International Journal of Pharmaceutical Research and Development
www.pharmaceuticaljournal.net
Online ISSN: 2664-6870; Print ISSN: 2664-6862; Impact Factor: RJIF 5.48
Received: 01-01-2020; Accepted: 02-02-2020: Published: 15-02-2020
Volume 2; Issue 1; 2020; Page No. 01-07

Hollow microspheres for drug delivery: A review

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Abstract
Controlled release of dosage forms has a non-uniform absorption profile, insufficient drug release and shorter residence time due to variation in gastric emptying. These dosage forms encounter several physiological constraints such as the inability to retain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract. These considerations led to the development of oral controlled release dosage forms with gastro-retentive properties. Hollow microspheres are one of the gastro-retentive drug delivery systems based on the non-effervescent approach. They are spherical empty particles without core and can remain in the gastric region for prolonged periods. They hold promise as one of the potential approaches for gastric retention. They can extend the gastric residence time of drugs significantly and help in improving the bioavailability. This review attempts to provide insight into the basics of hollow microspheres, recent advances and future potential of this drug delivery system.

Keywords: hollow microspheres, gastro retentive, controlled release, floating drug delivery

Introduction

The oral route is the most acceptable mode for the administration of drugs to the systemic circulation. Some drugs have characteristics for good absorption throughout the gastrointestinal tract (GIT), while some of the drugs have certain limitations. In several cases, the variability of the gastrointestinal tract physiology and its transit time leads to unpredictable bioavailability and non-reproducible therapeutic effects. Oral controlled drug delivery system would be successful if the drug has good absorption throughout the GIT preferably through passive diffusion. These considerations have led to the development of oral controlled release dosage forms with gastro-retentive properties [1]. Gastro-retentive systems have the ability to remain in the gastric region for a longer period and significantly prolong the gastric residence time of the drug. Thus, they improve the bioavailability, reduce drug waste, and enhance the solubility of the drug [2]. Several approaches have been used to increase gastric retention time (GRT) of a dosage form in the stomach by employing a variety of concepts (Figure 1) [3].

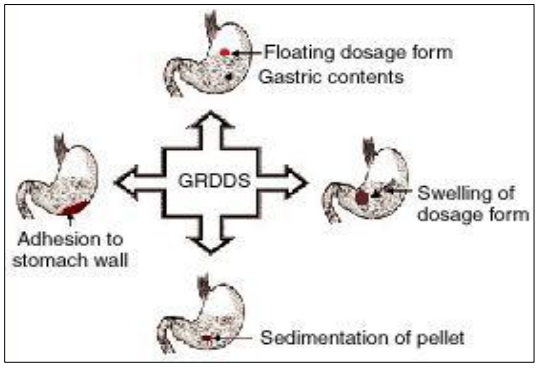

Fig 1: Types of gastro-retentive drug delivery systems

Floating Drug Delivery Systems

Several floating systems have been generated based on granules, powders, capsules, tablets, laminated films, beads, and hollow microspheres. Classification of floating systems is presented in Figure 2 [4].

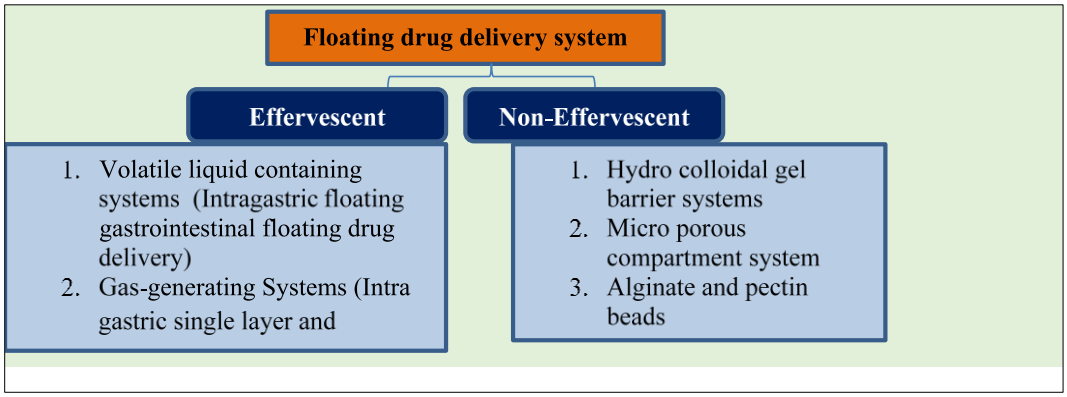

Fig 2: Classification of floating drug delivery system

This review focus on the non-effervescent floating drug delivery system, hollow microsphere and discusses the mechanism, advantages and
Limitations, its properties, several preparation techniques, evaluation methods, applications, recent advancements, and future trends.

Hollow Microspheres

Definition of hollow microspheres

Hollow microspheres are gastro-retentive drug delivery systems based on a non-effervescent approach. Hollow microspheres, micro-balloons or floating microparticles are used synonymously for floating microspheres. Floating microspheres are spherical empty particles without a core. These are free-flowing particles with size ranging from 1 to 1000 μm [1, 2].

Mechanism of floating microspheres

When hollow microspheres come in contact with gastric fluid the polysaccharides, gel formers and polymers hydrate to form a colloidal gel barrier. This gel barrier controls the rate of fluid penetration into the device and consequently releases the drug [5]. As the exterior surface of the dosage form dissolves; the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer decreases the density and confers appropriate buoyancy to the microspheres in the presence of gastric content. However, minimal gastric content needed to allow proper achievement of buoyancy. Hollow microspheres of acrylic resins, eudragit, polyethylene oxide, and cellulose acetate; polystyrene floatable shells; polycarbonate floating balloons and Gelucire floating granules are the recent developments

Advantages and Disadvantages

Table 1: Advantages and disadvantages/limitations[1]

Advantages	Disadvantages/Limitations
Reduces dosing frequency and thereby improves patient compliance.	Higher fluid levels are required in the stomach for the hollow microspheres to function effectively by floating
Enhances bioavailability by avoiding fluctuations in plasma drug concentration and provides continuous drug release.	Dosage form should be administered with at least 200 mL to 250 mL of water
Superior to single-unit floating dosage forms as they release drugs uniformly without risk of dose dumping	Not suitable for drugs which have solubility/stability problem in gastric fluids
Increases gastric retention time due to buoyancy	Drugs that undergo the first-pass metabolism are not suitable candidates
Enhanced absorption of drugs which solubilize only in the stomach	Irritant drugs to the gastric mucosa are not suitable for gastro-retentive systems.
Controlled drug release for a long period	
Site-specific drug delivery to the stomach can be achieved	
Sustained release effect decreases gastric irritation	
The better therapeutic effect of short half-life drugs can be achieved	

Properties of Hollow Microspheres

Microspheres are one of the most favorable buoyant systems with the unique advantages of multiple unit systems as well as better floating properties, because of central hollow space inside the microsphere. The slow release of drug at the desired rate and better-floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers such as polylactic acid, Eudragit® S and hydroxypropyl methylcellulose acetate are used in the formulation of hollow microspheres, and the release of the drug can be modulated by optimizing polymer concentration and the polymer -plasticizer ratio [5, 6].

Techniques of Preparation

Several techniques have been developed for the preparation of hollow microspheres such as simple solvent evaporation method, emulsion-solvent diffusion method, single emulsion technique, double emulsion technique, phase separation coacervation technique, polymerization technique, spray drying and spray congealing method and hot melt encapsulation method. Some of the commonly used techniques are discussed in Table 2 [5].

Table 2: Techniques used for the preparation of hollow microspheres [1, 5]

Solvent evaporation technique	Emulsion solvent diffusion method	Spray drying
This technique is widely used to obtain a controlled release of drugs	This is based on enteric acrylic polymers containing the drug in the polymeric shell prepared hollow microspheres	Most widely employed industrial process for particle formation and drying
The drug and polymer is dissolved in an organic phase and dispersed in an excess amount of aqueous continuous phase using an agitator to form en emulsion	This method involves the dispersion of the solution of polymer and drug in a mixture of dichloromethane and ethanol into an agitated aqueous solution of surfactants.	A polymer is first dissolved in a suitable volatile organic solvent (e.g. dichloromethane, acetone) to form a slurry
Based on the hydrophobicity or hydrophilicity of drugs various methods are used to prepare microspheres by this method (Figure 3)	Ethanol partitions into the external aqueous phase quickly and the polymer precipitates around dichloromethane droplets. The subsequent evaporation of the entrapped dichloromethane leads to the formation of internal cavities within the microspheres (Figure 4)	The slurry is then sprayed into the drying chamber, the concentration gradient of the solute forms inside the small droplet with the highest concentration being at the droplet surface. Subsequently, a solid shell appears leading to the formation of microspheres

Advantage: simplest method for fabrication of microspheres. The process can be controlled easily, and the formed microspheres show good product yield and high encapsulation efficiency.	Advantage: uniform and narrow size distribution of formed microspheres and the high efficiency of the process	A cyclone separator is used to separate solid products from the gases while the vacuum dryer removes the traces of solvent and the products are saved for later use (Figure 5).
Limitation: The rate of solvent removal may affect the physicochemical properties of formed hollow microspheres. It also requires additional processing for removal of residual solvent.	Limitation: relatively complex process, which cannot be controlled easily	Advantages: an easily controlled simple process with ease of scale-up. Besides, narrow particle size distribution and required particle size can be obtained in a single step.
Some of the hollow microspheres prepared by the solvent evaporation method are presented in Table 3.	Various hollow microspheres prepared by the emulsion solvent diffusion method are presented in Table 3.	Limitation: the product morphology is affected by various processing variables and the high cost of the process.
		Various hollow microspheres prepared by the spray drying method are presented in Table 3.

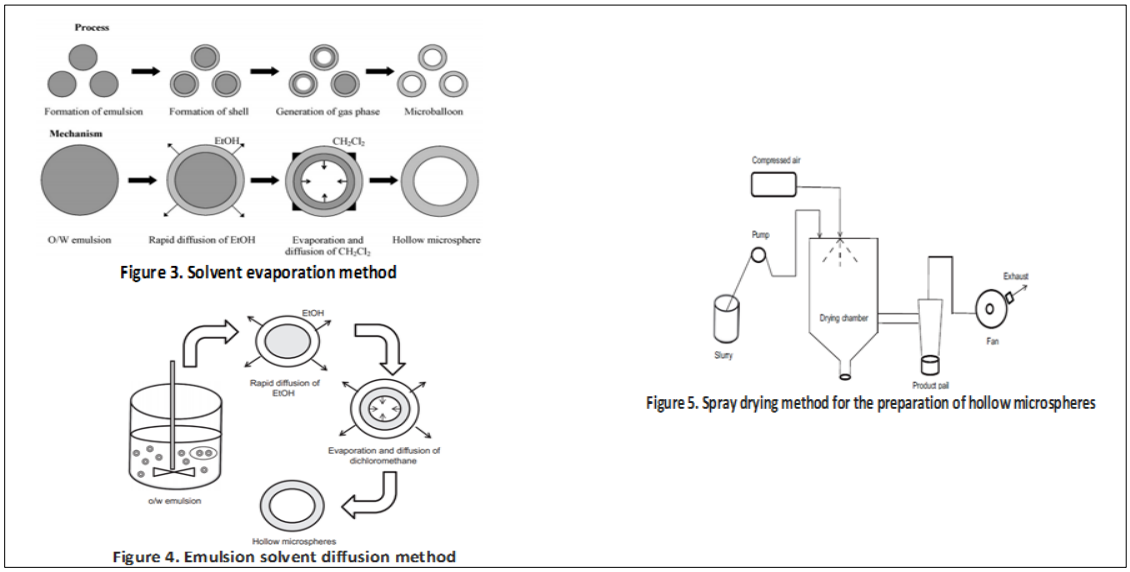

Fig 3: various methods for the preparation of hollow microspheres

Table 3: Hollow microspheres prepared by different methods [1, 7, 20]

Drug	Polymer	Comments
Hollow microspheres prepared by the solvent evaporation method		
Valacyclovir HCl	Ethylcellulose	Localizes the drug in the upper part of the gastrointestinal tract for improved absorption [7].
Captopril	Eudragit® S 100, ethylcellulose	It is a sustained release floating microsphere which reduces the dosing frequency of drug [8].
Rosiglitazone maleate	HPMC, ethylcellulose	Prevents drug degradation as pH increases and reduces the gastric disturbances [9].
Cimetidine	HPMC, ethylcellulose	Showed excellent floatability, good buoyancy and prolonged drug release [10].
Various hollow microspheres prepared by emulsion solvent diffusion method		
Aceclofenac	Eudragit® S 100, Eudragit L 100	A novel approach (floating pulsatile drug delivery system) developed for the site and time-specific release of aceclofenac [11].
Curcumin	HPMC, ethylcellulose, PVP, Eudragit RS 100	Floating microspheres prepared by using emulsion solvent diffusion method and evaluated for anti-inflammatory and anti-arthritic activity [12].
Glipizide	Eudragit® S	Incorporation of a porous carrier (calcium silicate) in the microspheres effective in achieving the desired release behavior and buoyancy [13].
Clarithromycin	Eudragit® S 100, RS 100, RL 100, L 100, L 100 55	The ability of Eudragit polymers to resist the acid environment of the stomach has been utilized to prepare and retain the microspheres in the stomach for a prolonged period [14].
Orlistat	Eudragit® S	The in vivo study confirmed the ability of hollow microsphere to modify the pharmacokinetic behavior of the drug as required with increased elimination half-life [15].
Various hollow microspheres prepared by spray drying method		
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 [16].
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 [17].
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

		spraying. The resultant hollow microspheres prepared with different amounts of ammonium bicarbonate were also characterized [18].
Budesonide	Chitosan	The drug release modifier and mucoadhesive properties of chitosan exploited while preparing sustained release formulations for pulmonary drug delivery [19].
Heparin	Eudragit S 100	Establish the feasibility of the spray drying for the preparation of microparticulate systems with an incorporated controlled-release mechanism to modify LMWH release [20].
HPMC – Hydroxypropyl methylcellulose; LMWH – Low molecular weight heparin; PVA – Polyvinyl alcohol; PVP – Polyvinyl pyrrolidone		

Evaluation of Hollow Microsphere

Percentage yield [5]

The percentage yield is determined for drug and is calculated using the following equation

Micromeritic Properties [21, 22]

Hollow microspheres are evaluated by the following micromeritic properties:

- **Particle shape and size:** determined by optical microscopy, and the average diameter of the particle is calculated with the help of a calibrated ocular micrometer (by measuring 200 to 300 particles).
- True density is determined by the liquid displacement method using a helium densitometer.
- Tapped density and compressibility index is calculated by measuring the change in volume using a bulk density apparatus;
- The angle of repose is determined by the fixed funnel method.
- Flow properties by carr's index and angle of repose.

The compressibility/carr's index is calculated using the following formula:

I = Vb –Vt / Vb x 100

Where, Vb is the bulk volume and Vt is the tapped volume.

The value <15% indicates good flow characteristics, while > 25% indicate poor flow ability.

- Porosity (e) is calculated by using the following equation:

e = {1- (tapped density/true density)} ×100

In vitro buoyancy [5]

The required quantity of hollow/empty microsphere is placed in 900 mL of 0.1N HCl and is stirred at 100 rpm for about 10 hours in the dissolution apparatus. Following this procedure, layers of buoyant microspheres are pipetted and separated by filtration. Buoyant microspheres and settled microspheres are dried in a desiccator until a constant weight is obtained. The fraction of the hollow/empty microsphere is weighed, and in vitro buoyancy is determined by the weight ratio of floating microspheres to the sum of floating and sinking microspheres.

Buoyancy (%) = {Wf / (Wf + WS)} × 100

Where, Wf and Ws are the weights of the floating and settled microspheres.

In vitro drug release studies

The release rate of hollow microspheres is determined in a United States Pharmacopoeia (USP) XXIII basket type dissolution apparatus. Hollow microspheres equivalent to a dose of the drug (filled into a hard gelatin capsule) is placed in the dissolution apparatus under a temperature of 37 ± 1 °C with a rotation speed as required. Perfect sink conditions should be carried out during the drug release study. About 5 mL of samples are withdrawn at each time interval and are analyzed using the Liquid chromatography / Mass spectroscopy method to determine the concentration of hollow microspheres present in the dissolution medium. The initial volume of the dissolution fluid is maintained by adding 5 mL of fresh dissolution fluid after each withdrawal. All experiments run in triplicate [4].

Scanning electron microscopy

Dry hollow microspheres are placed on an electron microscope brass stub a coated with gold in an ion sputter. This is followed by taking pictures of the microsphere using Spectro random scanning of the stub. The microspheres are viewed at an accelerating voltage of 20KV [5].

Swelling studies

Swelling studies are performed to calculate molecular parameters of swollen polymers. These are determined by using dissolution apparatus, optical microscopy and other sophisticated techniques, which include H1NMR imaging, Confocal laser scanning microscopy (CLSM), Cryogenic scanning electron microscopy (Cryo-SEM), Light scattering imaging (LSI), etc. The swelling studies by using Dissolution apparatus (USP dissolution apparatus USP-24) lab India disso 2000) is calculated as per the following formula [5].

Swelling ratio = Weight of wet formulation / Weight of formulations

In vivo Profiling of Hollow Microspheres

In vivo investigations are an integral part of the evaluation of hollow microspheres. The in vivo studies are performed on suitable animal models such as a rat, beagle dogs, etc. The floating behavior can be investigated by radiographical studies using barium sulfate micro-balloons. Some of them are described below:

Gamma scintigraphy

Gamma scintigraphy is one of the most popular methods to investigate the gastrointestinal performance of the product. This 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 radio-labelled 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 [23, 24].

Radiopharmaceuticals labeled with (99 MTC) technetium are most commonly used. Also, radionuclides such as indium, ytterbium (175Yb), Samarium (68Sm) can be used. The advantages associated with this method include modest radiation exposure to the subjects compared with X-ray methods. It also

offers non-invasiveness and *in vivo* evaluation of dosage forms is possible under normal physiological conditions.[1]

Radiography

This technology has been used for several years for the
Assessment of gastric transit of dosage forms throughout the gastrointestinal tract. In this technique, radio-opaque material is included in an oral drug delivery system to evaluate it's *in vivo* behavior by radiological procedures. It is simple and cost-effective [25, 26].

Ultrasonography

Ultrasonic imaging is used for visualizing internal body structures. An ultrasonic image is formed when a beam of high-frequency sound impulse (1.5 to 10 MHz) is sent into a subject and reflected to a varying degree (depending upon the density of the medium) through which it is passing. It is safe and noninvasive technique [1].

Lack of sharp acoustic mismatches for the majority of the dosage forms limits the use of ultrasonography for the evaluation of floating drug delivery systems. This method characterizes assessment of the intragastric location of the hydrogels and interactions between gastric wall and floating microspheres during persistalsis [1].

Alternating current Biosusceptometry

This is an innovative, non-invasive and radiation-free bio magnetic technique to evaluate floating systems in the gastrointestinal tract. In this technique, a variation of magnetic flux from an ingested magnetic material is recorded by a set of induction coils [27].

The material (ferrites like MgFe2O3) need not be pre-magnetized 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. 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 [27].

Magnetic resonance imaging

This is a noninvasive imaging technique based on the principle of nuclear magnetic resonance [27]. The high spatial resolution in combination with very good contrast resolution makes magnetic resonance imaging an admirable tool in gastrointestinal research for the analysis of gastric emptying, motility and intragastric distribution of macronutrients and drug models [27].

The advantages of magnetic resonance imaging include avoidance of ionization radiation, excellent anatomical imaging, high scan volumes and use of harmless magnetic resonance imaging contrast agents. However, the magnetic resonance imaging encounters the problems of acquisition time and the signal to noise ratio. To solve these problems, different strategies can be followed. The 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 [27].

Differential scanning calorimetry

Dextromethorphan controlled release hollow microspheres were analyzed using differential scanning calorimetry (DSC) on pure sample of drug and its formulation using DSC-Q200 apparatus. Calorimetric measurements were made with empty cell (high purity alpha alumina discs) as the reference. The dynamic scans were then taken in nitrogen atmosphere at the heating rate of 10°C min^{-1}. The energy was measured as joules per kilocalorie [28].

X-ray diffraction analysis

Simvastatin-loaded PLGA Microspheres were analyzed using x-ray diffraction analysis. In this method, X-ray diffraction patterns were obtained at room temperature using a very high-resolution Cu-Kα radiation diffraction system (Equinox 3000, INEL, Artenay, France) operating at a voltage of 40 kV and current of 30 mA. Calcium phosphate cement was analyzed in the 2θ angle range of 0–80° [29].

Transmission electron microscope

The morphologies of Ag-coated glass microsphere core–shell particles and silver hollow microspheres are observed by an H-7000FA transmitted electron microscope (TEM) at an acceleration voltage of 75 kV. The morphologies of Ag-coated glass microsphere core–shell particles and silver hollow microspheres are observed by an H-7000FA transmitted electron microscope (TEM) at an acceleration voltage of 75 kV. The samples for TEM studies are prepared by placing small drops of the solution (acetone) on copper grids and allowing the solvent to slowly evaporate under vacuum at room temperature.

The samples of hollow microspheres for transmission electron microscope studies are prepared by placing small drops of the solution (acetone) on copper grids and allowing the solvent to slowly evaporate under vaccum at room temperature [30].

The morphologies of silver-coated glass microsphere core-shell particles and silver hollow microspheres are observed by an H-7000FA transmitted electron microscope at an accelerated voltage of 75 kV [30].

Applications [5]

- Hollow microspheres can ameliorate the pharmacotherapy of the stomach by releasing the drug locally leading to higher drug concentration in the gastric mucosa. This process leads to the elimination of helicobacter pylori from the submucosal tissue of the stomach and helps in the treatment of stomach and duodenal ulcers, gastritis, and esophagitis.
- They allow sustained drug release and release the drug for a prolonged period. They are fabricated as a floating controlled drug delivery system.
- Hollow microspheres of NSAIDs are successful for controlled release and also reduce the side effects of gastric irritation.
- They can be used to transport drugs with absorption windows such as antiviral, antifungal, and antibiotic agents.
- They provide site-specific drug delivery for drugs that are absorbed from the stomach or the proximal part of the small intestine.

Recent advances in the Development of Hollow Microspheres [31, 32].

- Hollow magnetite microspheres: Francisco Marquez *et al*., developed synthesized monodisperse hollow magnetite microspheres by a one-step process through a template-free hydrothermal approach.
- Yuning Huo *et al.*, developed hollow CdS-TiO2 microspheres with enhanced visible-light photocatalytic activity.
- Kazuhiro S *et al*., used calcite microspheres as a precursor to developing fabrication of hollow carbonate apatite microspheres as bone substitutes.
- Changchun Wang *et al.*, recently developed a uniform double-shell hollow microsphere from a new polymer backbone transition method as effective acoustic echo imaging contrast agent.
- Kapil Kumar and AK Rai have been opened a new doors for the development of hollow microspheres of curcumin as herbal drug delivery systems.
- Padmavathy *et al*. summarized a systematic approach for designing and development of ofloxacin floating tablets to enhance the bioavailability and therapeutic efficacy of the drug.
- Jani *et al*. developed controlled release floating multiparticulate drug delivery system of tolperisone hydrochloride.
- Patil *et al*. carried out a study to develop floating tablets of Ofloxacin designed to prolong the gastric residence time after oral administration.
- Chandiran *et al*. were investigated the use of biodegradable polymers for microencapsulation of aceclofenac using solvent evaporation technique.
- Prabu *et al*. encapsulated aceclofenac within biodegradable polymer rosin and evaluated the effect of different formulation variables such as concentration of drug, polymer, polyvinyl alcohol and solvent.
- Jain *et al*. studied to prepare floating microspheres consisting of calcium silicate as porous carrier; orlistat, an oral anti-obesity agent; and Eudragit S as polymer, by solvent evaporation method and to evaluate their gastro-retentive and controlled-release properties.
- Gupta *et al*. prepared floating tablets of acyclovir containing polyvinyl pyrrolidon (PVP), polyvinyl alcohol (PVA) and hydroxy propyl methyl cellulose (HPMC) as the polymers and sodium bicarbonate as a gas generating agent to reduce floating lag time.

Future Prospects

The control of drug release profiles has been a major aim of pharmaceutical research and development in the past 2 decades and might result in the availability of new products with new therapeutic possibilities with substantial benefits for patients [5, 31].

New drug products using gastro-retentive drug delivery technology can make use of hollow microspheres for maximum applications. The upcoming investigations may focus on the concept of hollow microspheres some of which are as follows [5, 31, 33].

- Design of an array of gastro retentive drug delivery systems having minimum gastric residence time as per the clinical requirement.
- Design and development of gastro retentive drug delivery systems as a beneficial strategy for the treatment of duodenal, gastric cancers and the treatment of Parkinson's disease.
- Various antibiotics to explore the eradication of Helicobacter pylori
- Development of several anti-reflux formulations using gastro-retentive technologies.
- Design and synthesis of novel polymers as per the clinical and pharmaceutical requirements.
- Design and synthesis of novel mucoadhesive agents to develop bioadhesive drug delivery systems for improved gastro-retention.
- Buoyant microparticles are considered as a beneficial strategy for the treatment of gastric and duodenal cancers.
- Floating multi-particulate systems may be used as a carrier for the drugs having narrow absorption windows. Antiviral, antifungal and antibiotic agents (Sulphonamides, quinolones, Penicillin's, cephalosporins, aminoglycosides and tetracyclines) are absorbed only from very specific regions of gastrointestinal tract and whose development has been halted due to the lack of pharmaceutical technologies.
- Hollow microspheres have the ability to continually supply the drug to its most efficient site of absorption. The dosage from may allow for more effective oral use of peptide and protein drugs such as calcitonin, erythropoietin, vasopressin, insulin, low molecular weight heparin.
- Floating microparticles of non-steroidal anti-inflammatory drugs are effective in reducing major side effects and gastric irritation. For example, floating microspheres of indomethacin are quite beneficial for rheumatic patients.

It is hoped that in the near future effective therapeutics in the form of hollow microspheres would be introduced in greater numbers in the clinics.

Conclusion

Hollow microspheres are free-flowing spherical empty particles with size ranging from 1 to 1000 µm. They have low-density, sufficient buoyancy to float over gastric contents and remain in the stomach for a longer period. Since these floats over the gastric contents, the drug is released slowly at the desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.

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