Review Article

Hollow microspheres as a drug carrier: An overview of fabrication and *in vivo* characterization techniques

Abstract

Oral controlled release dosage forms encounter several physiological constraints like inability to retain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variation in gastric emptying. This leads to non-uniform absorption profile, insufficient drug release and shorter residence time of the dosage form in the stomach. As the fallout of this event, there is incomplete absorption of the drug having absorption window especially, in the upper part of GIT. These considerations have led to the development of oral controlled release dosage forms with gastroretentive properties. Hollow microspheres hold promise as one of the potential approaches for gastric retention. Hollow microspheres are spherical empty particles without core and can remain in the gastric region for prolonged periods. They significantly extend the gastric residence time of drugs, thereby improving bioavailability, reduced the drug waste and improved solubility for drugs that are less soluble at a higher pH environment. This review attempts to bring more insight into recent advances in methods of fabrication techniques and applications of hollow microspheres.

Key words:
Controlled release, floating microspheres, gastric retention, hollow microspheres, low density, oral

Introduction

The oral route is the most acceptable mode for the administration of pharmacologically active substance to the systemic circulation. Some drugs have ideal characteristics for good absorption throughout the gastrointestinal tract (GIT), whereas others have difficulties.[1] To achieve the effective oral drug delivery, oral controlled release dosage form have been developed over many decades. They offer considerable therapeutic advantages in terms of ease of administration, reduced dosing frequency, better patient compliance and flexibility in formulation.[2] However, in this approach several physiological difficulties have been encountered due to inability to retain and locate the controlled drug delivery system within the desired region of GIT. These problems are manifested due to variation in gastric emptying, leading to non-uniform absorption profile, insufficient drug release and shorter residence time of the dosage form in the stomach.[3] This leads to incomplete absorption of the drug having absorption window, especially in the upper part of GIT.[4] These considerations have led to the development of oral controlled release dosage form with gastroretentive properties.

The ability of gastroretentive systems to remain in the gastric region for a longer period significantly prolong the gastric retention time of drugs. Improved bioavailability, reduction in drug waste and improvement in solubility of drugs that have limited solubility in high pH environment can be achieved by prolonging gastric retention of drugs.[5,6]

Approaches to Gastric Retention

Various approaches have been reported to achieve gastric retention of an oral dosage form. These include.

Hydrodynamically balanced systems

In hydrodynamically balanced systems, drug with gel-forming hydrocolloids are meant to remain buoyant over the stomach

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content. This prolongs gastric retention time and maximizes the amount of drug that reaches its absorption sites. These hydrocolloids on contact with gastric fluid, hydrates and forms a colloid gel barrier around its surface.[7]

Effervescent systems

The gas generating agents such as carbonates (e.g., sodium bicarbonate) and other organic acid (e.g., citric acid and tartaric acid) are utilized in the formation effervescent systems. The density of the present system is reduced due to the production of carbon dioxide by the reaction of gas generating agents with gastric acid, thus allowing the system to float on the gastric fluid.[8]

Low-density systems

Floating systems are based on low density approach. Floating drug delivery systems by virtue of their bulk density lower than gastric fluids (<1 g/ml), float over the gastric fluid and release the drug slowly for a longer period of time. They are prepared by incorporating low-density materials, entrapping oil or air. Most are multiple unit systems and are also called "microballoons" because of their low-density core.[9]

Raft systems

Raft systems upon contact with gastric fluid form a viscous cohesive gel, which swells to form a continuous layer called a raft. Generation of CO_2 by a gel forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) makes the raft float on gastric fluid.[10]

Bioadhesive or mucoadhesive systems

Bioadhesive systems bind to the gastric epithelial cell surface and extend the residence time of the dosage form in the stomach, thereby facilitating an intimate contact of drug with the biological membrane for prolonged duration. This approach involves the use of bioadhesive polymers such as polycarbophil, carbopol, lectins, chitosan and gliadin.[11]

High-density systems

High-density systems have a density (3 g/ml) far exceeding that of normal stomach contents (1 g/ml) and are thus retained in the fold of the stomach for a longer period of time. This is achieved by coating the drug with heavy inert materials such as barium sulfate, zinc oxide, titanium dioxide, iron powder, etc.[12]

Hollow Microspheres

Hollow microspheres are gastroretentive drug delivery systems based on non-effervescent approach. They are spherical empty particles without core. They possess the unique advantages of multiple unit systems and their center hollow space imparts good floating properties making them promising buoyant systems. These microspheres are free flowing low density powders, having a size less than 200 μm, comprising of either proteins or synthetic polymers.[13] The sustained release of drug from the buoyant systems improves the gastric retention and reduces the fluctuations in plasma drug concentration.[14] The quantity of polymers, the plasticizer-polymer ratio and the solvent used for formulation modulates buoyancy and drug release from the dosage form. Commonly used polymers to develop hollow microspheres include polycarbonate, HPMC, cellulose acetate, calcium alginate, Eudragit S, chitosan and low methoxylated pectin. Several investigations have shown that the hollow microspheres are capable of floating continuously over the surface of an acidic dissolution media containing surfactant for >12 h.[9] Figure 1 is a schematic representation of the floating microspheres.

Advantages

Hollow microspheres offer various advantages including:

1. Improves patient compliance by reducing dosing frequency.[15]
2. Enhanced bioavailability despite the first-pass effect because fluctuations in plasma drug concentration is avoided; a desirable plasma drug concentration is maintained by continuous drug release.[15]
3. Increased gastric retention time due to buoyancy.[16]
4. Enhanced absorption of drugs, which solubilize only in the stomach.[17]
5. Controlled drug release for a prolonged period.[16]
6. Site-specific drug delivery to stomach can be achieved.[16]
7. Avoidance of gastric irritation due to sustained release effect.[17]
8. Better therapeutic effect of short half-life drugs can be achieved.[18]

Limitations

Although hollow microspheres have a number of potential advantages, their use can be limited due to the following:

1. High level of fluids in the stomach is required for the hollow microspheres to float and work efficiently.[4]
2. The dosage form should be administered with a full glass of water (200-250 ml).[19]
3. Not suitable for drugs having solubility or stability problem in gastric fluids.[19]
4. The drugs that undergo first-pass metabolism (nifedipine, propranolol, etc.) are not suitable candidates.[5]
5. Irritant drugs to the gastric mucosa are not suitable for gastroretentive systems.[19]

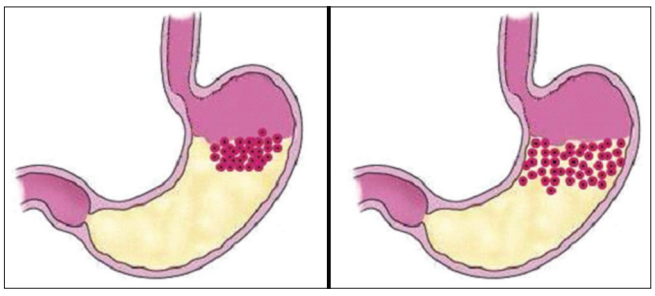

Figure 1: Schematic representation of floating microspheres

Techniques for Preparation of Hollow Microspheres

Various methods have been developed for the preparation of hollow microspheres. These include solvent evaporation, emulsion solvent diffusion, spray drying and miscellaneous methods. These techniques are discussed in detail in the following section.

Solvent evaporation method

Solvent evaporation technique is widely employed to obtain the controlled release of drug. In this method, the drug and polymer are dissolved in an organic phase (usually methylene chloride) and dispersed in an excess amount of aqueous continuous phase, with the aid of an agitator to form an emulsion [Figure 2]. Depending upon the hydrophilicity or the hydrophobicity of drugs, different methods are used to prepare microspheres by solvent evaporation technique [Table 1]. The oil-in-water method is frequently utilized for insoluble or poorly water-soluble drugs, whereas for hydrophilic drugs, this method is inappropriate due to dissolution and extensive loss of drug. Hence, for incorporation of hydrophilic drugs water in oil in water double emulsion method, oil in water co-solvent method and oil in oil non-aqueous solvent evaporation method can be employed.[20]

Solvent evaporation is the simplest method for fabrication of microspheres where process can be controlled easily and the formed microspheres show good product yield and

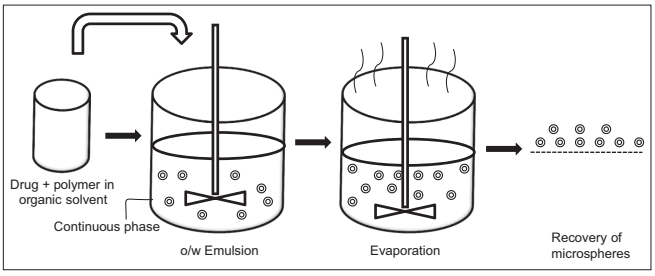

Figure 2: Schematic representation of solvent evaporation method

Table 1: Various hollow microspheres prepared by solvent evaporation method

Drug	Polymer (s)	Remarks	Reference
Valacyclovir HCl	EC	Floating microspheres developed to localize the drug in upper part of GIT, for improved absorption	[22]
Captopril	Eudragit S 100, EC	Sustained release floating microspheres to reduce the dosing frequency of drug	[23]
Stavudine	EC, dibutylphthalate	Novel polymeric combinations for controlled release microspheres to improve the very short half-life (1.30 h) of drug	[24]
Metformin HCl	HPMC, EC	Floating microballoons to achieve an extended retention in upper GIT	[25]
Metformin HCl	Eudragit RS 100, Eudragit RL 100	The drug release could be controlled by changing polymer ratio.	[26]
Boswellic acid	HPMC, EC	Prolonged gastric retention achieved by using HPMC and EC as polymers	[27]
Ranitidine HCl	HPMC K 100, Xanthan gum, Eudragit S 100	The GI retention enhanced by combining acrylic and hydrophilic polymer; frequency of administration could also be decreased	[28]
Rosiglitazone maleate	HPMC, EC	Floating microspheres to prevent the degradation of drug as pH increases and to reduce the gastric disturbances	[29]
Cephalexin	EC	Concentration of EC had significant effect on the floating ability as well drug release	[30]
Fomatidine	HPMC, EC	Utilization of rate controlling polymers to develop a sustained release formulation with appropriate balance between buoyancy and drug release rate	[31]
Cefpodoxime proxetil	HPMC K 100M, EC	The relative bioavailability of the drug increased by more than 1.5 times by formulating it into microspheres	[32]
Rabeprazole sodium	HPMC, methyl cellulose	Floating microspheres to overcome the limited absorption from the lower GIT and improve the short elimination half-life (3 h)	[33]
Cefpodoxime proxetil	HPMC K4M, EC	Non-aqueous solvent evaporation method has been used to prepare floating microspheres in order to study the influence of polymer ratio on microspheres	[34]
Ketoprofen	HPMC, EC	HPMC and two different grades of EC as polymer utilized for safe and effective sustained drug delivery	[35]
Fomatidine	Acrylocoat S 100, cellulose acetate	Characteristics of two polymers compared; cellulose acetate containing microspheres showed a desirable high drug content, good flow properties, buoyancy and adequate release characteristics	[36]
Clarithromycin	HPMC, 15M, K4M, 100 LV, EC	Non-aqueous solvent evaporation method for preparation of clarithromycin microspheres for better eradication of *H. pylori* infection	[37]
Famotidine	Acrycoat S 100, chitosan	Polymers type and concentration influenced the physical and floating behavior of prepared microspheres	[38]
Cimetidine	HPMC, EC	Floating microspheres showed excellent floatability, good buoyancy and prolonged drug release	[39]

GIT – Gastrointestinal tract; HPMC – Hydroxy propyl methyl cellulose; HCl – Hydrochloride; *H. pylori* – *Helicobacter pylori*; EC – Ethyl cellulose; GI – Gastrointestinal; LV – Low viscosity

high encapsulation efficiency.[21] However, the limitation remains that the rate of solvent removal may affect the physicochemical properties of formed hollow microspheres and it requires additional processing for removal of residual solvent. Table 1 lists the various hollow microspheres prepared by this method.

Emulsion solvent diffusion method

Kawashima *et al*. proposed hollow microspheres (so-called "microballoons") prepared by novel emulsion solvent diffusion method based on enteric acrylic polymers containing the drug in the polymeric shell.[9,40] The preparation method and mechanism of microballoon formation is schematically illustrated in Figure 3. Typically, the method involves dispersion of solution of polymer and drug in a mixture of dichloromethane and ethanol into an agitated aqueous solution of surfactants. The ethanol rapidly partitions into the external aqueous phase and the polymer precipitates around dichloromethane droplets. The subsequent evaporation of the entrapped dichloromethane leads to the formation of internal cavities within the microspheres.[40,41] The major advantages of emulsion solvent diffusion method include uniform and narrow size distribution of formed microspheres and the high efficiency of the process. However, it is relatively complex process, which cannot be controlled easily. Table 2 summarizes the various drugs entrapped by this method.

Spray drying

Spray drying is the most widely employed industrial process for particle formation and drying. It is an ideal process where the required particle size distribution, bulk density and particle shape can be obtained in a single step.[68]

In this technique polymer is first dissolved in a suitable volatile organic solvent (e.g., dichloromethane, acetone) to form a slurry. The slurry is then sprayed into the drying chamber, concentration gradient of the solute forms inside the small droplet with the highest concentration being at the droplet surface. This is because the time of the solute diffusion is longer than that of the solvent in the droplets evaporating during the drying process. Subsequently, a solid shell appears leading to the formation of microspheres. Separation of the solid products from the gases is usually accomplished by means of a cyclone separator while the traces of solvent are removed by vacuum drying and the products are saved for later use[69] [Figure 4].

Spray drying method has advantages of being an easily controlled simple process with ease of scale-up. In addition, narrow particle size distribution and required particle size can be obtained in a single step. The limitations include that the product morphology is affected by various processing variables and the high cost of the process. Table 3 presents the various hollow microspheres prepared by spray drying method.

Miscellaneous

Apart from the above mentioned techniques, several modifications in the fabrication of hollow microspheres have been attempted to achieve the various objectives. Some of these approaches are summarized in Table 4.

In vivo Profiling of Hollow Microspheres

In vivo investigations are an integral part for the evaluation of hollow microspheres. Some of these studies are discussed in the following section and summarized in Table 5.

Gamma scintigraphy

Gamma scintigraphy has become one of the most popular method to investigate the gastrointestinal performance of the product.[84] Gamma scintigraphy is a technique by which the transit of a dosage form through its intended site of delivery can be noninvasively imaged *in vivo* by the introduction of a radiolabelled drug formulation. The gamma radiations emitted by the incorporated radionuclide with energies between 100 and 250 KeV are captured by external detectors such as gamma cameras coupled to a sophisticated data processing system and used to quantify the formulation *in vivo*.[85] Radiopharmaceuticals labeled

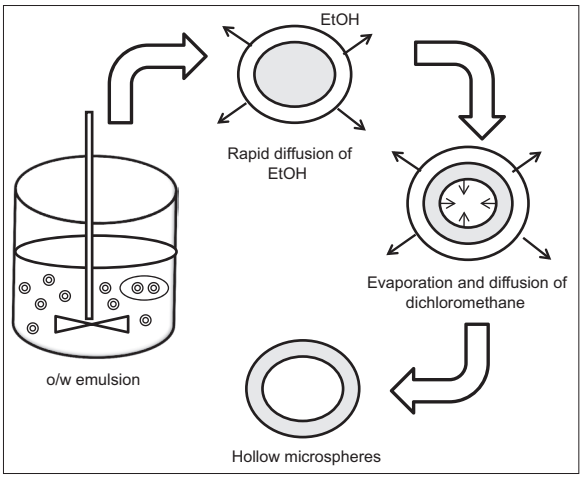

Figure 3: Schematic illustration of hollow microsphere formation by emulsion solvent diffusion method

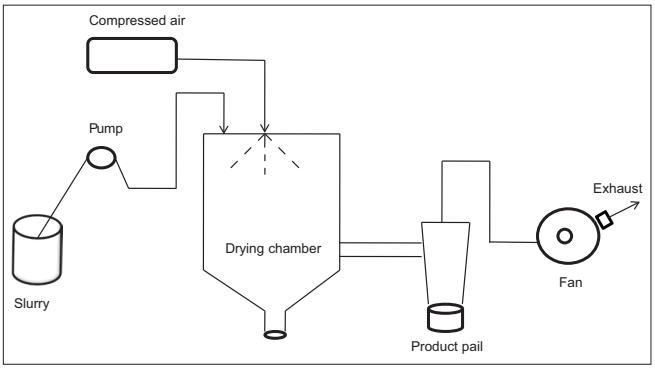

Figure 4: Schematic presentation of spray drying method

Table 2: Various hollow microspheres prepared by emulsion solvent diffusion method

Drug	Polymer (s)	Remarks	Reference
Acelofenac	Eudragit S 100, Eudragit L 100	A novel approach (floating pulsatile drug delivery system) developed for site and time specific release of aceclofenac	[42]
Curcumin	HPMC, EC, PVP, Eudragit RS 100	Floating microspheres prepared by using emulsion solvent diffusion method and evaluated for anti-inflammatory and anti-arthritic activity	[43]
Glipizide	Eudragit S	Incorporation of porous carrier (calcium silicate) in the microspheres effective in achieving the desired release behavior and buoyancy	[44]
Stavudine	Eudragit RS 100	The floating microspheres prepared to reduce frequency of dosing, minimize the side effects and increase the effectiveness of the drug	[45]
Clarithromycin	Eudragit S 100, RS 100, RL 100, L 100, L 100 55	The ability of Eudragit polymers to resist the acid environment of stomach has been utilized to prepare and retain the microspheres in the stomach for prolonged period	[46]
Amoxycillin trihydrate	HPMC, EC	An attempt has been made for the eradication of *H. pylori* infections with amoxicillin trihydrate by using the FDDS	[47]
Nateglinide	HPMC, EC	w/o/o double emulsion solvent diffusion method is used to microencapsulate the drug	[48]
Amoxicillin	HPMC, EC	Calcium silicate used as the floating carrier. Microsphere with adsorbed drug and polymer coating showed a good floatability and drug release; great potential for its use powder form encapsulation	[49]
Lovastatin	Eudragit S 100, Eudragit L 100	Floating microspheres displayed better cholesterol lowering effect	[50]
Atenolol	Eudragit S	Low density carrier used to increase the extent of absorption and bioavailability of the drug	[51]
Aceclofenac	Eudragit S 100, Eudragit RL 100	Floating microspheres prepared to minimize the irritant effect of drug on the stomach by avoiding direct contact with the mucosa and providing a mean of low dosage for prolonged period	[52]
Glipizide	Acrycoat S 100, Eudragit RS 100	A multiple unit dosage form approach to achieve uniform drug release throughout the stomach which suppresses the gastric irritation caused by glipizide	[53]
Dextromethor-phan hydrobromide	EC	Drug release from microspheres coated with the optimized formulation showed a controlled release pattern, as compared to a commercial product	[54]
Rifampicin	Eudragit RLPO	Prevent acid decomposition and achieve controlled release profile of rifampicin for prolonged period of time	[55]
Glipizide	EC, Eudragit S 100	Developed a sustained release microparticulate system in order to extend the drug release for about 12 h of duration	[56]
Carbamazepine	Eudragit RLPO, HPMC	Prepare short-term sustained release microspheres for controlled drug release and prevent the re-crystallization of drug in GIT	[57]
Nifedipine	PVP, EC	Nifedipine loaded hollow microspheres with hydrophilic and hydrophobic polymers successfully prepared. The weight ratio of polymer blends played a key role in the improvement of the *in vitro* release behavior of the drug	[58]
Silymarin	EC, HPMC, Eudragit S 100, Eudragit RL	Floating microspheres exhibited prolonged drug release in simulated gastric fluid for at least 12 h and potentially improved the bioavailability of the drug as well as patient compliance	[59]
Cyclobenza-prine HCl	EC	Designed floating microspheres to achieve extended retention in upper GIT and thereby improve bioavailability	[60]
Ketoprofen	Eudragit S 100, Eudragit L 100	Drug: Polymer ratio influenced particle size, *in vitro* buoyancy, drug release pattern of floating microspheres	[61]
Metformin HCl	HPMC K4M, Eudragit RS 100	FDDS prepared to optimize the pharmacokinetics and pharmacodynamics of the drug for effective control of non-insulin dependent diabetes mellitus	[62]
Curcumin	HPMC K 100 poloxamer 188	The poloxamer based microspheres showed controlled release kinetics as compared to HPMC based microspheres	[63]
Ketorolac trometamol	EC, HPMC K4M, Eudragit R 100, Eudragit S 100	The microspheres prepared by using EC alone were spherical in shape with smooth surface than the microspheres prepared by using Eudragit S 100, Eudragit R 100 and EC/HPMC K4M based microspheres	[64]
Ranitidine HCl	EC	Pharmacokinetic analysis showed that the drug bioavailability from hollow microspheres alone was about 3.0-times that of common gelatin capsules and it was about 2.8 times that of the solid microspheres	[65]
Orlistat	Eudragit S	The *in vivo* study of floating microspheres confirmed its ability to modify the pharmacokinetic behavior of the drug in the desired manner with enhanced elimination half-life	[66]
Repaglinide	Eudragit S	The drug bioavailability could be increased by combining excellent buoyant ability and suitable drug release pattern of designed system	[67]
Riboflavin	Eudragit S 100, HPMC	Pharmacokinetic parameters (excretion half-life time, total urinary excretion) were well correlated with the GRT of microballoons	[40]

EC – Ethyl cellulose; HPMC – Hydroxy propyl methyl cellulose; PVP – Polyvinyl pyrrolidone; *H. pylori* – *Helicobacter pylori*; GIT: Gastrointestinal tract; GRT – Gastric residence time; FDDS – Floating drug delivery system

Table 3: Various hollow microspheres prepared by spray drying method

Drug	Polymer (s)	Remarks	Reference
Cephalexin	Sodium alginate, PVA	Floating microspheres successfully formulated with optimized spray dryer conditions. A Taguchi orthogonal array design was used to study the effect of formulation and process parameters in the development of microspheres	[70]
Ketotifen fumarate	Chitosan	*In vivo* evaluation of the systems carried out by intraperitoneal administration in rats to evaluate plasma levels of the drug and possible tissue affectation	[71]
Hydroxyapatite	Ammonium bicarbonate	HA microspheres fabricated by spray drying method; ammonium bicarbonate used as a gas forming agent, which can generate carbon dioxide and ammonia gas bubbles during the spraying. The resultant hollow microspheres prepared with different amounts of ammonium bicarbonate were also characterized	[72]
Budesonide	Chitosan	The drug release modifier and mucoadhesive properties of chitosan exploited while preparing sustained release formulations for pulmonary drug delivery	[73]
Heparin	Eudragit S 100	Establish feasibility of the spray drying for the preparation of microparticulate systems with incorporated controlled-release mechanism to modify LMWH release	[74]

HA – Hydroxyapatite; PVA – Polyvinyl alcohol; LMWH – Low molecular weight heparin

Table 4: Hollow microspheres prepared by miscellaneous techniques

Hollow microspheres with modifications	Remarks	Reference
HA microspheres as a device for controlled delivery of proteins	Sustained release of BSA was achieved over 7-14 days from hollow HA microspheres showing their potential as a device for controlled local delivery of proteins such as growth factors	[75]
HA microspheres prepared by a glass conversion method	The effect of process variables such as pH, K_2HPO_4 concentration and temperature on the microstructure of microspheres was studied for controlled release of therapeutics	[76]
Hollow quaternized chitosan microspheres	Insulin analog was successfully encapsulated in chitosan microspheres with a high loading content. It protected the drug from cross-linking reaction and maintain its activity	[77]
Water-dispersible PVA-based dry microballoons	The microballoons fabricated after further surface functionalization were utilized in ultrasound imaging and targeted drug delivery	[78]
Preparation of mesoporous silica microspheres with multi-hollow cores	By adopting a double-template technique silica microspheres were prepared for sustained release applications	[79]
Porous wall hollow glass microspheres	The combination of a hollow central cavity that can carry soluble therapeutic agents with mesoporous walls for controlled release is a unique characteristic that makes hollow glass microspheres suitable carrier for biomedical applications	[80]
Synthesis of pH-sensitive hollow polymer microspheres with movable magnetic core	The pH-sensitive hollow polymer microspheres were fabricated to achieve pH dependent release and targeting	[81]
Novel process to synthesize magnetic hollow silica microspheres	A novel method was used to prepare magnetic hollow silica microspheres by combining a sol-gel technology with low temperature drying having potential for controlled drug release	[82]
Biodegradable polymeric hollow microspheres using o/o/w emulsion stabilized by Labrafil	Hollow microspheres were successfully prepared. It can be employed as an imaging contrast agent and a novel drug delivery vehicle	[83]

BSA – Bovine serum albumin; HA – Hydroxyapatite; PVA – Polyvinyl alcohol

Table 5: *In-vivo* evaluations of hollow microspheres

Technique (s)	Drug	Polymer compositions	Outcome	Reference
X-ray imaging	Valacyclovir HCl	EC	Floating microspheres remained buoyant for more than 12 h	[22]
X-ray imaging	Curcumin	EC, HPMC, Eudragit RS 100	Prolonged gastric retention, improved the bioavailability of the herbal drug	[43]
Gamma scintigraphy	Rifampicin	Microcrystalline cellulose, carbopol, HPMC	The formulation was retained in the stomach for more than 6 h	[93]
X-ray imaging	Rosiglitazone maleate	HPMC K15M, Eudragit L100, EC	The hollow microspheres extended the duration of action of drug with prolonged floating time	[94]
Gamma scintigraphy	Orlistat	Calcium silicate, Eudragit S100	Elimination half-life ($t_{1/2}$) of the drug was increased by ~1.5 times	[66]
Gamma scintigraphy	Repaglinide	Calcium silicate, Eudragit S	Hollow microspheres remained buoyant and uniformly distributed in the gastric contents for the period of 6 h	[95]
Gamma scintigraphy	Riboflavin	Eudragit RS100, HPMC	Both $t_{1/2}$ and total urinary excretion increased, due to the prolonged GRT of dosage forms up to 6 h	[96]

HCl – Hydrochloride; EC – Ethyl cellulose; HPMC – Hydroxy propyl methyl cellulose; GRT – Gastric residence time

with (99 mTc) technetium are most commonly used, however, other sources of radionuclides such as (111In) indium, (175Yb) ytterbium, (68Sm) Samarium, etc., can also be employed.[86] The prime advantages of gamma scintigraphy

include modest radiation exposure to the participating subjects compared with roentgenography (i.e., X-ray methods), both qualitative and quantitative observations can be recorded that are not feasible with other techniques. It also offers total non-invasiveness and *in vivo* evaluation of dosage forms is possible under normal physiological conditions.

Radiography

Radiography has been used for many years for the assessment of gastric transit of dosage forms throughout the GIT. It involves the inclusion of a radio-opaque material into an oral drug delivery system to evaluate its *in vivo* behavior by radiological procedures.[87] Its major advantages over gamma scintigraphy are the simplicity and cost. However, the major drawbacks are repeated exposure to X-rays, necessity to modify the physical state of the dosage form in order to make it radioopaque and qualitative nature of the data collected. A commonly used contrast agent for radiography is barium sulphate.[88]

Ultrasonography

Ultrasonic imaging can be employed for visualizing internal body structures. An ultrasonic image is formed when beam of very high frequency sound impulse (1.5-10 MHz) is sent into a subject and is reflected back to a varying degree depending upon the density of the medium through which it is passing.[84] It is a noninvasive and safe technique.[89] Most of the dosage forms do not have sharp acoustic mismatches across their interface with the physiological milieu, thereby limiting the use of ultrasonography for the evaluation of floating drug delivery systems. The characterization includes assessment of intragastric location of the hydrogels and interactions between gastric wall and floating microspheres during peristalsis.

Alternating current biosusceptometry

Alternate current biosusceptometry (ACB) is an innovative, non-invasive and radiation free biomagnetic technique used to evaluate floating systems in the GIT. In this technique, variation of magnetic flux from an ingested magnetic material is recorded by a set of induction coils. The material (ferrites like $MgFe_2O_3$) does not need to be premagnetized as it is continuously magnetized by an alternating field with a frequency of 10 kHz and a magnetic field of 20G generated by the excitation coils.[90] The magnetic signals detected by the ACB sensors depend on the surface area of the detection coil, number of turns, rate of change of the magnetic flux, amount of ferromagnetic material and distance among the sensors.[91]

Magnetic resonance imaging

Magnetic resonance imaging is a noninvasive imaging technique that is based on the principle of nuclear magnetic resonance. The high spatial resolution in combination with very good contrast resolution makes MRI an admirable tool in gastrointestinal research for the analysis of gastric emptying, motility and intra gastric distribution of macronutrients and drug models. The advantages of MRI include avoidance of ionization radiation, excellent anatomical imaging, high scan volumes and use of harmless MR imaging contrast agents. However, the magnetic resonance imaging encounters the problems of acquisition time and the signal to noise ratio. In order to solve these problems different strategies can be followed.[91] Use of either paramagnetic or ferromagnetic contrast agents (ferromagnetic iron oxides) for the labeling of the delivery system is very common. A combination of materials with very different contrast properties can also be used to specifically enhance or suppress signal of fluids and tissues of interest and thus permit better delineation and study of organs.[92]

Table 5 enlists the various *in vivo* investigations performed with hollow microspheres.

Conclusion

The process of gastrointestinal drug absorption is highly variable. Among the drugs currently in clinical use are several narrow absorption window drugs. Drugs that possess a narrow absorption window in the upper parts of the gastrointestinal tract are ideal candidates for a gastroretentive drug delivery system as prolonging gastric retention of the dosage form extends the time for the drug absorption. In spite of extensive research conducted to develop controlled or sustained release delivery systems, very few systems have been developed, which are retained in the stomach for a long time.

A wide variety of active agents of different therapeutic functions such as anti-inflammatory, antibiotics, anti-ulcer, anti-diabetic, have been formulated into hollow microspheres with promising *in vitro* and *in vivo* results. Hollow microspheres are expected to provide an economical, safe and more bioavailable formulation for the effective management of diverse diseases. Some of the hollow microsphere-related patents have been listed in Table 6.

It is expected that extension of applications of imaging techniques and recently developed methods may yield a deeper insight into the mechanisms of gastroretentivity. This will ensure the successful advancements in the area of gastroretentive microspheres therapy so as to optimize the delivery of molecules in a more efficient manner. Furthermore, recent innovations in pharmaceutical investigation will surely provide real prospects for the establishment of novel and effective means in the development of this promising drug delivery system.

Table 6: Patents for some hollow microspheres based gastroretentive drug delivery systems

Patent no.	Year	Patent title	Inventor	Reference
US006207197B1	2001	Gastroretentive controlled release microspheres for improved drug delivery	Illum *et al.*	[97]
US2006/0013876	2006	Novel floating dosage form	Lohray *et al.*	[98]
US2010/0015224A1	2010	Programmable buoyant delivery technology	Singh *et al.*	[99]
EP 2329810 A1	2011	Gastric retention drug delivery system, preparation method and use thereof	Jiang *et al.*	[100]
US2012/0201892A1	2012	Porous wall hollow glass microspheres as carrier for biomolecules	Li *et al.*	[101]
EP 2444064 A1	2012	Process for making multiparticulate gastroretentive dosage forms	Sylvain *et al.*	[102]

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