

Review Article

Microballoons: A Better Approach for Gastro RetentionRAKHI NEGI¹, LAXMI GOSWAMI¹, PREETI KOTHIYAL²¹Department of Pharmaceutics, Division of Pharmaceutical Sciences, Shri Guru Ram Rai Institute of Technology and Science, Patelnagar Dehradun, 248001²Department of Pharmacology, Division of Pharmaceutical Sciences, Shri Guru Ram Rai Institute of Technology and Science, Patelnagar Dehradun, 248001**ARTICLE DETAILS***Article history:*

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The purpose of this review is to accumulate the recent study on floating drug delivery system with special emphasis on microballoons as drug delivery. Microballoons are emerging as the most promising drug delivery as it overcome many limitations of conventional drug delivery system. As microballoons delivery system provides longer retention in gastric pH, hence longer is the residence time and therefore enhance the solubility of drugs that are less soluble in high pH environment. The formation of cavity inside the microsphere depends upon the preparation temperature and the surface smoothness determines the floatability and the drug release rate of the microballoons. The review includes the classification, advantages, disadvantages, method of preparation and future aspects of microballoons. Basic anatomy and physiology of stomach is also studied.

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INTRODUCTION

One of the most interesting fields of research in pharmaceutics is the development of new delivery systems for the controlled release of drugs [1]. Gastro retentive 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. Gastro retentive dosage form can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity.

To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time [2]. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste and improves the drug availability that are less soluble in a high pH environment [3].

Physiology of Stomach [4]

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions (Fig.1). Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an inter-digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 h. This is called the inter digestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 phases (Fig. 2).

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1. Phase I (Basal phase) lasts from 30 to 60 min with rare contractions.
2. Phase II (Pre burst phase) lasts for 20 to 40 min with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 10 to 20 min. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
4. Phase IV lasts for 0 to 5 min and occurs between phases III and I of 2 consecutive cycles.

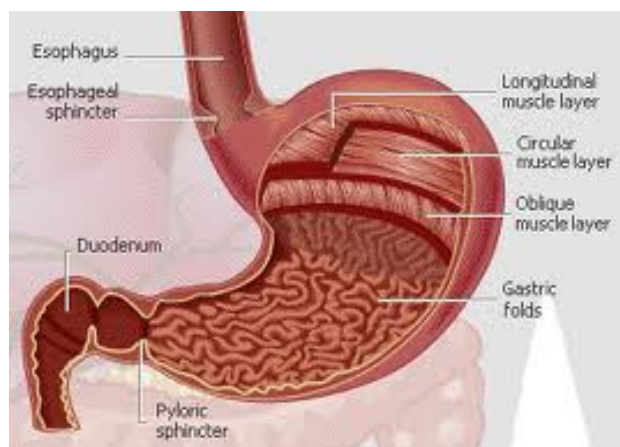


Figure 1: Anatomy of stomach

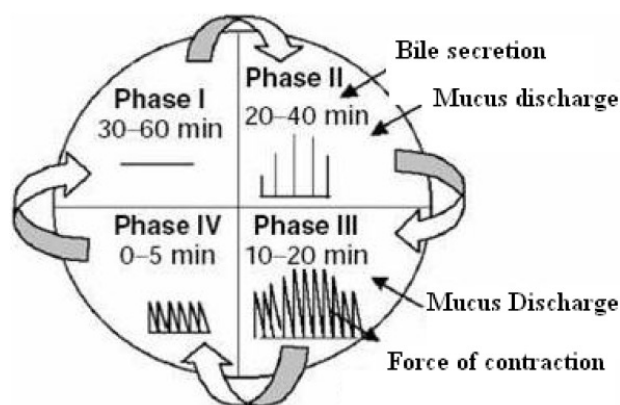


Figure 2: Figure showing inter-digestive motility

Floating Drug Delivery System [5]

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system floats on gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increase in gastric retention time and a better control of fluctuations in plasma drug concentrations. However, besides a

minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight (RW) has been reported in the literature. The RW apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if RW is on the higher positive side (Fig.3). This apparatus helps in optimising FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intra-gastric buoyancy capability variations.

$$RW \text{ or } F = F_{\text{buoyancy}} - F_{\text{gravity}} = (D_f - D_s) gV$$

Where, RW = total vertical force, D_f = fluid density, D_s = object density, V = volume and g = acceleration due to gravity [6].

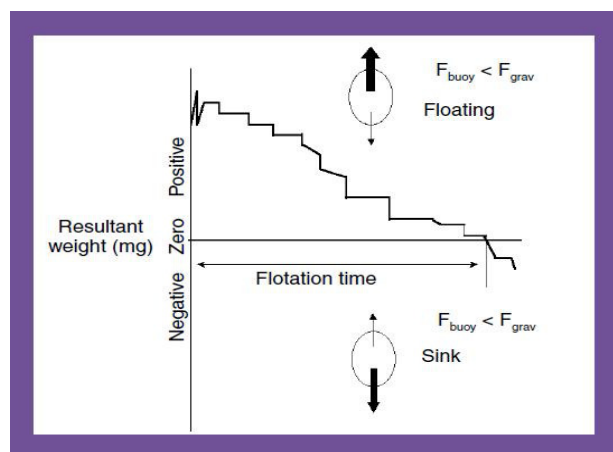


Figure 3: Effect of resultant weight during buoyancy on the floating tendency of FDDS

Mechanism of Floating Systems

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric emptying delaying drugs. Among these, the floating dosage forms are the most commonly used. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is

floating on the gastric contents, the drug is released slowly at the desired rate from the system (Fig. 4). After release of drug, the residual system is eliminated from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention effect, a minimal level of floating force is also required to maintain the buoyancy of the dosage form on the surface of the meal [7].

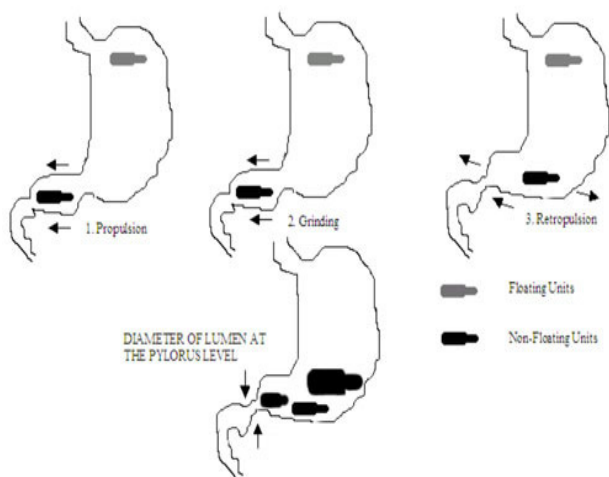


Figure 4: Intra-gastric residence positions of floating and non-floating units.

Classification

Floating systems can be classified into two systems:

- 1) Effervescent systems
 - Volatile liquid containing systems
 - Gas-generating Systems
- 2) Non-Effervescent Systems
 - Colloidal gel barrier systems
 - Microporous Compartment System
 - Alginate beads
 - Hollow microspheres

Effervescent Floating Dosage Forms

This approach provides floating drug delivery systems based on the formation of CO_2 gas. It utilizes effervescent components such as sodium bicarbonate (NaHCO_3) or sodium carbonate, and additionally citric or tartaric acid. Upon contact with the acidic environment, a gas is liberated, which produces an upward motion of the dosage form and maintains its buoyancy. A decrease in specific gravity causes the dosage form to float on the chyme. Generally, effervescent systems suffer from the disadvantage not to float immediately after swallowing because the

process of gas generation takes some time (Fig.5). Therefore, they could be cleared from the stomach before becoming effective. The performance of low-density, floating drug delivery systems is strongly dependent on the filling state of the stomach [8].

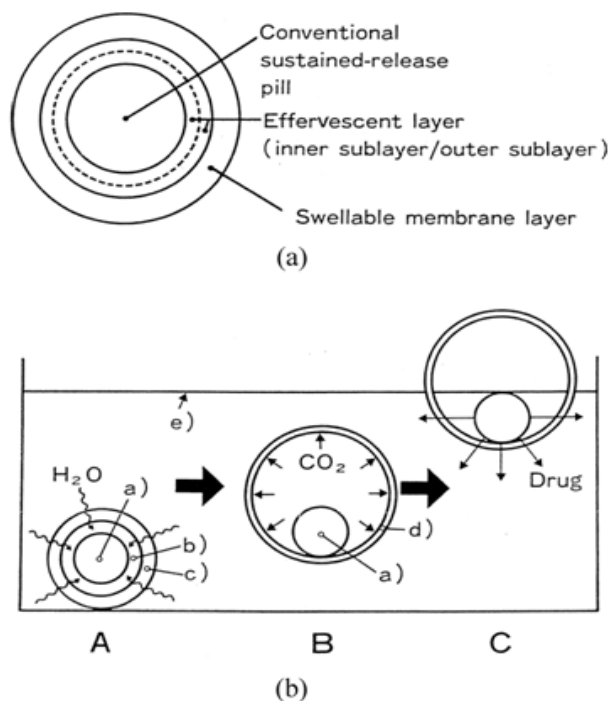


Figure 5: (a) multiple unit oral floating drug delivery system (b) working principle of effervescent floating drug delivery system

Non-Effervescent Floating Dosage Forms

This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. These systems may be referred to as the 'plug-type systems' since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms [9].

Colloidal Gel Barrier System

These systems contain drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. These are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers. Hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium

carboxymethyl cellulose (NaCMC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans or alginic acid are commonly used excipients to develop these systems. The polymer is mixed with drugs and usually administered in hydro dynamically balanced system capsule. (Fig. 6) The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period. Because, continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form [10].

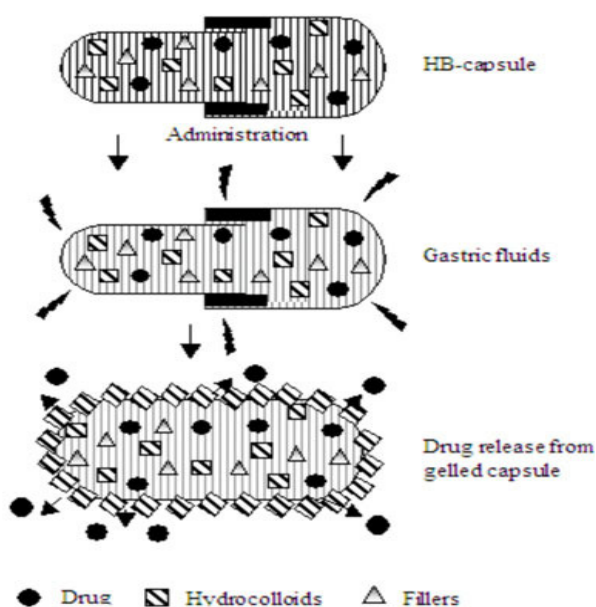


Figure 6: Schematic diagram of Hydro dynamically balanced system

Microporous Compartment System

This approach is based on the principle of the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the device were completely sealed to prevent any direct contact of the gastric surface with the undissolved drug. In the stomach the floatation chamber containing entrapped air causes the delivery system to float in the gastric fluid. Gastric fluid enters through the aperture, dissolves the drug and causes the dissolved drug for continuous transport across the intestine for drug absorption [11].

Alginate Beads

Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium

alginate solution into aqueous solutions of calcium chloride, causing precipitation of calcium alginate. The beads are then separated and frozen in liquid nitrogen, and freeze dried at -40° for 24 h, leading to the formation of porous system, which can maintain a floating force over 12 h [12].

Hollow Microspheres

Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres (microballoons) are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than $200\mu\text{m}$. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs. Gastro-retentive floating microspheres are low density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration [5]. Hollow microspheres loaded with drugs in their polymer shell were prepared by simple solvent evaporation or solvent diffusion / evaporation methods to prolong the gastric retention time (GRT) of the dosage form with continuously floating over the surface of an acidic dissolution media containing surfactant for >12 h (Fig. 7) [13].

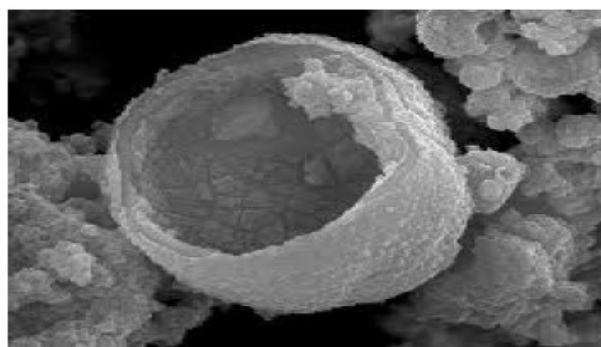


Figure 7: Hollow microspheres

Methods of Preparation

Solvent Evaporation Method

Floating multiparticulate dosage form can be prepared by solvent diffusion and evaporation methods to create the hollow inner core. The polymer is dissolved in an organic solvent and the drug is either dissolved or dispersed in the

polymer solution. The solution containing the drug is then emulsified into an aqueous phase containing suitable additive (surfactants /polymer) to form oil in water emulsion. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring. The solvent removal leads to polymer precipitation at the oil/water interface of droplets, forming cavity and thus making them hollow to impart the floating properties. The polymers studied for the development of such systems include cellulose acetate, chitosan, Eudragit, Acrycoat, Methocil, polyacrylates, polyvinylacetate, carbopol, agar, polyethylene oxide and polycarbonate (Fig 8).

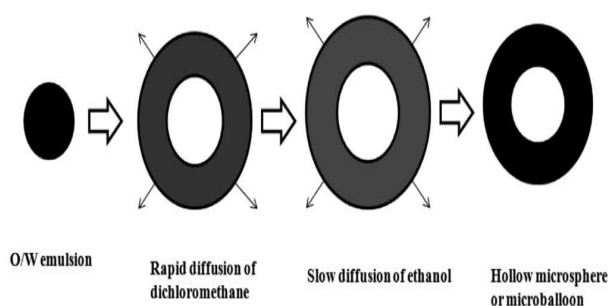


Figure 8: Formulation of floating hollow microsphere or microballoon

Emulsion Solvent Diffusion Method

In the emulsion solvent diffusion method the affinity between the drug and organic solvent is stronger than that of organic solvent and aqueous solvent. The drug is dissolved in the organic solvent and the solution is dispersed in the aqueous solvent producing the emulsion droplets even though the organic solvent is miscible. The organic solvent diffuses gradually out of the emulsion droplets into the surrounding aqueous phase and the aqueous phase diffuses into the droplets by which drug crystallizes [5].

Characterization of the Optimized Microballoons

Determination of Bulk Density, Tapped Density and Particle Density

Different fractions of the optimized formulation (1g) were taken into a 10ml graduated measuring cylinder separately and the volume was noted down. The graduated measuring cylinder was tapped 50 times using USP bulk density apparatus. The bulk density and tapped densities were determined using the following formula:

$$\text{Bulk density} = \frac{\text{Weight of the floating microballoons}}{\text{Initial volume}}$$

$$\text{Tapped density} = \frac{\text{Weight of the floating microballoons}}{\text{Final volume after tapping}}$$

Particle density of different fractions was determined by the liquid displacement method by suspending the microballoons in a solvent in which the microballoons were insoluble like distilled water [14].

Particle Size Analysis

Particle size analysis was carried out using the optical microscopic method with the help of a calibrated eye piece micrometer. The size of around 100 particles was measured and median diameter was calculated [15].

Scanning Electron Microscopy (SEM)

SEM was performed for morphological characterization of microspheres using scanning electron microscope. They were mounted directly onto the SEM sample stub using double-sided sticking tape and coated with gold film (thickness, 200nm) under reduced pressure (0.001mmHg) [16].

In vitro Drug Release Study

A USP (United State Pharmacopoeia) basket apparatus has been used to study *in vitro* drug release from microballoons. In this, drug release was studied using a USP dissolution apparatus type I at 100 rpm in distilled water and 0.1mol HCl (pH 1.2) as dissolution fluid (900 ml) maintained at $37 \pm 0.5^\circ\text{C}$. Withdrawn samples were analyzed spectrophotometrically. The volume was replenished with the same amount of fresh dissolution fluid each time to maintain the sink condition [17].

Buoyancy Percentage

Appropriate amount of Microspheres were placed in 900 ml of 0.1N hydrochloric acid. The mixture was stirred at 100 rpm in a dissolution apparatus for 8 hrs. After 8 hrs, the layer of buoyant microspheres were pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in a dessicator until constant weight. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

$$\% \text{ Buoyancy} = \left[\frac{W_f}{W_f + W_s} \right] \times 100$$

Where 'Wf' and 'Ws', are the weights of the floating and settled microspheres. [18]

Stability Studies

During the storage if one performs studies at normal temp it will take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product is stored under extreme conditions of temperature. Optimized formulation sealed in aluminum packaging coated inside with polyethylene, and various samples were kept in the humidity chamber maintained at 40°C and 75% RH for 2 months. At the end of studies, samples were analyzed for the physical appearance, drug content and drug release [19].

Release Kinetics

Data obtained from *in-vitro* release studies were fitted to various kinetic equations to find out the mechanism of drug release from the ethyl cellulose microsphere. The kinetic models used were:

$$Q_t = K_0 t \dots\dots\dots \text{(Zero-order equation)}$$

$$\ln Q_t = \ln Q_0 - K_1 t \dots \text{(First-order equation)}$$

$$Q_t = K_h t^{1/2} \dots\dots\dots \text{(Higuchi equation)}$$

Where Q_t is the amount of drug release in time t , Q_0 is the initial amount of drug in the microsphere, and K_0 , K_1 and K_h are rate constants of zero order, first order and Higuchi equations, respectively. Further to confirm the mechanism of drug release, the first 60% of drug release was fitted in Korsemeyer-Peppas model (power law).

$$M_t / M_\infty = k t^n$$

where M_t is the amount of drug release at time t and M_∞ is the amount release at time $t = \infty$, thus M_t / M_∞ is the fraction of drug released at time t , k is the kinetic constant, and n is the diffusion exponent which can be used to characterize both mechanism for both solvent penetration and drug release [20].

Advantages [21, 22]

- Reduces the dosing frequency and there by improve the patient compliance.
- Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects and despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.
- Hollow microspheres are used to decrease material density and Gastric retention time is increased because of buoyancy.
- Enhanced absorption of drugs which solubilise only in stomach.

- Drug releases in controlled manner for prolonged period.
- Site-specific drug delivery to stomach can be achieved.
- Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
- Avoidance of gastric irritation, because of sustained release effect.
- Better therapeutic effect of short half-life drugs can be achieved.

Limitation [23]

- The modified release from the formulations.
- The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.
- Differences in the release rate from one dose to another.
- Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
- Dosage forms of this kind should not be crushed or chewed.

Applications [24, 25]

- Solid and hollow microspheres vary widely in density and, therefore, are used for different applications. Hollow microspheres are typically used as additives to lower the density of a material. Solid microspheres have numerous applications depending on what material they are constructed of and what size they are.
- Hollow microspheres can greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentrations at the gastric mucosa, thus eradicating helicobacter pylori from the sub-mucosal tissue of the stomach and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis.
- These microspheres systems provide sustained drug release behavior and release the drug over a prolonged period of time.
- The drugs recently reported to be entrapped in hollow microspheres include Prednisolone, Lansoprazole, Celecoxib, Piroxicam, Theophylline, Diltiazemhydrochloride, Verapamil hydrochloride and Riboflavin, Aspirin, Griseofulvin, Ibuprofen, Terfenadine.

- Floating microspheres can greatly improve the pharmacotherapy of stomach through local drug release. Thus, eradicating *Helicobacter pylori* from sub-mucosal tissue of the stomach are useful in the treatment of peptic ulcers, chronic gastritis, gastro esophageal reflux diseases etc. Hollow microspheres of ranitidine HCl are also developed for the treatment of gastric ulcer.
- Floating microspheres are especially effective in delivery of sparingly soluble and insoluble drugs. It is known that as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. For weakly basic drugs that are poorly soluble at an alkaline pH, hollow microspheres may avoid chance for solubility to become the rate-limiting step in release by restricting such drugs to the stomach. The gastro-retentive floating microspheres will alter beneficially the absorption profile of the active agent, thus enhancing its bioavailability.
- The floating microspheres can be used as carriers for drugs with so-called absorption windows, these substances, for example antiviral, antifungal and antibiotic agents (Sulphonamides, Quinolones, Penicillins, Cephalosporins, Aminoglycosides and Tetracyclines) are taken up only from very specific sites of the GI mucosa.
- Hollow microspheres of non-steroidal anti inflammatory drugs are very effective for controlled release as well as it reduces the major side effect of gastric irritation; for example floating microspheres of Indomethacin are quite beneficial for rheumatic patients.
- The quantitative efficiency of gastro retentive drug delivery systems in the fasted and fed states.
- Determination of minimal cut-off size above that dosage forms retained in the GIT for prolonged period of time.

Floating multiparticles can greatly improve the pharmacotherapy of the stomach through local drug release, used to eradicate *helicobacter pylori* from the sub-mucosal tissue of the stomach most effectively and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis. This system allows administration of non-systemic, controlled release antacid formulation containing calcium carbonate and also locally acting anti-ulcer drugs in stomach. Buoyant microparticles are considered as a beneficial strategy for the treatment of gastric and duodenal cancers. Floating multiparticulate systems may be used as a carrier for the drugs having narrow absorption windows, for example antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides and tetracyclines) are absorbed only from very specific regions of GI tract and whose development has been halted due to the lack of pharmaceutical technologies. In addition, by continually supplying the drug to its most efficient site of absorption, the dosage form may allow for more effective oral use of peptide and protein drugs such as calcitonin, erythropoietin, vasopressin, insulin, low molecular weight heparin. Floating microparticles of NSAIDs are very effective for reducing their major side effect, gastric irritation as well as for controlled release, e.g. floating microspheres of indomethacin are quite beneficial for rheumatic patients. It is hoped that in near future bio pharmaceutically better therapeutic systems in the form of floating multiparticulate systems would be introduced in clinics in greater number [11].

Future Potential

The control of drug release profiles has been a major aim of pharmaceutical research and development in the past two decades and might result in the availability of new products with new therapeutic possibilities and substantial benefits for patients. It is anticipated that various novel products using gastro retentive drug delivery technologies may enhance 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 diseases.

CONCLUSION

Floating drug delivery system (FDDS) provides an additional advantage to release drug at the desirable rate for prolonged time by increasing the gastric retention time of drugs. Among various approaches of FDDS, microballoons as delivery system is emerging as the innovative, most reliable drug delivery for specially those drugs that can't withstand the acidic pH of the stomach. Besides many advantages of microballoons drug delivery, there are few disadvantages too on which work is still going to eradicate or overcome them.

REFERENCES

- [1] Bharath P, Sruthi K, Krishna KVM, KesavaRao TKV. Microballoons for drug delivery: A review. *World J of pharmacy and pharma sci.* 2013; 2(5):3303-3312.
- [2] Nayak AK, Maji R, Das B. Gastro retentive drug delivery systems: a review. *Asian J Pharma and Clinical Research.* 2010; 3 (1):01-09.
- [3] Pal P, Sharma V, Singh L.A review on floating type gastroretentive drug delivery system. *IRJP* 2012;3(4):37-39.
- [4] Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating Drug Delivery Systems: A Review. *AAPS PharmSciTech.* 2005; 6 (3):372-387.
- [5] Joshi VK, Jaimini M. Microballons drug delivery system: A review. *AJPRD.* 2013; 1(1):07-17.
- [6] Kawatra M, Jain U, Ramana J. Recent advances in Floating microspheres as gastroretentive drug delivery system: A Review. *Int J of Recent Adv in Pharma Res.* 2012; 2(3): 5-23.
- [7] Patel N, Jani D, Nagesh C, Chandrashekhar S, Patel J. Floating drug delivery system: An innovative acceptable approach in Gastro retentive drug delivery. *Asian J. Pharm. Res.* 2012; 2(1):7-18.
- [8] Samaligy SE. Floating Systems for Oral Controlled Release Drug Delivery. *Tag der mündlichen Prüfung.* Berlin. 2010.
- [9] Chandel A, Chauhan K, Parashar B, Kumar H, Arora S. Floating drug delivery systems: A better approach. *Int Current Pharma J.* 2012; 1(5):110-118.
- [10] Rathod H, Patel V, Modasia M. Floating drug delivery system: Innovative approach of gastroretention. *Int J of PharmaSci Review and Res.* 2010; 4(3):183-192.
- [11] Pattan SR, Wani NP, Shelar MU, Nirmal SA, Chaudhari PD, Gude RS. Scope and significance of floating drug delivery system. *Indian drugs.* 2012; 49(10):1-8.
- [12] Dwivedi S, Kumar V. Floating Drug Delivery Systems- A Concept of Gastroretention Dosages Form. *Inter J of Res Pharma Biomed Sci.* 2011;2(4):1413-1425.
- [13] Patel DM, Patel MJ, Patel CN. Multi Particulate System: A Novel Approach in Gastro-Retentive Drug Delivery. *IJAPR.* 2011; 2(4):96-106.
- [14] 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.
- [15] Chandrakala V, Saralam. Quality by design approach in formulation of bioadhesive levodopa microspheres. *Int J of Pharmacy and Pharm Sci.* 2013; 5(4): 172-178.
- [16] Yadav VK, Kumar B, Prajapati SK, Shafaat. Design and evaluation of mucoadhesive microspheres of repaglinide for oral controlled release. *Int J of Drug Delivery.* 2011; 3: 357-370.
- [17] Yadav A, Jain DK. Gastroretentive microballoons of metformin: Formulation Development and Characterization. *J of advPharma Tech and Res.* 2011;2(1):51-56.
- [18] Aphale S, Shinde S, Dhat S, Bagul U, Saluja J. Development and evaluation of hollow microspheres of Clarithromycin as a gastroretentive drug delivery system using eudragit polymers. *Int J of Pharma and Bio Sci.* 2011; 2(3): 344-355.
- [19] Gandhi NS, Shirolkar SV, Tawar MG. Development and evaluation of microballoons of pioglitazone hydrochloride using Eudragit S-100. 2012; 3(1):201-212.
- [20] Bansode SD, Kasture VS, Pawar SS, Kasture SB. Formulation and evaluation of telmisartan microspheres by emulsion solvent evaporation technique. *Journal of Applied Pharmaceutical Science.* 2012; 2 (10):113-116.
- [21] Dhole AR, Gaikwad PD, Bankar VH, Pawar SP. A Review on Floating Multiparticulate Drug Delivery System- A Novel Approach to Gastric Retention. *IJPSRR.* 2011; 6(2): 205-211.
- [22] Somwanshi SB, Dolas RT, Nikam VK, Gaware VM, Kotade KB, Dhamak KB, Khadse AN. Floating Multiparticulate Oral Sustained Release Drug Delivery System. *J.Chem.Pharm Res* 2011; 3(1): 536-547.
- [23] Kunchu K, Ashwani RV. Albumin Microspheres: A Unique system as drug delivery carriers for non steroidal anti-inflammatory drugs. 2010; 5(2): 12.
- [24] Pujara ND, Patel NV, Thacker AP, Raval BK, Doshi SM, Parmar RB. Floating microspheres: a novel approach for gastro Retention. *World j of pharmacy and pharma sci.* 2012; 1(3):872-895.
- [25] 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.