EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 7
207-215
Year: 2020

MICROBALLOONS – A NOVEL FLOATING DRUG DELIVERY SYSTEM

Rithu Kadagala*[1], Hema Kumari[2] and Naga Haritha Pamujula[3]

[1]M.Pharmacy 2nd Year, Department of Pharmaceutics, St.Pauls College of Pharmacy, Affiliated to Osmania University, Hyderabad, Telangana, India.
[2]B.Pharmacy IV Year, Department of Pharmaceutics, St.Pauls College of Pharmacy, Affiliated to Osmania University, Hyderabad, Telangana, India.
[3]Assistant Professor, Department of Pharmaceutics, St.Pauls College of Pharmacy, Affiliated to Osmania University, Hyderabad, Telangana, India.

***Corresponding Author: Rithu Kadagala**
M.Pharmacy 2nd Year, Department of Pharmaceutics, St.Pauls College of Pharmacy, Affiliated to Osmania University, Hyderabad, Telangana, India.

Article Received on 24/04/2020 **Article Revised on 15/05/2020** **Article Accepted on 05/06/2020**

ABSTRACT
The purpose of this review on microballoons is to collect the recent literature with a special focus on the novel technological advancements in floating drug delivery system to achieve gastric retention. Microballoons (Hollow microsphere) promises to be a potential approach for gastric retention. Microballoons drug-delivery systems are based on noneffervescent system containing empty particles of spherical shape without core ideally having a size less than 200 micrometer. Microballoons drug delivery systems have shown to be of better significance in controlling release rate for drugs having site specific absorption. The floating microballoons showed gastroretentive controlled release delivery with efficient means of enhancing the bioavailability by means of enhancing the gastric retension. Optimized hollow microspheres will find the central place in novel drug delivery, particularly in safe, targeted and effective in vivo delivery promises to be a potential approach for gastric retention. The advantages, limitations, methods of preparation of hollow microsphere, applications, characterizations of microballoons and formulation aspects with various evaluation techniques and marketed products are included in detail.

KEYWORDS: Hollow microspheres, Gastroretentive, Floating, Controlled release.

INTRODUCTION

The oral delivery of drugs is the most favored route of administration because of ease of administration. Drug bioavailability of oral dosage forms is subjective by various factors. One of the significant factor is a Gastric residence time (GRT) of these dosage forms. Truly, gastric retention has received important interest in the past few years as many of the conventional oral delivery systems have some limits related to fast gastric emptying time. Gastroretentive dosage form is a type of novel drug delivery system which can persist in the stomach for prolonged period of time and thus increases the GRT of drugs.[1]

The conventional drug delivery system achieves and also maintains the drug concentration in the therapeutically effective range desired for treatment, only when taken numerous times in a day.[2] A drug that has a narrow absorption window in the GIT(Gastro Intestinal Tract) may have poor absorption. For these drugs, GRDDS(Gastro Retentive Drug Delivery Systems) offer the advantages in extending the gastric emptying time.

Many problems are faced in preparing controlled release systems for better absorption and improved bioavailability. Drug absorption from the GIT is a complex process and is subject to several variables.[3] It is broadly, recognised that the extent of GIT drug absorption is correlated to contact time with small intestinal mucosa. GRDDS can persist in the GI region for many hours and therefore significantly extend the GRT of drugs. Extended gastric retention increases bioavailability, decreases drug waste and increases solubility of drugs which are less soluble in high pH environment.

Anatomy of Stomach

The stomach is J shaped enlargement of GIT directly inferior to the diaphragm in epigastric, umbilical and left hypochondriac regions of the abdomen. It connects esophagus to the duodenum, the first part of the small intestine and provides a barrier to the delivery of drugs to the small intestine.[4] The stomach has four regions: Cardia, Fundus, Body & Pylorus

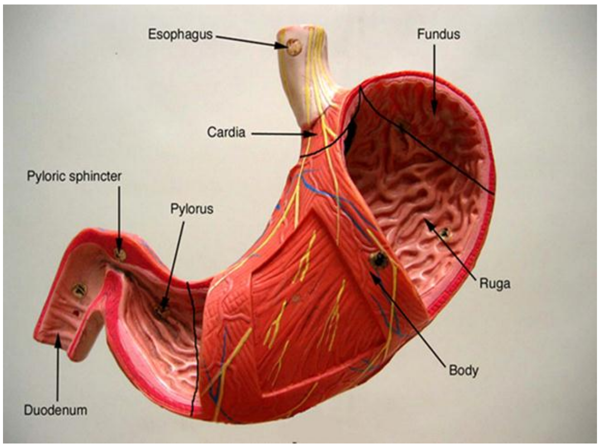

Figure 1: Anatomy of stomach.

Physiology of Stomach

The main Function of stomach is to store food temporarily, grind it and then release it to duodenum. The end portion of stomach and starting of intestine means duodenum is joined to pyloric sphincter, which is a valve type unit and it can open maximum up to 12.8 mm. So dosage forms having higher size are retained more time in stomach.

The gastric fluid volume in stomach is minimum of 25-50ml at resting stage. pH of gastric fluid is generally 1.5-2 in fasted state and may be raised up to 2-6 in fed conditions, but it comes back to normal soon by secretion of more gastric acid.

Gastric Retention Time (GRT) of any dosage form is generally 1-2.5 hours in fasted state but in fed condition GRT is increased, especially with fatty food. Food is passed out from stomach to intestine by gastric motility. There is specific motility pattern in fasted condition called as Migrating Myoelectric Complex (MMC) cycle. MMC is subdivided into four phases.[5]

PHASE I is a basal phase, which is silent period of 30-60 minutes and characterized by lack of secretory, electrical and contractile activity and there is no contractions.

PHASE II is pre-burst phase, which exhibit intermittent action of 20-40 minutes. Some bile secretion started and contractile motions increases frequency. Mucus discharge is started during later part of phase II.

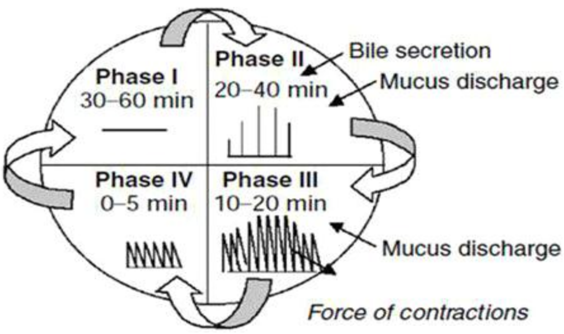

Figure 2: Gastrointestinal motility patterns.

PHASE III is burst phase, which is characterized by intense and large regular contractions termed as **"house keeper waves"**. These waves sweep off undigested food by maximizing the pyloric opening and lasts for 10-20 minutes. Thus, these phases enables efficient evacuation of the stomach contents.

PHASE IV is transition period up to 5minutes,between phase III and I.

The whole MMC cycle is repeated every 2-3 hours. The motor activity in the fed condition is induced 5-10 min after the ingestion of the meal and persist as long as food remains in the stomach. The larger the amount of food ingested, the longer the period of fed activity, with usual time spans of 2-6 hours and more typically 3-4 hours. Its phasic contractions are similar to those seen during phase II of the MMC.

Requirements For Gastric Retention

Physiological factors in the stomach, it must be noted that, to achieve gastric retention, the dosage form must satisfy certain requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms. To function as a gastric retention device, it must resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease.[6]

Need For Gastric Retention

Oral dosage forms pose low bioavailability problems because of their fast gastric transition from the stomach, particularly in case of drugs that are less soluble at an alkaline pH of the intestine. Also the drugs that produce their local action in the stomach get quickly emptied and do not get sufficient residence time in the stomach. Therefore, frequency of dose administration in such condition is increased. To avoid such problem floating drug delivery system has been developed.[7]

Gastroretentive Drug Delivery System

Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs.

Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach, low density (floating) systems that causes buoyancy in gastric fluid, mucoadhesive systems that causes bioadhesion to stomach mucosa, unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach, superporous hydrogel systems, magnetic systems etc. [8]

The current review deals with various gastroretentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery systems.

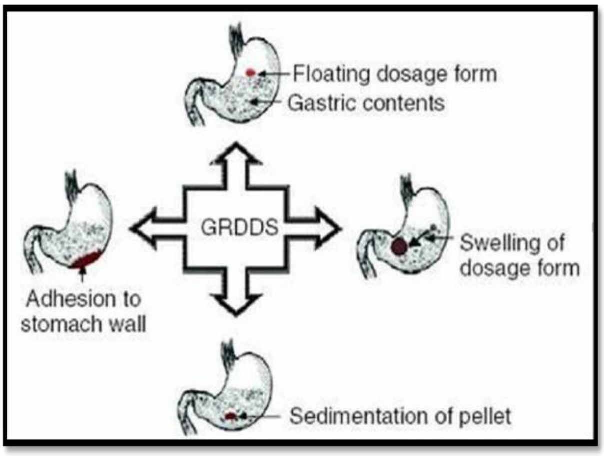

Figure 3: Various forms of GRDDS.

Factors Affecting Gastric Retention Time of The Dosage Form.[9]

1) **Density**: Gastric retention time (GRT) is a function of dosage form buoyancy which is dependent on the density. The density of the dosage form must be lower than the gastric contents (1.004 gm/ml).
2) **Size**: Dosage form units having a diameter of greater than 7.50 mm are stated to have an improved GRT related with those having a diameter of 9.90 mm.
3) **Shape Of The Dosage Form**: Tetrahedron and ring shaped devices having a flexural modulus of 48 and 22.50 kilo pounds per square inch are reported to have a better GRT at 24 hours compared with other shapes.
4) **Single Or Multiple Unit Formulation**: Multiple unit formulations show a more expectable release profile and insignificant damaging of performance because of failure of units, allow co- administration of units that have dissimilar release profiles related with single unit dosage forms.
5) **Fed/Unfed State**: In fasting conditions, gastrointestinal motility is categorized by periods of strong motor activity that occurs every 1.5 to 2h and if timing of administration of the formulation overlaps with that of the MMC, the gastric retention time of unit can be anticipated to be very short. However, in fed state, MMC is postponed and gastric retention time is significantly longer.
6) **Nature Of Meal**: Feeding of fatty acid salts or indigestible polymers can modify the motility pattern of stomach to a fed state, hence reducing the gastric emptying rate.
7) **Caloric Content**: GRT can be improved by 4 to 10 h with a meal which is high in proteins and fats.
8) **Age**: Elderly people, mostly those over 70 years, have a significantly longer gastric retention time.
9) **Frequency Of Feed**: Gastric retention time can rise by over 400 minutes, when consecutive meals are given related with a single meal because of the low frequency of MMC.
10) **Gender:** Mean ambulatory gastric retention time in males (3.4 ± 0.6 hours) is less correlated with their age and race matched female counterparts (4.6 ± 1.2 hours), regardless of the weight, body surface and height
11) **Posture**: Gastric retention time can be differing between supine and upright ambulatory states of patients.
12) **Concomitant Drug Administration**: Anticholinergics like atropine and propentheline increase the GRT. Metoclopramide and Cisapride decrease GRT.
13) **Disease State**: Gastric ulcer, diabetes and hypothyroidism increase the GRT. Hyperthyroidism and duodenal ulcers decrease the GRT.

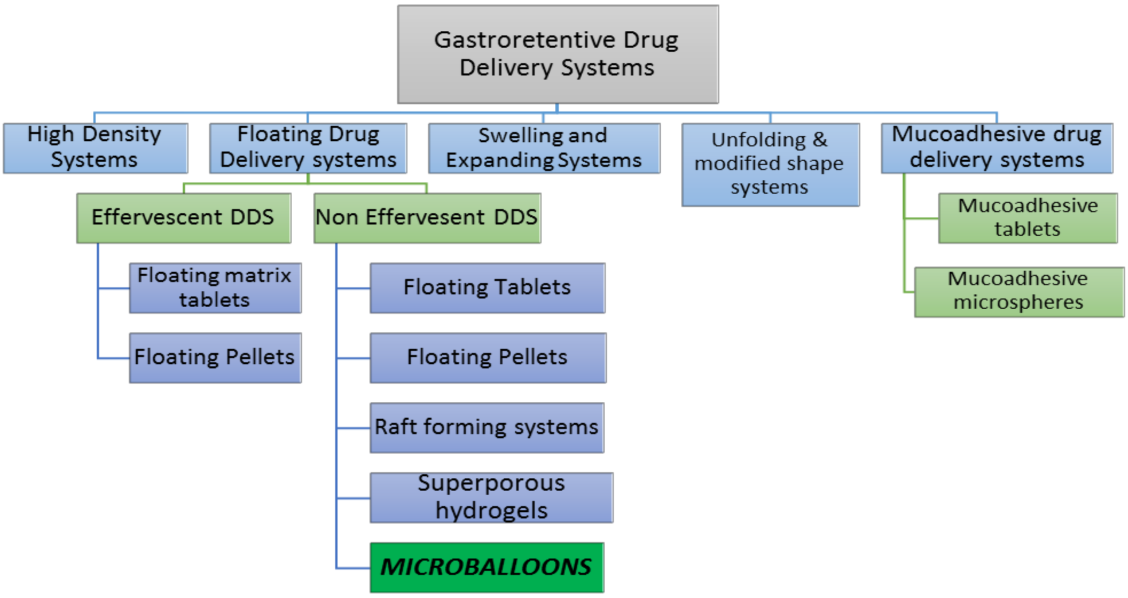

Figure 4: Classification of GRDDS.

Advantages[10,11]

- Increase in bioavailability and curative efficiency of drugs and economic usage of dosage.
- Minimised factor of risk in resistance in antibiotics owing to stabilised therapeutic levels over prolonged periods removing fluctuations.
- Optimised release in case of short half-life drugs, causes flip flop pharmacokinetics and also ensures patient compliance with reduced dosage frequency.
- They are advantageous against drawbacks of the gastric retention time (GRT) as well as the gastric emptying time (GET). The system remains buoyant on gastric fluid because of lower bulk density than gastric fluids.
- These are efficient in repairing stomach and small intestine related problems. Its attributed to the fact that gastroretentive drug delivery sustains drug release and hence, avail local therapy in these organs.
- This method provides with a systematic and controlled drug delivery system which minimises chances of drug over exposure at the diseased site.
- Providing a narrow curative index, the gastroretentive dosage forms minimises variance in concentrations of drugs and effects.
- This system provides higher efficiency due to reduced counter activity by body.
- As the system provides with controlled rates of fluctuation, a wider array is provided for selectivity in receptor activation.

Disadvantages[10,11]

Need for increased level of fluids in the stomach.

Unsuitable for such drugs as:

- Problematic with solubility in gastric fluid
- Causing G.I irritation
- Inefficient in acidic environment
- Drugs intended for selective release in the colon.
- Unpredictable adherence owing to state of constant renewal of mucus wall of stomach.
- GRDDS is fed into the system after the meal as time of stay in stomach depends on digestive state.
- The ability of the drug to remain in the stomach depends upon the subject being positioned upright.
- Hydrogel based swelling system takes longer time to swell.
- Upon multiple administrations, size increasing drug delivery systems pose the threat to life owing to possible hazard of permanent retention in stomach.
- Superporous systems having drawback like problematical storage of much easily hydrolysable, biodegradable polymers.

Microballoons

Microballoons are gastro retentive drug-delivery systems with non-effervescent approach. Microballoons (Hollow microsphere) are in strict sense, empty particles of spherical shape without core. These microspheres are characteristically free flowing powders comprising of proteins or synthetic polymers, ideally having a size less than 200 micrometer.[12]

Microballoons are considered as one of the most favourable 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 novel techniques involved in their preparation include 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. The slow release of drug at 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 hydroxy propyl methyl cellulose cellulose acetate are used in the formulation of hollow microspheres, and the release of drug can be modulated by optimizing polymer concentration and the polymer -plasticizer ratio.[13]

Hollow microspheres / microballoons loaded with drug in their outer polymer shell are prepared by a novel methods such as solvent evaporation or solvent diffusion/evaporation to create a hollow inner core. The drug and an enteric acrylic polymer mixture is dissolved in ethanol/dichloromethane solution and it is poured into an agitated solution of Poly Vinyl Alcohol (PVA) that as thermally controlled at 40ºC. After the formation of stable emulsion, the organic solvent is evaporated from the emulsion by increasing the temperature under pressure or by continuous stirring.[14] The gas phase is generated in the droplet of dispersed polymer by the evaporation of dichloromethane and thus formed the hollow internal cavity in the microsphere of the polymer with drug. The microballoon is continuously float over the surface of an acidic dissolution media containing surfactant for more than 12 hours.[15,16]

Mechanisms of Microballoons

Microballoons are low-density systems that have sufficient buoyancy to float over gastric fluid and remain in stomach for prolonged period of time. As the system floats over gastric fluid, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. When microballoons come in contact with gastric fluid, the gel forms and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the outer 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 makes the density lower than the gastric fluid and confers buoyancy to the microspheres. However, a minimal gastric content needed to allow proper achievement of buoyancy[17,18]. Hollow microspheres (Microballoons) of acrylic resins, eudragit, hypromellose, polyethylene oxide, cellulose acetate, polystyrene floatable shells, polycarbonate floating balloons and gelucire floating granules are the recent advancements.[19]

Method of preparation

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. Depending upon the hydrophilicity or the hydrophobicity of drugs, different methods are used to prepare microspheres by solvent evaporation technique. 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.[20,21]

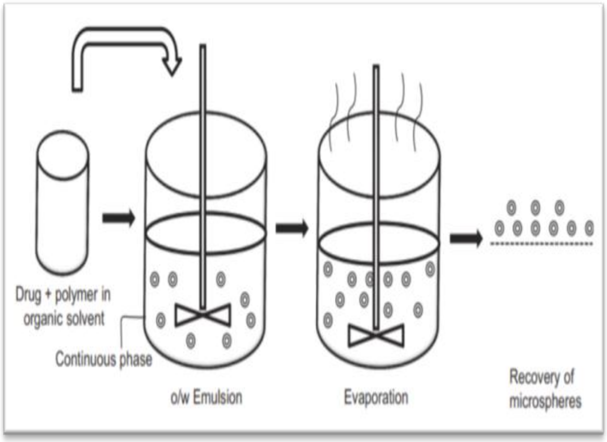

Figure 5: Solvent Evaporation method.

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 high encapsulation efficiency. 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.

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. The preparation method and mechanism of microballoon formation is schematically illustrated in the following Figure.

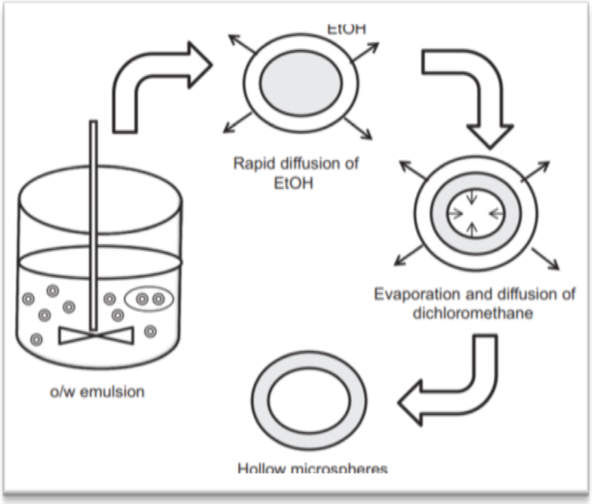

Figure 6: Emulsion Solvent Diffusion Method.

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. 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.[20,21]

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.

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.

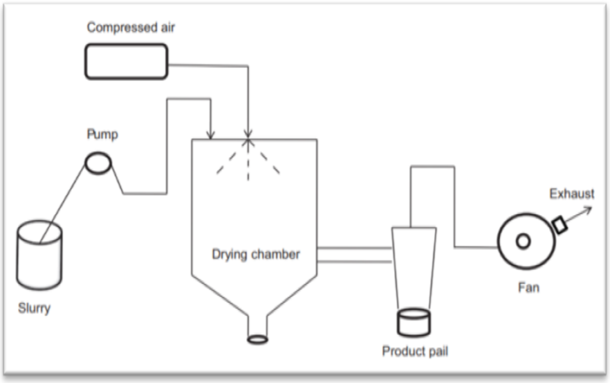

Figure 7: Spray drying method.

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.[22,23]

EVALUATION OF HOLLOW MICROSPHERES

Percentage Yield

The percentage yield of the hollow microspheres is determined for drug and is calculated using the following equation.[24,25,26]

Yield=M/Mo x 100

Where M = weight of beads

Mo = total expected weight of drug and polymer.

Micromeritic properties[27,28]

Microballoons are evaluated by their micromeritic properties such as particle shape and size, bulk density, tapped density, Hausner's ratio and flow properties which is determined by carr's index and angle of repose37. Particle size is determined by an optical microscopy, and average diameter of particle is calculated with the help of calibrated ocular micrometer (by measuring 200 to 300 particles)38. 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. The hollow nature of microspheres is confirmed by scanning electron microscopy.

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

$$I = Vb - Vt / Vb \times 100$$

Where, Vb is the bulk volume and Vt is the tapped volume. The value given below 15% indicates a powder with usually give rise to good flow characteristics, whereas above 25% indicate poor flow ability. True density is determined using a Helium densitometer. Porosity (e) is calculated using the following equation:

$$e = \{1- (\text{tapped density}/\text{true density})\} \times 100$$

Angle of repose of the micro balloons are determined by the fixed funnel method.

In vitro buoyancy

Appropriate quantity of hollow/empty microspheres are placed in 900 ml of 0.1N HCl. The mixture is stirred at 100 rpm for 8-10 hours in dissolution apparatus. After 8 to 10 hours, the layers of buoyant microspheres are pipetted and separated by filtration. Particles which lies in the layer of sinking particulate are separated by filtration. Particles of both types (buoyant microspheres and settled microspheres) are dried in a desiccator until constant weight is achieved. Both the fractions of empty/hollow microspheres are weighed, and In vitro buoyancy is determined by the weight ratio of floating microspheres to the sum of floating and sinking microspheres.[29]

$$\text{Buoyancy } (\%) = \{Wf / (Wf + Ws)\} \times 100$$

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

Scanning electron microscopy

Dry hollow microspheres are placed on an electron microscope brass stub a coated with gold in an ion sputter. Then pictures of microsphere are taken by spectro random scanning of the stub. The microspheres are viewed at an accelerating voltage of 20KV.[30]

In-vitro drug release studies

The release rate of hollow microspheres are determined in a United States Pharmacopoeia (USP) XXIII basket type dissolution apparatus.

A weighed amount of hollow microspheres (filled into a hard gelatin capsule) equivalent to dose of drug and place in the basket of dissolution rate apparatus containing dissolution medium. The dissolution fluid is maintained at 37 ± 1 °C and rotation speed at a specific rpm. Perfect sink conditions carry out during the drug release study. Few ml (5 ml) of samples are withdrawn at each time interval and analyzes using Liquid chromatography / Mass spectroscopy method to determine the concentration of microballoons 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 are run in triplicate.[31]

Data analysis of release studies

Five kinetic models including the zero order (Equation 1), first order (Equation 2), Higuchi matrix (Equation 3), Peppas- Korsmeyer (Equation 4) and Hixon-Crowell (Equation 5)release equations are applied to process the in vitro release data to find the equation with the best fit using PCP Disso v3 software.[32,33]

Swelling studies

Swelling studies are performed to calculate molecular parameters of swollen polymers. Swelling studies 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.[34]

Swelling ratio = Weight of wet formulation / Weight of formulations

In-vivo studies

The in-vivo studies are performed on suitable animal models example such as rat, beagle dogs etc. The floating behavior can be investigated by radiographical studies using barium sulphate microballoons6.[35]

Applications of Microballoons

- The empty microspheres allow sustained drug release behavior and release the drug over a prolonged period of time. Hollow microspheres are fabricated as a floating controlled drug delivery system.
- It is recently described that drugs is to be entrapped in hollow microspheres and reduces the fluctuations include Prednisolone, Lansoprazole, Celecoxib, Piroxicam, Theophylline, Diltiazem hydrochloride, Verapamil hydrochloride and Riboflavin, Aspirin, Griseofulvin, Ibuprofen, Terfenadine.
- Floating microspheres can greatly enhance the absorption of those drugs which have poorbioavailability and thus it improves absolute bioavailability.[36,37]
- Floating microspheres are site specific drug delivery especially for those drugs which are specifically absorbed from stomach or the proximal part of small intestine.
- Microballoons can be used to transport the drugs with so-called absorption windows, these substances, for example, antiviral, antifungal and antibiotic agents (Sulphonamides, Quinolones, Penicillins, Cephalosporins, Amino glycosides and Tetracyclines) are taken up only from very specific sites of the GI mucosa.
- Empty microspheres of NSAIDS drugs are very successful for controlled release as well as it reduces the side effect of gastric irritation; for example floating microspheres of Indomethacin is quite beneficial for rheumatic patients.[37]

Future Potential

- It is expected that various new products using gastro retentive drug delivery technologies may magnify this possibility. Further investigations may concentrate on the microballoons concepts:
- Design of an array of gastro retentive drug delivery systems, each having narrow GRT for use according to the clinical need, e.g., dosage and state of disease.
- Determination of minimal cut-off size above that dosage forms retained in the GIT for prolonged period of time.
- Design and development of gastro retentive drug delivery systems as a beneficial strategy for the treatment of gastric, duodenal cancers and treat Parkinson’s disease.
- Development of various anti-reflux formulation utilizing gastro retentive technologies.
- Exploring the eradication of Helicobacter pylori by using various antibiotics.

List of drugs formulated as microballoons

S. No.	Drugs	Polymers	Method	Reference
1	Atenolol	Ethyl cellulose & HPMC	Emulsion solvent evaporation technique	[38]
2	Curcumin	Ethyl cellulose, Eudragit S100 & HPMC	Emulsion solvent evaporation technique	[39]
3	Tolperisone	Ethyl cellulose (EC), & HPMC 15 cPs	Non-aqueous solvent evaporation technique	[40]
4	Famotidine	HPMC and Ethyl cellulose (EC)	Solvent evaporation (Oil-in-water emulsion) technique	[41]
5	Captopril	HPMC(K4M) and Ethyl cellulose (EC)	Ionotropic gelation technique	[42]
6	Ketoprofen	Eudragit S100 and Eudragit L 100	Emulsion solvent diffusion method	[43]
7	Ketorolac trometamol.	Ethyl cellulose, HPMC K4M, Eudragit R100 &Eudragit S100	Emulsion solvent diffusion method	[44]
8	Glipizide	Acrycoat S100, Eudragit RS100.	Emulsion solvent diffusion technique	[45]
9	Rabeprazole	HPMC K15M and Ethyl cellulose	Emulsion solvent Evaporation	[46]
10	Orlistat	Eudragit S	Emulsion solvent Evaporation	[47]
11	Esomeprazole	HPMC and Methyl cellulose	Solvent evaporation method	[48]
12	Cimetidine	HPMC and Ethyl cellulose	Solvent evaporation method	[49]
13	Stavudine	Eudragit RS100	Emulsion solvent diffusion	[50]
14	Metformi	Eudragit RS100 and Eudragit RL	Non aqueous solvent evaporation	[51]
15	Aceclofenac	Ethyl cellulose	Solvent evaporation	[52]

CONCLUSION

Based on the literature surveyed, it may be concluded that gastroretentive drug delivery offers various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper gastrointestinal tract (GIT) and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability. Due to complexity of pharmacokinetics and pharmacodynamics parameters, in vivo studies are required to establish the optional dosage form for a specific drug.

Microballoons are low-density, sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. The drug is released slowly at desired rate when it floats over gastric contents resulting reduced fluctuations in plasma drug concentration.

It is efficient means of enhancing the bioavailability. Optimized microballoons will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective in vivo delivery.

ACKNOWLEDGEMENTS
We would like to express our thanks to our HODs Dr.K.Venu Madhav, Department of Pharmaceutics, Dr.P.Sunil K Chaitanya Department of Pharm. Analysis for their continuous support and suggestions in the project and management of St.Pauls college of Pharmacy for their best wishes for the successful completion of this review article. No source of funding was used to assist in the preparation of this review.

REFERENCES

1. Omidian H, Park K. Oral targeted drug delivery systems: gastric retention Devices. *Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice*, John Wiley and Sons Inc., 2010; 185.
2. Narang N. An updated review on: Floating drug delivery system (FDDS). Int J Appl Pharm., 2011; 3: 1–7.
3. Wilson C, Washington N, Washington C. *Physiological Pharmaceutics: Barriers to Drug Absorption*. 2nd ed. Taylor and Francis, 2001.
4. Fell JT. Targeting of drugs and delivery systems to specific sites in the gastrointestinal tract. J Anat, 1996; 189: 3: 517–9.
5. Chawla G, Gupta P, Koradia V, Bansal AK. Gastroretention a means to address intestinal drug absorption. Pharm Technol, 2003; 27: 50–68.
6. El Samaligy S. Floating systems for oral controlled release drug delivery. University of Berlin, n.d., 2010.
7. Wen H, Park K. Introduction and overview of oral controlled release formulation design. In: Wen H, Park K. editors. Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice, John Wiley and Sons Inc., 2010; 21.
8. Zou H, Jiang X, Kong L, Gao S. Design and evaluation of a dry coated drug delivery system with floating–pulsatile release. J Pharm Sci., 2008; 97: 263–73. Doi:10.1002/jps.21083.
9. Kumar R, Patil MB, Patil S, Paschapur M. Formulation and evaluation of effervescent floating tablet of famotidine. Int J PharmTech Res., 2009; 1: 754–63.
10. Someshwar K, Chithaluru K, Ramarao T, Kalyan Kumar KK. Formulation and evaluation of effervescent floating tablets of tizanidine hydrochloride. Acta Pharm., 2011; 61: 217–26.
11. Chaitanya K, Velmurugan S. Formulation and evaluation of levodopa effervescent floating tablets. Int J Pharm Pharm Sci., 2015; 7: 189–93.
12. Vyas SP, Khar RK. Targeted and Controlled Drug Delivery Novel Carrier System, New Delhi: CBS Publishers and Distributors, 2002; 417-54.
13. Kawashima Y, Niwa T, Takenchi H, Hino T, Itoh Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. J. Pharm. Sci., 1992; 81: 135-140.
14. Streubel A, Siepmann J, Bodmeier R. Floating microparticles based on low density foam powdering. J. Pharm., 2002; 241(2): 279-292.
15. Pujara ND, Patel NV, Thacker AP, Raval BK, Doshi SM, Parmar RB. Floating microspheres: A novel approach for gastroretention. World journal of pharmacy and pharmaceutical sciences, 2012; 1(3): 872-89.
16. Garg R, Gupta GD. Progress in controlled gastroretentive delivery systems. Trop. J. Pharm. Res., 2008; 7(3): 1055-10665.
17. Garg S, Sharma S. Gastroretentive Drug Delivery System. Bussiness Briefing. Pharmatech, 2003; 13(1): 160-166.
18. Ichikawa M, Watanabe S, Miyake Y. A new multiple unit oral floating dosage system II: In vivo evaluation of floating and sustained – release characterstics with para amino benzoicacid and isosorbidedinitrate as model drugs. J. Pharm. Sci., 1991; 80: 1153-1156.
19. Somwanshi SB, Dolas RT, Nikam VK, Gaware VM, Kotade KB, Dhamak KB and Khadse AN, Floating Multiparticulate Oral Sustained Release Drug Delivery System. J.Chem. Pharm. Res., 2011; 3(1): 536-547.
20. Sheth PRTJ. The Hydrodynamically balanced systems (HBSTM): a novel drug delivery system for oral use. Drug Dev Ind Pharm., 1984; 10: 313–39.
21. Kumar MK, Shah MH, Ketkar A, Mahadik KR, Paradkar A. Effect of drug solubility and different excipients on floating behaviour and release from glyceryl monooleate matrices. Int J Pharm., 2004; 272: 151–60.
22. Yan HX, Zhang SS, He JH, Liu J P. Application of ethyl cellulose, microcrystalline cellulose and octadecanol for wax based floating solid dispersion pellets. Carbohydr Polym, 2016; 148: 143–52.
23. Oh TO, Kim JY, Ha JM, Chi SC, Rhee YS, Park CW, et al. Preparation of highly porous gastroretentive metformin tablets using a sublimation method. Eur J Pharm Biopharm, 2013; 83: 460–7.
24. Jain SK, Awasthi AM, Jain NK, Agrawal GP. Journal of Controlled Release, 2007; 107(2):

300-309.
25. Shah M, Jadhav N, Agrawal YK. Fullerenes, Nanotubes and Carbon Nanostructures, 2009; 17(5): 528-547.
26. Awasthi R., Kulkarni GT. Development and characterization of amoxicillin loaded floating microballoons for the treatment of Helicobacter pylori induced gastric ulcer. Asian J. of pharma. Sci., 2013; 8: 174-180.
27. Gattani, YS, Kawtikwar PS, Sakarkar DM. Formulation and evaluation of gastroretentive multiparticulate drug delivery system of aceclofenac. Int. J. Chem. Tech. Res., 2009; 1: 1-10.
28. Sarkar BS, Tanwar SS, Soni P,Jain P. Formulation, characterization and in vitro evaluation of floating microspheres of Esomeprazole. Int. J. of Bioassay, 2012.
29. Mali AD, Bathe RS. An updated review on microballoons for better approach in gastroretnton. Asian J. Res. Pharm. Sci., 2015; 5(3): 188-192.
30. Pusp RN, Myung KC, Hoo KC. Preparation of floating microspheres for fish farming. International Journal of Pharmaceutics, 2007; 341: 85-90.
31. Rani U, Nagaraju R. A review on approaches of floating microspheres, 2015: 4(12): 646-655.
32. Wu PC, Tsai MJ, Huang YB, Cheng JS, Tsai YH.In Vitro and In Vivo evaluation of Potassium chloride sustained release formulation prepared with saturated polyglycolyed glycerides matrices. Int. J. Pharm., 2002; 243: 119-124.
33. Polli JE, Rehki GS, Augsburger LL, Shah VP. Methods to compare dissolution profiles and a rationale for wide dissolution specification for Metoprolol tartrate tablets. J. Pharm. Sci., 1997; 86: 690-700.
34. Singh B, Kim KH. Floating Drug Delivery Systems: An Approach of Oral Controlled Drug Delivery via Gastric Retention. J. Controlled Release, 2000; 63: 235-259.
35. Chouhan M, Agrawal GP, Jain A. Design of buoyant Famotidine loaded Microballoons directed for upper small intestinal absorption window. IJRPS, 2013; 3(2): 216-228.
36. Pujara ND, Patel NV, Thacker AP, Raval BK, Doshi SM, Parmar RB. Floating microspheres: A Novel approach for gastro retention. World Journal of Pharmacy and Pharmaceutical Sciences, 2012; 1(3): 872-895.
37. Moursy NM, Afifi NH, Ghorab DM, El-Saharty Y. Formulation and Evaluation of sustained release floating capsules of Nicardipine hydrochloride. Pharmazie, 2003; 58: 38-43.
38. Patil K, Tekade BW, Thakare VM, Patil VR. Formulation and Evaluation of Atenolol Floating Microsphere. Pharma Tutor Pharmacy Infopedia.
39. Kumar K,Rai AK. Development and Evaluation of Floating Microspheres of Curcumin. Tropical Journal of Pharmaceutical Research, 2012; 11(5): 713-719.
40. Jani P, Vadalia K, Bagdai H, Dedania R, Manseta P. Formulation and evaluation of controlled release floating microspheres of Tolperisone hydrochloride. Asian Journal of Pharmaceutics, 2012; 6(3): 190-197.
41. Singh B, Kanoujia J, PandeyM, Saraf SA. Formulation and evaluation of floating microspheres of Famotidine. International Journal of Pharm. Tech. Research, 2010; 2(2): 1415-1420.
42. Abhijeet A. Durgavale, Archana R. Dhole, Shrinivas K. Mohite, Chandrakant S. Magdum. Formulation and evaluation of floating microsphere of Captopril using different gas forming agents. Am. J. Pharm. Tech. Res., 2012; 2(2): 56-63.
43. Najmuddin M, Sachinshelar, Asgarali, Patel V, Khan T. Formulation and in-vitro evaluation of floating microspheres of Ketoprofen prepared by emulsion solvent diffusion method. International journal of applied pharmaceutics, 2010; 2(1): 125-134.
44. Barhate SD, Rupnar YS, Sonvane RM, Pawar KR, Kumar R, Rahane D. Formulation and evaluation of floating microspheres of Ketorolac trometamol. IJPRD, 2009; 1(9): 302-315.
45. Sarode SM, Mittal M, Magar RM, Shelke AD, Shrivastava B, Vidyasagar G. Formulation and evaluation of floating microspheres of Glipizide. J. Chem. Pharm. Res., 2011; 3(3): 775-783.
46. Shwetha S, Kamath K, Kumar SK. Design and Evaluation of floating microspheres of Rabeprazole sodium. International Journal of Pharmacy and Pharmaceutical Sciences, 2012; 4(3): 104-120.
47. Jain SK, Agrawal GP, Jain NK. Evaluation of porous carrier-based floating Orlistat microspheres for gastric delivery. AAPS Pharm. Sci. Tech., 2006; 7(4): E54–E62.
48. Sarkar BK, Tanwar SS, Soni P, Jain P. Formulation, characterization and in vitro evaluation floating microspheres of Esomeprazole. International journal of bio assays, 2012; 1: 208-219.
49. Srivastava AK, Ridhurkar DN, Wadhwa S. Floating microspheres of Cimetidine: formulation, characterization and in vitro evaluation. Acta Pharm., 2005; 55(3): 277-85.
50. Osephine LJ, Mehul RT, Wilson B, Shanaz B and Bincy R. Formulation and in vitro evaluation of floating microspheres of anti-retro viral drug as a gastro retentive dosage form. International Journal of Research in Pharmacy and Chemistry (IJRPC), 2011; 1(3): 362375.
51. Dhulipati R. Formulation and evaluation of floating microspheres of Metformin hydrochloride. Pharmatutor Art, 1055.
52. Das T, Muthuprasanna P, Bhaskaran S, Vaijayanthi V. Formulation and evaluation of Aceclofenac floating microspheres, 2008; 4(4): 69-82.