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GASTRORETENTIVE FLOATING MICROSPHERES: A REVIEW

Deepali D. Wagh*, Madhav S. Mule¹, Dipali S. Jain²

Agnihotri College of Pharmacy, Wardha,

¹School of Pharmacy, S.R.T.M.U. Nanded,

Email:dipalidwagh143@gmail.com

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Abstract

Various scientific and technological attempts have been made in the development of gastroretentive dosage forms to overcome several physiological adversities, such as short gastric residence time, unpredictable gastric emptying time etc. These dosage forms can be retained in the stomach for prolonged period of time in a predetermined manner. Gastroretentive drug delivery technology is one of the promising approach for enhancing the bioavailability and controlled delivery of drugs that exhibit narrow absorption window. In pursuit of this endeavour, different novel strategies have been undertaken for the designing of several gastroretentive drug delivery systems including floating microspheres. This manuscript highlights various developmental approaches, characterization aspects, potential drug candidates along with diverse advantages and applications of floating microspheres. Numerous significant research findings in the vistas of these multiparticulates have also been described.

Keywords: Gastroretentive technology, Floating microspheres, Bioavailability.

1. Introduction

The high level of patient compliance has been observed in taking oral dosage forms is due to the ease of administration and handling of these forms. Although a lot of advancements have been seen in oral controlled drug delivery system in the last few decades, this system has been of limited success in case of drugs with a poor absorption window throughout the GIT (Gastro Intestinal Tract). To modify the GI transit time is one of the main challenge in the development of oral controlled drug delivery system. Gastric emptying of pharmaceuticals is highly variable and

dependent on the dosage form and the fed/fasted state of the stomach. Normal gastric residence time usually ranges between 5 minutes to 2 hours. In the fasted state the electrical activity in the stomach – the interdigestive myoelectric cycle or migrating myoelectric complex (MMC) governs the activity and the transit of dosage forms. It is characterized by four Phases.¹

Phase I– Period of no contraction (40-60 minutes)

Phase II– Period of intermittent contractions (20-40 minutes)

Phase III– Period of regular contractions at the maximal frequency also known as housekeeper wave (10-20 minutes)

Phase IV– Period of transition between Phase III and Phase I (0-5 minutes)

Drugs having a short half-life are eliminated quickly from the blood circulation and therefore bioavailability of the drug suffers. Gastro retentive dosage form improves bioavailability, therapeutic efficacy and may allow a reduction in the dose because of steady therapeutic levels of drug, for example furosemide and ofloxacin. The reduction of fluctuations in the therapeutic levels minimizes the risk of resistance especially in case of β -lactam antibiotics (penicillin and cephalosporin).² Gastric emptying of dosage forms is an extremely variable process. The ability of a dosage form to prolong and control the gastric emptying time is a valuable asset for drugs acting on GIT. Drug absorption from the GIT is a complex procedure and is subjected to many parameters to become bioavailable. It is widely acknowledged that the contact time with the small intestinal mucosa is related with the degree of GIT drug absorption.³ thus small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. Gastro retention provides better availability of new products with new therapeutic possibilities and substantial benefits for patients. Controlled release drug delivery systems that retain in the stomach for a long time have many advantages over sustained release formulations. Such retention systems (i.e. GRDDS) are important for the drugs that are degraded in intestine or for drugs like antacids or certain enzymes that act locally in the stomach. Gastric retention may increase solubility for the drugs which are

poorly soluble in intestine due to alkaline pH before they get emptied from the stomach. These systems are also advantageous in improving GIT absorption of drug having narrow absorption windows and site-specific absorption limitations. These systems are useful in case of those drugs which are best absorbed in stomach for eg. Albuterol.⁴ Hence, this review article focuses on the current technological developments and advancements in gastro retentive drug delivery system with special emphasis on the approaches and the advantages along with some marketed preparations of GRDDS.⁵

2. APPROACHES TO GASTRIC RETENTION¹²

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. These includes in

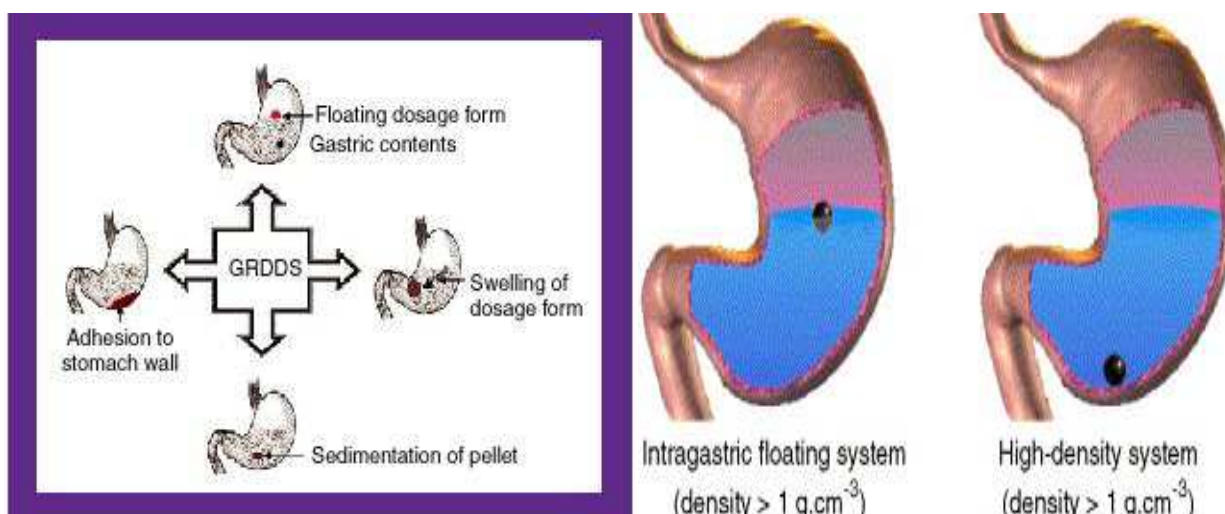


Figure: Illustration of types of Gastroretentive drug delivery systems.

a) 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 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. Floating systems can be classified into two distinct categories, noneffervescent and effervescent systems.⁷

b) Swelling and Expanding Systems :

These are dosage forms, which after swallowing swell to an extent that prevents 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 lodged at the pyloric sphincter.

c) High density systems :

These systems with a density of about 3 g/cm³ are retained in the rugae of stomach and are capable of withstanding its peristaltic movements. A density of 2.6- 2.8 g/cm³ 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.

d) 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 meals rich in fats is largely caused by saturated fatty acids with chain length of C10-C14.

e) 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.⁸

f) 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 somotically 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.⁷

g) **High density systems**- They include coated pellets and have density greater than that of the stomach content (1.004 gm/cm³). This formulation of high-density pellet is based on assumption that heavy pellet might remain longer in the stomach, since they are position in the lower part of the antrum.⁹

h) Low density approach

Floating systems come under low density approach. In this approach, the density of pellets should be less than 1 g/ml, so as to float the pellets or tablets in the gastric fluid and, release the drug slowly for a longer period of time. This type is also called as Hydrodynamically Balanced System (HBS). Polypropylene foam powder (Accurel MP 1000®).¹⁰

i) **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.¹¹

- a) Hydration-mediated adhesion.
- b) Bonding-mediated adhesion.
- c) Receptor-mediated adhesion.

3. Types of drugs can benefit from using gastric retentive devices. These include:

- Acting locally in the stomach.
- Primarily absorbed in the stomach.
- Poorly soluble at an alkaline pH.
- Narrow window of absorption.

- Absorbed rapidly from the GI tract.
- Degrade in the colon.

4. SUITABLE DRUG CANDIDATES FOR GASTRORETENTION

In general, appropriate candidates for CRGRDF are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT:

- Narrow absorption window in GI tract, e.g., riboflavin and levodopa.
- Primarily absorbed from stomach and upper part of GI tract, e.g., calcium supplements, flordiazepoxide and cinnarazine.
- Drugs that act locally in the stomach, e.g., antacids and misoprostol.
- Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole.
- Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.

Floating Drug Delivery systems and its mechanism¹³

Floating drug delivery systems (FDDS) have bulk density lesser than gastric fluids, so they 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 as shown in fig. 2(a). 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 has been reported in the literature. The 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 F is on the higher positive side as shown in fig. 2(b). This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations¹².

$$F = F \text{ buoyancy} - F \text{ gravity}$$

$$= (D_f - D_s) gv \text{--- (1)}$$

Where, F= total vertical force,

D_f = fluid density,

D_s = object density,

v = volume,

g = acceleration due to gravity.

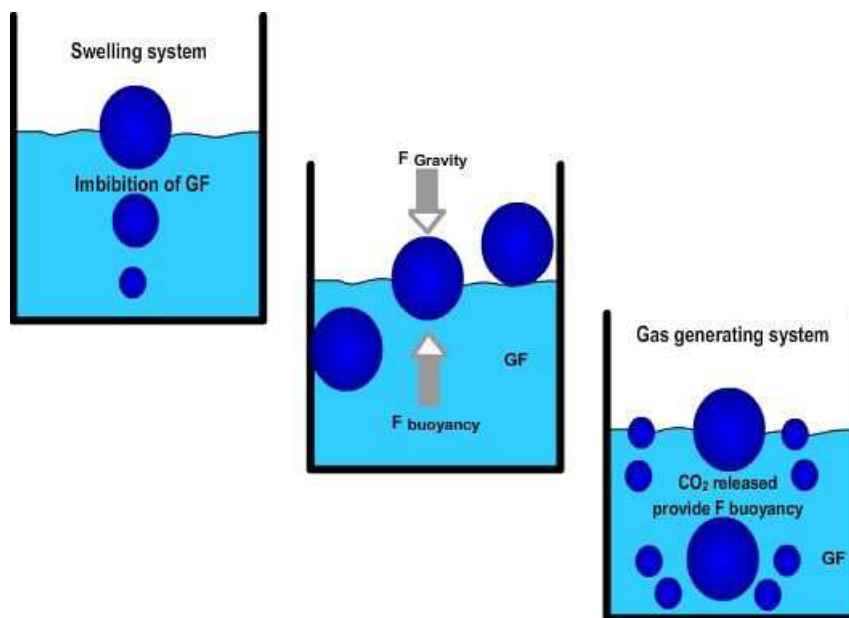


Fig. 2: Mechanism of floating systems, GF= Gastric fluid.

5. ADVANTAGES OF FLOATING DRUG DELIVERY ^[14-17]

- a. Enhanced bioavailability
- b. Enhanced first-pass biotransformation
- c. Sustained drug delivery/reduced frequency of dosing
- d. Targeted therapy for local ailments in the upper GIT
- e. Reduced fluctuations of drug concentration
- f. Improved receptor activation selectivity
- g. Reduced counter-activity of the body

- h. Extended time over critical (effective) concentration
- i. Minimized adverse activity at the colon
- j. Site specific drug delivery
- k. Less inter- and intra-subject variability.
- l. Minimizes the counter activity of the body leading to higher drug efficiency.
- m. Fluctuations in drug concentration are minimized. Therefore, concentration dependent adverse effects can be reduced.
- n. Sustained mode of drug release enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.
- o. Flexibility in dosage form design.
- p. Extend patent protection, globalize product, and provide new business opportunities.

6. LIMITATIONS ^[18, 19]

- a. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
- b. Not suitable for drugs that have solubility or stability problem in GIT.
- c. Drugs such as nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.
- d. Drugs which are irritant to gastric mucosa are also not suitable.
- e. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
- f. The dosage form should be administered with a full glass of water (200-250 ml).
- g. These systems are not advantageous over the conventional dosage forms for those drugs, which are absorbed throughout the gastrointestinal tract.

7. METHOD OF PREPARATION

Wide ranges of developmental techniques are available for the preparation of Gastroretentive floating microspheres [20]. However, solvent evaporation technique and ionotropic gelation method have been extensively employed by large number of scientific investigators worldwide to explore the different vistas of floating microspheres. During the preparation of floating controlled release microspheres, the choice of optimal method has utmost relevance for the efficient entrapment of active constituents. Selection of fabrication technique generally depends upon the nature of the polymer, the drug, and their intended use [21,22].

Characteristic features of materials and the process engineering aspects strongly influence the properties of microspheres and the resultant controlled release rate. These techniques (i.e. Solvent evaporation and ionotropic gelation) are discussed in the subsequent section with pictorial representations (Figure 1 and Figure 2).

a. Solvent Evaporation Technique

This technique is widely employed by large number of pharmaceutical industries to obtain the controlled release of drug [23]. This approach involves the emulsification of an organic solvent (usually methylene chloride) containing dissolved polymer and dissolved/dispersed drug in an excess amount of aqueous continuous phase, with the aid of an agitator. The concentration of the emulsifier present in the aqueous phase affects the particle size and shape. When the desired emulsion droplet size is formed, the stirring rate is reduced and evaporation of the organic solvent is realized under atmospheric or reduced pressure at an appropriate temperature. Subsequent evaporation of the dispersed phase solvent yields solid polymeric microparticles entrapping the drug. The solid microparticles are recovered from the suspension by filtration, centrifugation, or lyophilisation [24]. For emulsion solvent evaporation, there are basically two systems which include oil-in-water (o/w) and water-in-oil (w/o) type.

b. Oil-In-Water Emulsion Solvent Evaporation Technique

In this process, both the drug and the polymer should be insoluble in water while a water immiscible solvent is required for the polymer [25]. In this method, the polymer is dissolved in an organic solvent such as dichloromethane, chloroform, or ethyl acetate, either alone or in combination. The drug is either dissolved or dispersed into polymer

solution and this solution containing the drug is emulsified into an aqueous phase to make an oil-in water emulsion by using a surfactant or an emulsifying agent. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring. Solvent removal from embryonic microspheres determines the size and morphology of the microspheres. It has been reported that the rapid removal of solvent from the embryonic microspheres leads to polymer precipitation at the o/w interface. This leads to the formation of cavity in microspheres, thus making them hollow to impart the floating properties ^[26-29]. Oil-in-water emulsion is widely used than water-in-oil due to simplicity of the process and easy cleans up requirement for the final product ^[30].

c. Oil-in-Oil Emulsification Solvent Evaporation Technique

This oil-in-oil (sometimes referred as water-in-oil) emulsification process is also known as non aqueous emulsification solvent evaporation. In this technique, drug and polymers are codissolved at room temperature into polar solvents such as ethanol, dichloromethane, acetonitrile etc. with vigorous agitation to form uniform drug-polymer dispersion. This solution is slowly poured into the dispersion medium consisting of light/heavy liquid paraffin in the presence of oil soluble surfactant such as Span. The system is stirred using an overhead propeller agitator at 500 revolutions per minute (rpm) and room temperature over a period of 2–3 h to ensure complete evaporation of the solvent. The liquid paraffin is decanted and the microparticles are separated by filtration through a Whitman filter paper, washed thrice with n-hexane, air dried for 24 h and subsequently stored in desiccators ^[31-35]. Span 60 is generally used which is non ionic surfactant. Span 60 has an HLB value of 4.3 and acts as a droplet stabilizer and prevents coalescence of the droplets by localizing at the interface between the dispersed phase and dispersion medium ^[35].

d. Ionotropic Gelation Method

In this method, cross linking of the polyelectrolyte takes place in the presence of counter ions to form gel matrix. This technique has been generally employed for the encapsulation of large number of drugs. Polyelectrolyte such as sodium alginate having a property of coating on the drug core and acts as release rate retardant contains certain anions in their

chemical structure. These anions forms meshwork structure by combining with polyvalent cations and induced gelation. Microspheres are prepared by dropping drug loaded polymeric solution using syringe into the aqueous solution of polyvalent cations. The cations diffuses into the drug loaded polymeric drops, forming a three dimensional lattice of ionically cross linked moiety. Microspheres formed left into the original solution for sufficient time period for internal gelification and they are separated by filtration. Natural polymers such as alginates can be used to improve drug entrapment and are widely used in the development of floating microspheres [36-38].

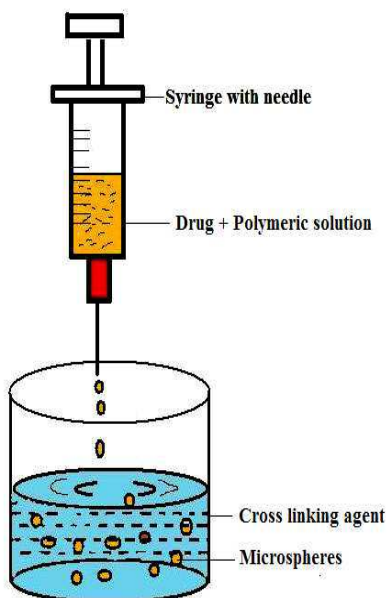


Figure 2: Schematic representation of preparation of floating microspheres by Ionotropic gelation.

8. EVALUATION OF FLOATING MICROSPHERE

Characterization of floating microspheres is an important phenomenon which helps in the evaluation of suitable drug delivery systems. Floating microspheres are characterized by following parameters:

a. Particle size analysis

Particle size of floating microspheres is determined by using an optical microscopy and size distribution is carried out by sieving method. This is useful in the determination of mean particle size with the help of calibrated ocular micrometer [39, 40].

b. Percentage yield

Percentage yield of floating microspheres is calculated by dividing actual weight of product to total amount of all non-volatile components that are used in the preparation of floating microspheres and is represented by following formula:

[41-43]

$$\text{Percentage yield} = \frac{\text{Actual weight of floating microspheres}}{\text{Total weight of excipients and drug}} \times 100$$

c. Drug entrapment efficiency

Estimation of drug content in floating microspheres can be carried out by dissolving the weighed amount of crushed microspheres in required quantity of 0.1 N HCl and analysed spectrophotometrically at a particular wavelength using the calibration curve. Each batch should be examined for drug content in a triplicate manner. The entrapment efficiency of floating microspheres is calculated by dividing the actual drug content by the theoretical drug content of microspheres [44,45].

d. Surface morphology

Surface characteristics of floating microspheres are analysed using a scanning electron microscopy. Samples are coated with gold dust under vacuum prior to observation. Cross sections should be made in order to observe the core and internal structure of the microspheres. These studies are useful in the examination of internal and external morphology of floating microspheres [46-47].

e. Swelling ratio

Swelling property of floating microspheres is studied by soaking the known weight of microspheres at $37 \pm 0.5^\circ\text{C}$ in 0.1 N HCl or phosphate buffer pH 6.8 in a glass beaker for the required period of time. The microspheres are allowed to swell and removed at different time intervals.

f. In vitro drug release studies

Release rate of drug from hollow floating microspheres is determined using USP dissolution apparatus type I or type II at $37 \pm 0.5^\circ\text{C}$. The dissolution test is carried out using 900 mL of 0.1 N HCl dissolution medium at 100 rpm for the

required period of time. At an appropriate interval, specific volume of aliquots are withdrawn and replaced with an equivalent volume of fresh dissolution medium to maintain the constant volume of dissolution medium. The sample solutions are filtered through Whatman filter paper and solutions are analysed using UV spectrophotometer^[48,49].

g. Buoyancy studies

In vitro floating tests can be performed in USP type II dissolution test apparatus by spreading the floating microspheres on a simulated gastric fluid (pH 1.2) containing the surfactant. The media is stirred at 100 rpm at 37 ± 0.5 °C. After specific intervals of time, both the fraction of microspheres (floating and settled microspheres) are collected and buoyancy of the floating microspheres is determined by using formula:^[50].

$$\text{Buoyancy (\%)} = \frac{Q_f}{Q_f + Q_s} \times 100$$

Where, Q_f and Q_s are the masses of floating and settled hollow microspheres, respectively.

h. Hausner's ratio: Hausner's ratio of floating microspheres is determined by comparing the tapped density to the fluff density using the equation:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Fluff density}}$$

9. SALIENT APPLICATIONS:

Floating microspheres are potential drug delivery systems with diverse advantages and variety of pharmaceutical applications. These are particularly advantageous for drugs with poor bioavailability because of narrow absorption window in the upper part of GIT. These systems retain the dosage form at the site of absorption and thus enhance the bioavailability. Some important examples are discussed in the following text^[51-55].

a. Gastroretentive floating microspheres are very effective in the reduction of major adverse effect of gastric irritation; such as floating microspheres of non-steroidal anti-inflammatory drugs i.e. indomethacin are beneficial for rheumatic patients.

- b. 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. Floating bioadhesive microspheres of acetohydroxamic acid are formulated for treatment of *Helicobacter pylori* infection. Hollow microspheres of ranitidine HCl are also developed for the treatment of gastric ulcer.
- c. These microparticulate systems provide sustained drug release behavior and release the drug over a prolonged period of time. Hollow microspheres of tranilast are fabricated as a floating controlled drug delivery system.
- d. Floating microspheres are very effective approach in delivery of drugs that have poor bioavailability because of their limited absorption in the upper GIT. These systems efficiently maximize their absorption and improve the bioavailability of several drugs. e.g furosemide, riboflavin etc.

10. Conclusion

Gastroretentive floating drug delivery technology has emerged as an efficient approach for enhancing the bioavailability and controlled delivery of various therapeutic agents. Significant attempts have been made worldwide to explore these systems according to patient requirements, both in terms of therapeutic efficacy and compliance. Floating microspheres as gastroretentive dosage forms precisely control the release rate of target drug to a specific site and facilitates an enormous impact on health care. Optimized multi-unit floating microspheres are expected to provide clinicians with a new choice of an economical, safe and more bioavailable formulation in the effective management of diverse diseases. These systems also provide tremendous opportunities in the designing of new controlled and delayed release oral formulations, thus extending the frontier of futuristic pharmaceutical development. Increased sophistication of this technology will ensure the successful advancements in the avenue of gastroretentive microspheres therapy so as to optimize the delivery of molecules in a more efficient manner. Furthermore, recent innovations in pharmaceutical investigation will surely provide real prospects for establishment of novel and effective means in the development of these promising drug delivery systems.

11. References

1. S.H. Shah, J.K. Patel, N.V. Patel, *Int. J. Pharm. Tech. Res.*, 2009, 1(3), 623-633.
2. B.M. Singh, K.H. Kim, *J. Control Rel.*, 2000, 63, 235-259.
3. J. Hirtz, *Br. J. Clin. Pharmacol.*, 1985, 19, Sppl. 2, 77S-83S.
4. G.A. Agyilirah, M. Green, R. DuCret, G.S. Banker, *Int. J. Pharm.*, 1991, 75, 241-247.
5. Pooja Mathur¹, Kamal Saroha² “An overview on recent advancements and developments in gastroretentive buoyant drug delivery system” *Der Pharmacia Sinica*, 2011, 2 (1): 161-169.
6. S. B. Gholap*, S. K. Banarjee, “Hollow Microsphere: A Review” Volume 1, Issue 1, March – April 2010; Article 015.
7. Deshpande, A. A., Shah, N.H., Rhodes, C.T., Malick, W., Development of a novel controlled release system for gastric retention, *Pharm. Res.* 1997; 14 (6): 815-9.
8. 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.* 1996; 42: 105-13.
9. Vyas SP, Khar RK. Gastroretentive systems. In: *Controlled drug Delivery*. Vallabh Prakashan, Delhi, India. 2006. p. 197-217.
10. Clarke GM, Newton JM, Short MD. Gastrointestinal transit of pellets of differing size and density. *Int J Pharm* 1993; 100(13): 81-92.
11. Moes A. Gastroretentive dosage forms. *Crit Rev Ther Drug Carrier Syst* 1993; 10: 143-95.
12. Faivre V. Aspects theoriques de la bioadhesion. In: Falson- Rieg V, Faivre V, Pirot F. ed. *Nonvelles forms medicamenteuses* , Editions Medicales Internationales, Editions TEC and DOC, Cachan. 2004. p. 1-24.
13. Garg S, Sharma S. Gastroretentive Drug Delivery System. *Business Briefing: Pharmatech*.2003; 160-166.
14. G. Chawla, P. Gupta, V. Koradia, A.K. Bansal, *Pharm. Tech.*, 2003, 27(2), 50-68.
15. R. Garg, G.D. Gupta, *Trop. J. Pharma. Res.*, 2008, 7(3), 1055-1066.
16. A. Hoffman, *Adv. Drug Deliv. Rev.*, 1998, 33, 185-199.

17. A. Hoffman, D. Stepensky, Crit. Rev. Ther. Drug Carrier Syst., 1999, 16, 571-639.
18. S. Sangekar, Int. J. Pharm., 1987, 35(3), 34-53.
19. P. Mojaverian, P.H. Vlasses, P.E. Kellner, M.L. Rocci, Pharm. Res., 1988, 10, 639-64.
20. S Benita. In: Microencapsulation, Marcel Dekker, New York, 1996, 1-21.
21. H Okada, H Toguchi. Critical Reviews in Therapeutics Drug Carrier Systems. 1995, 12, 1, 1-99.
22. Vyas. In: Jain N.K. Pharmaceutical Product Development, 1st ed., CBS Publishers, New Delhi, 2006; 112-138.
23. M Li, O Rouaud, D Poncelet. International Journal of Pharmaceutics, 2008, 363, 1-2, 26-39.
24. PJ Watts, MC Davis, CD Melia. Critical Reviews in Therapeutics Drug Carrier Systems, 1990, 7, 3, 235-258.
25. R Jalil, JR Nixon, Journal of Microencapsulation, 1990, 7, 3, 297-325.
26. KS Soppimath, AR Kulkarni, WE Rudzinski, TM Aminabhavi. Drug Metabolism Reviews, 2001, 33, 2, 149-160.
27. JH Lee, TG Park, HK Choi. Journal of Microencapsulation, 1999, 16, 6, 715-729.
28. R Garg, GD Gupta. Tropical Journal of Pharmaceutical Research, 2010, 9, 1, 59-66.
29. MRP Rao, SG Borate, KC Thanki, AA Ranpise, GN Parikh. Drug Development and Industrial Pharmacy, 2009, 35, 7, 834-842.
30. HP Huang, I Ghebre-sellassie. Journal of Microencapsulation, 1989, 6, 2, 219-225.
31. AA Hincal, S Calis. In: Handbook of Pharmaceutical Controlled Release Technology, 1st ed., Marcel Dekker, Inc, New York, 2005, 329 -343.
32. YS Gattani, DA Bhagwat, AP Maske. Asian Journal of Pharmaceutics, 2008, 2, 4, 228- 231.
33. VS Mastiholimath, PM Dandagi, AP Gadad, R Mathews, AR Kulkarni. Journal of Microencapsulation, 2008, 25, 5, 307-314.
34. Y Miyazaki, S Yakou, F Yanagawa, K Takayama. Drug Development and Industrial Pharmacy, 2008, 34, 11, 1238-1245.
35. HN Shivakumar, R Patel, BG Desai. Indian Journal of Pharmaceutical Sciences, 2008, 70, 3, 408-413.

36. N Ma, L Xu, Q Wang, X Zhang, W Zhang, Y Li, L Jin, S Li. *International Journal of Pharmaceutics*, 2008, 358, 1-2, 82-90.
37. JS Patil, MV Kamalapur, SC Marapur, DV Kadam. *Digest Journal of Nanomaterials and Biostructures*, 2010, 5, 1, 241-248.
38. F Lim, AM Sun. *Pancreas. Sci*, 1980, 210, 4472, 908.
39. Z Yang, B Song, Q Li, H Fan, F Ouyang. *Journal of Applied Polymer Science*, 2004, 94, 1, 197-202.
40. RB Umamaheshwari, S Jain, NK Jain. *Drug Delivery*, 2003, 10, 3, 151-160.
41. SK Jain, AM Awasthi, NK Jain, GP Agrawal. *Journal of Controlled Release*, 2005, 107, 2, 300-309.
42. M Shah, N Jadhav, YK Agrawal. *Fullerenes, Nanotubes and Carbon Nanostructures*, 2009, 17, 5, 528-547.
43. K Abu-Izza, L Garcia-Contreras, DR Lu. *Journal of Pharmaceutical Sciences*, 1996, 85, 6, 572-576.
44. SS Patel, JK Patel, GN Patel, PD Bhardia, MM Patel. Available at <http://www.pharmaquility.com/ME2/Audiences/dirmod.asp> accessed on 12th July 2010.
45. PK Choudhury, M Kar, CS Chauhan. *Drug Development and Industrial Pharmacy*, 2008, 34, 4, 349-354.
46. Y Miyazaki, Y Onuki, Yakou S, Takayama K. *International Journal of Pharmaceutics*, 2006, 324, 2, 144-151.
47. S Stithi, W Chen, JC Price. *Journal of Microencapsulation*, 1998, 15, 6, 725-737.
48. I El-gibaly. *International Journal of Pharmaceutics*, 2002, 249, 1-2, 7-21.
49. VB Junyaprasert, S Pornsuwannapha. *Drug Delivery*, 2008, 15, 5, 331-341.
50. BV Basavaraj, R Deveswaran, S Bharath, S, Abraham, S Furtado, V Madhavan. *Pakistan Journal of Pharmaceutical Sciences*, 2008, 21, 4, 451-454.
51. Y Kawashima, T Niwa, H Takeuchi, T Hino, Y Itoh. *Journal of Pharmaceutical Sciences*, 1992, 81, 2, 135-140.
52. RB Umamaheswari, S Jain, PK Tripathi, GP Agrawal, NK Jain. *Drug Delivery*, 2002, 9, 4, 223-231.

Correspondent address

**D/o dattatraya atmaram wagh
At Post. Dahivad, tal. Chalisgaon,
Dist. Jalgaon.-424106
Maharashtra.**