Review Article

A REVIEW ON GASTRO RETENTIVE DRUG DELIVERY SYSTEM (GRDDS) WITH SPECIAL EMPHASIS ON FORMULATION AND DEVELOPMENT OF FLOATING MICROSPHERES

Kamini Vasava, Rajesh Ks, Lalit Lata Jha*
Department of Pharmaceutics, Parul Institute of Pharmacy, Waghodia, Vadodara, Gujarat, India.
***Corresponding author's E-mail:** lalit_lata@hotmail.com

Accepted on: 25-08-2011; **Finalized on:** 20-11-2011.

ABSTRACT

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. The most convenient and commonly employed route of drug delivery is by oral ingestion. But drugs that are easily absorbed from the GIT and having a shorter half-life are eliminated quickly from the blood circulation. To avoid these problems oral controlled drug delivery systems have been developed as they release the drug slowly into the GIT and maintain a constant drug concentration in the serum for longer period of time. However, incomplete release of the drug and a shorter residence time of dosage forms in the upper gastrointestinal tract, a prominent site for absorption of many drugs, will lead to lower bioavailability. Therefore efforts to improve oral drug bioavailability have grown in parallel with the pharmaceutical industry. Gastro retentive dosage forms, which prolong the residence time of the drugs in the stomach and improve their bioavailability, have been developed. They are primarily controlled release drug delivery systems, which gets retained in the stomach for longer periods of time, exhibiting an absorption window and thus useful for the spatial and temporal delivery of many drugs. The present review describes the Gastro Retentive Drug Delivery System (GRDDS) with special emphasis on Floating Microspheres, its preparation methods, advantages as a drug delivery system and useful formulation ingredients.

Keywords: Gastro Retentive Drug Delivery System (GRDDS); Floating Microspheres; Controlled Drug Delivery Systems.

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. The most convenient and commonly employed route of drug delivery has historically been by oral ingestion. Drugs that are easily absorbed from the GIT and having a short half-life are eliminated quickly from the blood circulation[1]. To avoid these problems oral controlled drug delivery systems have been developed as they release the drug slowly into the GIT and maintain a constant drug concentration in the serum for longer period of time. However, incomplete release of the drug and a shorter residence time of dosage forms in the upper gastrointestinal tract, a prominent site for absorption of many drugs, will lead to lower bioavailability. Efforts to improve oral drug bioavailability have been grown in parallel with the pharmaceutical industry. As the number and chemical diversity of drugs has increased, new strategies are required to develop orally active therapeutics. Thus, gastro retentive dosage forms, which prolong the residence time of the drugs in the stomach and improve their bioavailability, have been developed. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time i.e. Gastro retentive Dosage Forms (GRDFs). These are primarily controlled release drug delivery systems, which gets retained in the stomach for longer periods of time, thus helping in absorption of drug for the intended duration of time. Gastric retentive drug delivery devices can be useful for the spatial and temporal delivery of many drugs[2]. Thus, control of placement of a DDS in a specific region of the GI tract offers numerous advantages, especially for drug exhibiting an 'absorption window' in the GI tract. The intimate contact of the DDS with the absorbing membrane and also the potential to maximize drug absorption may influence the rate of drug absorption. These considerations have led to the development of oral controlled release (CR) dosage forms possessing gastric retention capabilities. Drug may not be absorbed uniformly over the length of the gastrointestinal tract, because dosage form may be rapidly transported from more absorptive upper regions of the intestine to lower regions where the drug is less absorbed and drug absorption from colon is usually erratic and inefficient. Moreover, certain drugs are absorbed only from the stomach or the upper part of small intestine. Gastric emptying of dosage form is extremely variable process and ability to prolong and control the emptying time is valuable assets for dosage forms, which reside in the stomach for longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled released system for better absorption and enhanced the bioavailability[3]. The uniform distribution of these multiple unit dosage form along the GIT could results in more reproducible drug absorption and reduced risk of local irritation; this gave birth to oral controlled drug delivery and led to development of Gastro-retentive floating microspheres[4].

ANATOMY AND PHYSIOLOGY OF STOMACH

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[5]. Pyloric antrum is separated from duodenum by the narrow and tubular pyloric canal. The mucosa of empty stomach contains longitudinal folds known as gastric rugae. The stomach is supplied by sympathetic nerves derived from T_6-T_{10} segments of the spinal cord, and parasympathetic nerves derived from vagi. Stimulation of parasympathetic nerves results in increased motility of stomach and secretion of gastric juice containing HCl and pepsin[6]. The physiological behavior of stomach varies, when it is empty or contains food. The nature of the GI motor functions is determined mainly by the stimulating effects of food in the GIT. When food enters the stomach, due to vagovagal reflex the muscular tone of the body wall of stomach reduces enabling it to expand outward and accommodating more quantities of food. Weak peristaltic constrictor waves initiated by the basic electrical rhythm, begin in the mid portion of the stomach wall and move towards the antrum at every 15-20s. These constrictor waves intensify as they proceed towards antrum, providing powerful constrictor rings which force the antral contents towards the pylorus at a high pressure. Because of these stomach contractions, the partially digested food is discharged into the small intestine and the undigested food is retropelled into the main part of the stomach for further digestion. At the end of digestion process, the stomach enters fasting state and begins a cycle called the Interdigestive Myoelectric Complex (IMMC). It causes the peristaltic waves to sweep slowly and rhythmically downward along the stomach and small intestine approximately every 2 h, sweeping the excess digestive secretions into the colon and preventing accumulation downward along the stomach secretions into the colon and preventing their accumulation in the upper GIT.

The IMMC could be divided into four phases:

Phase 1: It is a quiescent period lasting from 30 to 60 minutes with no contractions.

Phase 2: It consists of intermittent contractions that gradually increase in intensity as the phase progresses, and it lasts about 20 to 40 minutes. Gastric discharge of fluid and very small particles begin later in this phase.

Phase 3: This is a short period of intense distal and proximal gastric contractions (4-5 contractions per min) lasting about 10 to 20 mins; these contractions, also known as "house keeper waves" sweep gastric content down the small intestine.

Phase 4: This is a short transitory period of about 0 to 5 min, and the contractions dissipate between last part of phase 3 and quiescence of phase 1. The stomach also experiences rhythmic peristaltic contractions known as hunger contractions, when empty. These contractions are powerful in young and healthy individuals with high GI tone. The gastric emptying is regulated by neural and hormonal reflexes of the body. Vagal tone, gastrin, cholecystokinin and motilin enhance the gastric motility, while glucagon, secretin, gastric inhibitory peptide and vasoactive intestinal peptide inhibit the distal stomach contractions and there by inhibiting the gastric emptying.

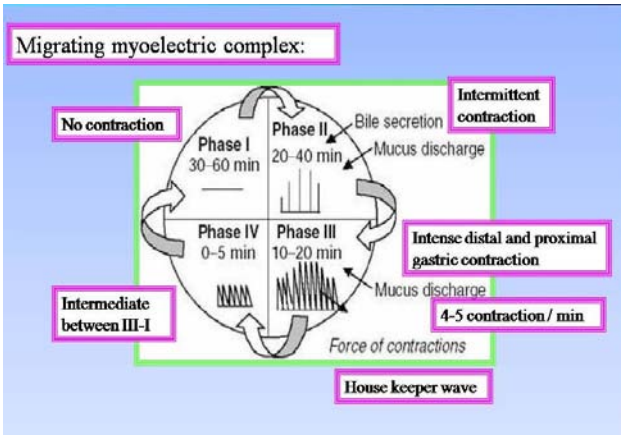

Figure 1: Schematic presentation of IMMC[2]

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.[5] Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically two complications, one is of short gastric residence time and second unpredictable gastric emptying rate.

NEED FOR GASTRO RETENTION

Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT), means they are specifically absorbed from specific site like from stomach or duodenum like upper GIT or in specific region of intestine. E.g. Riboflavin and Levodopa. When such drugs are incorporated in SR system, only few amt of drug is dissolved at absorption region and all other drug is going waste. When GRDDS of that drug is made, it will slowly release the drug in dissolved form to the absorption site, giving almost complete absorption. Drugs that act locally in the stomach e.g. antacids and Misoprostol particularly useful for the treatment of peptic ulcers caused by H. Pylori Infections. Drugs that are less soluble or are degraded by the alkaline pH they encounter at the lower part of GIT. e.g. Ranitidine HCL and Metronidazole[6]. Drugs that disturb normal colonic bacteria. E.g. Amoxicillin trihydrate.

FACTORS CONTROLLING THE GASTRO RETENTION OF THE DOSAGE FORMS[6]

Physico-chemical factors

pH dependent absorption

According to pH partition theory, only unionized form of the drug has passive absorption throughout the GIT. So, acidic drugs or weak acidic drugs are remained unionized in acidic pH only, and as gastric fluid has acidic pH, acidic drugs are more absorbed from stomach then intestine.

Higher solubility at acidic pH

Weakly basic drugs are more soluble at acidic pH So, when conventional SR of weakly basic drug is prepared, it shows good release in stomach but show poor release due to lesser solubility in intestinal region. So, SR of such drugs are made with GRDDS and allow it to solubilized at acidic pH and then go to the intestine in soluble form. e.g. Cinnarizine, Diazepam, Verapamil, Chlordiazepoxide

pH dependent stability

Some drugs are degraded at higher pH and stable at lower acidic pH and therefore having lower absorption from the intestine.e.g. Captopril.

Drugs for local effect

Directly acting antacids like aluminum and magnesium hydroxide require its effect against acidity in stomach only. So, when SR effect is required and made conventional SR dosage form releases the drug in intestine where it is useless. So, these require GRDDS.

Similar to direct acting antacids, effect of other antacids like ranitidine is improved when it has higher local concentration. Misoprostol is anti-ulcer agent having direct action on gastric mucosa. Helicobacter pylori is the causative bacteria for chronic gastritis and peptic ulcers. So, Antibiotic drugs like amoxicillin, Tetracycline, acetohydroxamic acid, etc are widely used for eradication of H.pylori. So, for prolong local effect GRDDS can be prepared.

Physiological factors

Mechanism of absorption

Some drugs are absorbed mainly via active or facilitated transport mechanisms. The preferences of such carriers or transporters are in some particular region of GIT, can show specific absorption sites.

Microbial degradation

The human colon contains around 400 different species of bacteria and has up to 10^{10} Bacteria per gram content. Some drugs are degraded by these bacteria show poor absorption in colon. E.g. Ranitidine, Metformin.

Effect of gender, posture and age

A study by Mojaverian et al found the females showed comparatively shorter mean ambulatory GRT than males, and the gastric emptying in women was slower than in men. The authors also studied the effect of posture on GRT, and found no significant difference in the mean GRT for individuals in upright, ambulatory and supine state. On the other hand, in a comparative study in humans by Gansbeke *et al*[16], the floating and non-floating systems behaved differently. In the upright position, the floating systems floated to the top of the gastric contents and remained for longer time, showing prolonged GRT. But the non-floating units settled to the lower part of the stomach and underwent faster emptying as a result of peristaltic contractions, and the floating units remained away from the pylorus. However, in supine position, the floating units are emptied faster than non-floating units of similar size.

Biochemical factors

Secretory (efflux transporter)

P-gp is a secretory transporter, which has a capacity to interact with a vast variety of drugs. Its function is throwback the absorbed drug from the cytoplasm of enterocytes back into intestinal lumen leading lower bioavailability.

Enzymatic degradation

Some drugs are acting as substrates for some enzymes (Intestinal metabolic enzymes, Cytochrome p450-CYP3A, which are present in a particular region of GIT, can lead to degradation of drug at that site and make absorptive window.

APPROACHES FOR GASTRO RETENTION[7-9]

A number of approaches have been used to increase gastric retention time (GRT) of a dosage form in stomach by employing a variety of concepts as shown in figure 2.[9]

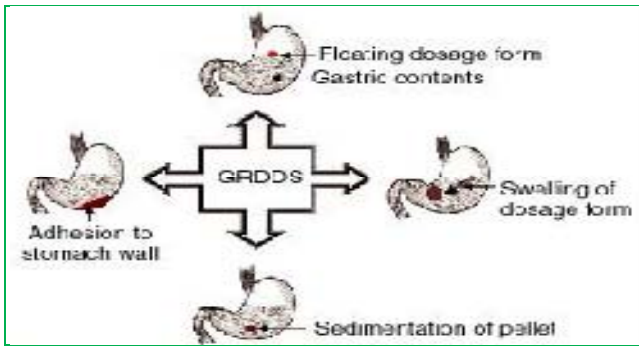

Figure 2: Illustration of types of Gastro Retentive Drug Delivery Systems[9]

Floating Systems

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 content, 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 concentration.

Floating systems can be classified in to two distinct categories, noneffervescent and effervescent systems.

Bio/Muco-adhesive Systems

Bio/muco-adhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending gastric residence time of drug delivery system in stomach, by increasing the intimacy and duration of contact of drug with the biological membrane. Binding of polymers to mucin/epithelial surface can be divided into three broad categories:

5.2.1 Hydration-mediated adhesion.

5.2.2 Bonding-mediated adhesion.

5.2.3 Receptor-mediated adhesion.

Swelling and Expanding Systems

These are dosage forms, which after swallowing, swell to an extent that prevent their exit from the pylorus. As a result, the dosage form is retained in stomach for a long period of time. These systems may be named as "plug type system", since they exhibit tendency to remain logged at the pyloric sphincter.

High density Systems

These systems with a density of about 3 gm/cm^3 are retained in the rugae of stomach and are capable of withstanding its peristaltic movements. A density of 2.6- 2.8 gm/cm^3 acts as a threshold value after which such systems can be retained in the lower parts of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc.

Incorporation of passage delaying food agents

Food excipients like fatty acids e.g. salts of myristic acid change and modify the pattern of stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in gastric emptying after meal rich in fats is largely caused by saturated fatty acids with chain length of C10-C14.

Ion exchange resins

Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads are then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide is released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.

Osmotic regulated systems

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two components – drug reservoir compartment and osmotically active compartment.

TYPES OF FLOATING DRUG DELIVERY SYSTEM[10, 11]

Effervescent Systems

Volatile liquid containing systems

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of PVA, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.[11]

Gas-generating Systems

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2, which gets entrapped in the jellified hydrocolloid layer of the system thus decreasing its specific gravity and making it to float over chyme. These buoyant systems utilize matrices prepared with swellable polymer like methocel, polysaccharide like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature[12]. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethylcellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach .Other approaches and materials that have been reported are highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology, etc[13].

Non-Effervescent Systems[11, 14]

This type of system, after swallowing, swells unrestrained via imbibition 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.

Colloidal gel barrier systems

Hydrodynamically balance system (HBS) was first designed by Sheth and Tossounian in 1975. Such system contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids e.g. HEC, HPMC, NaCMC, Polysacchacarides and matrix forming polymers such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsules. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to this dosage forms.[14]

Microporous Compartment System

This technology is based on the encapsulation of drug reservoir inside a microporous compartment with aperture along its top and bottom wall. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolved drug. In stomach the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the apertures, dissolves the drug, and carries the dissolved drug for continuous transport across the intestine for absorption.

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 a sodium alginate solution in to aqueous solution of calcium chloride, causing precipitation of calcium alginate. The beads are then separated snap 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 hr.

Hollow microspheres

Hollow microspheres (microballons), loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured in to an agitated aqueous solution of PVA that was thermally controlled at 40°. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres of the polymer with drug. The microballons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 h *in vitro*.

DEVELOPMENT OF FLOATING MICROSPHERES

Microspheres are small spherical particles, with diameter in the micrometer range (typically 1 µm to 1000 µm (1 mm). Microspheres are sometimes referred to as microparticles[15.] Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. These microspheres are characteristically free flowing powder consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs[16,17]. 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. When microspheres come in contact with gastric fluid the gel formers, polysaccharides, 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 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 lowers the density and confers buoyancy to the microspheres. However a minimal gastric content needed to allow proper achievement of buoyancy[18-21].

MECHANISM OF FLOATING MICROSPHERES[22]

- When microspheres come in contact with gastric fluid the gel formers, polysaccharides, 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 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 lowers the density and confers buoyancy to the microspheres.
- However a 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.

LIST OF POLYMERS USED IN FLOATING MICROSPHERES[23]

Cellulose acetate, Chitosan, Eudragit, Acrycoat, Methocil, Polyacrylates, Polyvinyl acetate, Carbopol, Agar, Polyethylene oxide, Polycarbonates, Acrylic resins etc.

ADVANTAGES AND DISADVANTAGES OF FLOATING MICROSPHERES[23, 24]

Advantages of Floating Microspheres

- Improves patient compliance by decreasing dosing frequency
- Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.
- Gastric retention time is increased because of buoyancy.
- Enhanced absorption of drugs which solubilize 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.

Disadvantages of Floating Microspheres

- Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently in stomach.
- The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidates.
- Some drugs present in the floating system causes irritation to gastric mucosa.

CHARACTERIZATION OF FLOATING MICROSPHERES

Floating microspheres are characterized by their micromeritic properties such as particle size, tapped density, compressibility index, true density and flow properties including angle of repose. The particle size is determined by optical microscopy; true density is determined by liquid displacement method; tapped density and compressibility index are calculated by measuring the change in volume using a bulk density apparatus; angle of repose is determined by fixed funnel method. The nature of microspheres is confirmed by scanning electron microscopy[24-26].

LIMITATION OF FLOATING MICROSPHERES[27]

- They require high level of fluid in stomach for floating and working efficiently. Thus more water intake is advisable with such dosage form.
- The floating systems in patients with achlorhydria can be questionable in case of swellable systems, faster swelling properties are required and complete swelling of the system should be achieved well before the gastric emptying time.
- Not suitable for drugs that may cause gastric lesions e.g. Non- steroidal anti inflammatory drugs.
- Drugs that are unstable in the strong acidic environment, these systems do not offer significant advantages over the conventional dosage forms for drugs, that are absorbed throughout the gastrointestinal tract.
- The mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.
- In all the above systems the physical integrity of the system is very important and primary requirement for the success of these systems.

CONCLUSION

Drug absorption in the stomach is a variable process which depends upon gastric emptying and other physiological factors. Floating delivery system can provide sufficient gastric retention which may help to provide sustained release dosage form with enhanced absorption and minimize fluctuation. In spite of its various limitations serious efforts are being done to commercialize this delivery system.

REFERENCES

1. Gholap SB, Hollow Microsphere: A Review, *International Journal of Pharmaceutical Sciences Review and Research,* 1, 2010, 74.
2. Hirtz J. The GIT absorption of drug in man: a review of current concepts and method of investigation. Br J Clin pharmacol, 19, 1985, 77-83.
3. Chine YW, Controlled and Modulated release drug delivery system. Encyclopedia of Pharmaceutical Technology. Marcel Dekker Inc, 1990, 280-285
4. Arora S, Ali J, Ahuja A, Khar RK and Baboota S, Floating Drug Delivery Systems: A Review, *AAPS PharmSci Tech.* 2005, 372-390.
5. Desai S, Bolton S, A floating controlled release drug delivery system: in vitro- in vivo evaluation. *PharmRes*. 10, 1993, 1321-1325.
6. Bardonnet, P.L, "Gastro retentive dosage form: Overview and special case of H.pylori", *J. Control Release.* 111,2006, 1-18.

7. Atyabi, F., Sharma, H.L., Mohammad, H., Fell, J. T., In-vivo evaluation of a novel gastroretentive formulation based on ion exchange resins, J. Control. Rel. 42:1996; 105-13.
8. www.rjptonline.org
9. Deshpande, A. A., Shah, N.H., Rhodes, C.T.Malick, W., Development of a novel controlled release system for gastric retention, Pharm. Res. 14 (6): 1997; 815-9.28
10. Gaba P,"Floating microspheres a: Review", *IJPS.* 6,2008, 6-10
11. Yyas SP, Khar RK. Controlled Drug Delivery Concepts and Advances. 1st Edition, New Delhin: 2002;196-217.
12. Chawla C, Gupta P, Koradia V, Bansal AK, Gastroretention: A Means to Address Regional Variability in intestinal drug Absorption. Pharmaceutical technology, 27(2):2003; 50-68.
13. Sangekar S. Evaluation of effect of food and specific gravity of the tablets on gastric retention time. Int J Pharm 35(3):1987; 34-53.
14. Jain NK. Progress in Controlled and Novel Drug Delivery Systems, 1st Ed. CBS Publishers and Distributors, New Delhi, Bangalore, 2004; 84-85.
15. www.Wikipedia.com
16. Vyas, S.P. & Khar., "Targeted and Controlled Drug Delivery Novel Carrier System", Ist Ed., CBS Publishers and Distributors, New Delhi, 2002, pp. 417-54.
17. Shiv Kr, H.G., Vishakanta, G.D., Pramod Kr, T. M**.,** I.J.P.E**.,** 38(4), 2004.
18. Chawla G,Gupta P,Koradia V and Bansal A, Pharm.Tech**.**, 27(7): 2003, 50-51.
19. Chickering, D.E., Jacob, J.S. and Matho W.E**.,** Reactive Polymers, (25): 1995, 189-206.
20. Shiv Kr, H.G., Vishakanta, G.D., Pramod Kr, T. M., I.J.P.E**.,** 38(4), Oct-Dec,2004.
21. Soppimath, K.S., Kulkarni, A.R., Aminabhavi, T.M., Drug Dev. Ind. Pharm**.**, 27(6): 2001, 507-15.
22. Uchida T,Yoshida K and Goto S,"Preparation and characterization polylactic acid microspheres conataining water soluble dye using a novel w/o/w emulsion solvent evaporation method", *J microencapsulation.* 13,1996, 219-228.
23. S. J. Hwang, H. Park, K.Park, "Gastric retentive drug delivery systems." Crit. Rev. Ther.Drug Carrier Syst., 15, 1998, 243–284.
24. Martin, A., Swarbrick, J., Cammarata, A., "Physical Pharmacy", III Ed, Varghese Publishing Company, Bombay, 1991, pp.492-520.
25. Carstensen, J., T., "Pharmaceutics of Solids and Solid Dosage forms", John Wiley and Sons, New York, 1976, pp.136, 230.
26. Umamaheshwari, R.B., Jain, S., Bhadra, D., Jain, N.K., J. Pharm. Pharmacol**.**, 55 (12), 2003: 1607-1613.
27. Yang L, Fassihi R. Zero order release kinetics from self correcting floatable configuration drug delivery system. *J Pharm Sci.* 85: 1996; 170-173. PubMed DOI: 10.1021/ js950250.

****