sub-mucosal tissue of the stomach most effectively and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis[80]. This system allows administration of non-systemic, controlled release antacid formulation containing calcium carbonate and also locally acting anti-ulcer drugs (such as Lansoprazole[81]) in stomach. Buoyant micro particles are considered as a beneficial strategy for the treatment of gastric and duodenal cancers.

Floating multiparticulate systems may be used as a carrier for the drugs having narrow absorption windows, these substances, for example antiviral, antifungal, and antibiotic agents (Sulphonamides, Quinolones, Penicillins, Cephalosporins, Aminoglycosides, and Tetracyclines) are absorbed only from very specific regions of GI tract. In addition, by continually supplying the drug to its most efficient site of absorption, the dosage form may allow for more effective oral use of peptide and protein drugs such as calcitonin, erythropoitin, vasopressin, insulin, low molecular weight heparin, and LHRH. Floating microparticals of NSAIDs are very effective for reducing their major side effect, gastric irritation as well as for controlled release; for example floating microspheres of Indomethacin are quite beneficial for rheumatic patient.

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Table 1

List of Floating Multiparticulate Marketed preparations

S.NO	BRAND NAME	DRUG (DOSE)	COMPANY (COUNTRY)	DOSAGE FORM
1	Conviron	Ferrous Sulfate	Ranbaxy, India	Colloidal Gel Forming FDDS
2	Cytotec®	Misoprostol (100/200 mcg)	Pharmacia	Bilayer floating capsule
3	Topalkan®	Al-Mg Antacid	Pierre Fabre Drug, France	floating liquid alginate preparation
4	MODAPAR®	Levodopa (100mg) Benserzide(25mg)	Roche products (USA)	Floating CR capsules
5	Liquid Gavison®	Al Hydroxide (95mg) Mg. Carbonate (358mg)	Glaxo Smith Kline, India	Effervescent floating liquid alginate preparation
6	Valrelease ®	Diazepam (15mg)	Hoffmann-LaRoche (USA)	Floating capsules

CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable phenomenon and prolonging gastric retention of the dosage form extends the time for drug absorption and attempts to make it more uniform as well as reproducible. Floating Multiparticulate Drug Delivery systems promises to be a potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing towards commercializing this technique. It is hoped that in the near future biopharmaceutically better therapeutic systems in the form of floating drug delivery devices would be introduced in clinics in greater number.

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