ISSN- 2230-7346
Journal of Global Trends in Pharmaceutical Sciences

A SHORT REVIEW ON FLOATING MICROSPHERES: ONE OF THE CREDIBLE GASTRO-RETENTIVE DOSAGE FORMS

Srinivasa Rao Akiri[1], Kumar Rupak[2], Srinivasa Rao Vulichi[1]*, Atul Kabra[3], Appa Rao Chippada[1, 4], Durga Srinivasa Murthy Sistla[3]

[1]S V University College of Pharmaceutical Sciences,S V University, Tirupati, India.
[2]CDSCO, Kotla Road, New Delhi, India.
[3]University Institute of Pharmaceutical Sciences, Chandigarh University, Mohali, India.
[4]Department of Biochemistry, S V University, Tirupati, India.

* Corresponding Author. E-mail: nivschem@gmail.com

ARTICLE INFO

Key words:
Controlled drug deliverysystem
Floating microspheres,
Gastric emptying

Access this article online
Website:
https://www.jgtps.com/
Quick Response Code:

ABSTRACT

Gastric emptying might be a complex process, one that's highly variable which makes in vivo performance of drug delivery systems uncertain. This system is mainly purposed for drugs of anti-diabetic (like metformin hydrochloride), anti-ulcer, anti-emetic (like meclizine hydrochloride) classes, so that, the drug would retain in the stomach and get released in a controlled manner for a better therapeutic response. Floating microspheres as controlled drug delivery system is concerned with systemic release of drug to maintain a therapeutic level in the body for a sustained period of time. The drugs in order to get absorbed in the upper part of the small intestine, should reside in the stomach for longer periods which is the fundamental quality of the controlled drug delivery systems. Non- uniform absorption of drugs is the key barrier to the drug delivery most of the times and this limitation can be overcome through controlled drug delivery systems. The floating microspheres could be one of the feasible options to achieve controlled and targeted delivery of drugs. These could be formulated using different methods and should be evaluated for the rate yield (%), actual drug content (%), floating time, and in-vitro drug release. The floating microspheres might be utilized for delayed delivery in the stomach for at least 8 hrs consequently improving the bioavailability and patient's compliance to an appreciable extent. The present review briefly enlightens about some of the crucial aspects of formulation and evaluation of floating microspheres with a special emphasis on the gastro-retentive dosage forms and drug candidates which have been successfully formulated as floating microspheres.

INTRODUCTION

Among the different routes of drug administration, the oral route has achieved the most attention, partly due to the ease of administration and in design of dosage form. Mostly, the significant variability of the gastrointestinal tract physiology and it transmits time prompts unstable bioavailability and non-reproducible Therapeutic effects [1]. For a successful oral delivery the drug should have good absorption throughout the gastrointestinal tract (GIT), preferably by passive diffusion [2]. Most drugs are well absorbed throughout the entire intestinal tract, but some compounds, usually polar, are poorly absorbed from the large intestine. For such drugs, the main area from which absorption

occurs is the small intestine [3]. The development of gastro-retentive dosage forms which are capable of staying in the stomach over an extended period may be particularly useful for drugs classes that may act locally in the stomach, e.g., antacids, antibiotics [4], drugs which are absorbed mainly in the stomach, e.g., albuterol, chlordiazepoxide [5], drugs that have a small absorption window are absorbed from the upper small intestine e.g., ofloxacin, levodopa, riboflavin, theophylline [6-8] and drugs that have low bioavailability that breakdown in the colon, e.g., ranitidine, metoprolol [9].

The present review briefly enlightens about some of the crucial aspects of formulation and evaluation of floating microspheres with a special emphasis on the gastro-retentive dosage forms and some important drug candidates which have been successfully formulated as floating microspheres.

Gastrointestinal Tract (GIT) Physiology:

The anatomy of the stomach has been divided into three important regions comprising: the fundus, body, and the antrum (pylorus) respectively. The fundus is considered as the proximal part, the body as the reservoir for the undigested material and the antrum serves as a pump for gastric emptying and regulates the peristaltic movements. Though gastric emptying occurs during both fasting and fed states, the motility pattern is known to be distinct in both the states. The myoelectric cycle (MEC)/migrating motor complex (MMC) of gastrointestinal smooth muscle is concerned with a distinct series of electrical events observed at the intervals between meals in the stomach and the intestine. This has been further divided into four phases as described below [10].

Stage I (basal phase): It lasts from 40 to 60 minutes with uncommon contractions.

Stage II (pre-burst phase): It lasts for 40 to 60 minutes with irregular activity potential and contractions.

Stage III (burst phase): It lasts for four to six minutes. It includes extreme and normal contractions for a small period.

Stage IV: It occurs between stages III and I of two successive cycles and lasts for 40 to 60 minutes with irregular activity potential and contractions.

After the intake of a blended meal, the mode of contractions changes from fasted to that of fed state. This is otherwise called digestive motility pattern and involves continuous contractions as in stage II of the fasted state. These contractions reduce the size of the food particles (to under 1 mm), in turn propelling towards the pylorus as a suspension. During the fed state, onset of MMC is slowed down, bringing about delayed gastric emptying rate [11].

Some of the Factors Influencing Gastric emptying:

Age, body mass index (BMI), gender, posture, disease state, viscosity, volume, caloric content, pH, alcohol, stress, drugs (like antibiotics, cholinergic agents, prokinetic agents, etc) [11].

Gastro-retentive Dosage Forms: Advantages and Disadvantages:

Gastro-retentive drug delivery systems (GRDDS) are generally opted for formulating drugs that: (i) are locally dynamic in the stomach; (ii) have a limited retention window in GIT (iii) are unstable in the intestinal or colonic environment, (iv) show low solubility at high pH regions [12-13].

Some of the Important Features of GRRDS include:

1. Low density dosage forms that float above the gastric liquid.
2. High density dosage forms that sinks in the lower part of the stomach.
3. Bio adhesion to the stomach mucosa.
4. Controlled release through the pyloric sphincter by gradual increase in size [14-17].

Advantages of Gastro-retentive Systems:

1. It reduces dosing frequency thereby improving the patient compliance.
2. It achieves site-specific drug delivery.
3. Promising in the treatment of certain complicated, gut associated disorders like peptic ulcer disease (PUD), inflammatory bowel disease (IBD), etc.
4. Better impact on drugs with short half-life.
5. Help sustain the therapeutic effect

for prolonged time.

6. Decrease the risk of gastric disturbances during the therapy [18-22].

Disadvantages of Gastro-retentive Systems:

1.Drugs which have solubility issues at acidic pH can't be utilized for GRDDS.

2.Drugs that have retention all through GIT is not helpful for this system such as, Isosorbide dinitrate, Nifedipine, etc

3.Fluctuation in gastric discharging time and rate is a significant drawback.

4.This system varies with the position (fed or fasting state) of the individual [18-19, 22].

Floating Microspheres

These are the part of the controlled drug delivery systems that have been designed to release the drug at pre-specified rate with a high effectiveness reduced adverse effects and enhance the bioavailability of drugs [23-24]. Floating microspheres are low density in which there is adequate buoyancy in the gastric contents for floating and retained in the stomach for a longer period. Drugs which have capability of more absorption rate solubilizes only in the stomach because of buoyancy, gastric retention time is multiplied [25].

Factors that are taken in to consideration for the Development of Floating Microspheres:

1. **Density:** Dosage forms with low density than gastric contents (1.004 g/L) are suitable for floating microspheres.
2. **Size:** Dosage form size should be greater than 7.5 mm and lesser than 9.5 mm, which shows gastric retention for a longer duration [19, 26].
3. **Shape:** Desired shape of floating microspheres could retain in the stomach for longer duration. There were various shapes screened in-vivo for gastric retention potential. From these shapes, tetrahedrons (Each leg 2 cm long) and rings (3.6 cm in breadth) have been noticed almost 100% retention for 24 h.
4. **Nature of diet:** Factors like nature of the diet, especially protein rich diet has been known to increase the retention time around 4-10 h [28-29].

Advantages of Floating Microspheres:

1. Improve drug absorption because of the increased gastric residence time thereby increasing the bioavailability of the encapsulated drug.
2. Controlled or sustained drug delivery system.
3. Delivery of drugs for localized action in the stomach.
4. Limits gastric inconvenience by drug delivery at a controlled rate.
5. Less frequent dosing.
6. Site-specific drug delivery [30].

Mechanism behind Flotation of the Microspheres:

Due to the interaction of floating microspheres with gastric liquid, the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of liquid entrance into the device and followed by drug release. As the outside surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent colloidal layer. Swollen polymer traps air which brings down the density and confers buoyancy to the microspheres. Anyway a minimal gastric content is required to allow desired level of buoyancy [31].

Mechanism of the Drug Release from the Floating Microspheres:

The drug release from the microspheres occurs by the following mechanisms:

Diffusion: On contact with gastric fluid the water enters into the drug particles where dissolution occurs in turn leading to the diffusion of drug from inside to the outside.

Erosion: In this mechanism, the coating layers erode step by step with the time and thereby liberating the drug entrapped within the microspheres.

Osmosis: Osmotic agents are employed which works by building up osmotic stress inside the particles leading to the successful expulsion of drug [32].

Various Techniques for the Preparation of Gastro-retentive Floating Microspheres:

Several methods are available for the preparation of gastro retentive floating microspheres. However, solvent evaporation technique and ionotropic gelation method have been commonly used by the investigators [33]. During the preparation of floating controlled release microspheres, the selection of optimal method has utmost relevance for the efficient entrapment of active constituents [34-35].

Solvent evaporation technique: 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 help of an agitator. The concentration of the emulsifier present within the aqueous phase affects the particle size and the shape. When the required emulsion droplet size is achieved, the stirring rate is reduced and organic solvent would be evaporated under atmospheric or reduced pressure at an appropriate temperature. Subsequent Evaporation of the scattered stage solvent yields strong polymeric micro particles entangling the drug. The solid micro particles are regained from the suspension by filtration, centrifugation, or lyophilisation [36].

Spray drying technique: This is used to prepare a polymeric blended microsphere loaded with drug. It includes scattering the core material into condensed coating material and afterward spraying the blend in the surroundings for solidification of coating followed by quick evaporation of the solvent. An Organic solution of poly- ε caprolactone (PCL) and cellulose acetate butyrate (CAB) in different weight ratios and drug was prepared and sprayed in different experimental conditions achieving drug-loaded microspheres. This is rapid but may lose crystallanity due to the fast-drying process [37].

Wet inversion technique: According to this method, chitosan solution in ethanoic acid is dropped into a solution of counter ion builder through a nozzle.

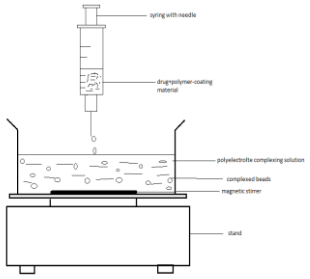

Fig. 1: An illustration of Ion gelation method

Microspheres produced were permitted to stand for 1 h and cross-linked with 5% ethylene glycol diglysidyl ether. Microspheres were then washed and freeze-dried. Altering the pH of the coagulation medium could modify the pore structure of chitosan microspheres. Complex Coacervation chitosan microspheres can also prepare by complex coacervation, Sodium alginate, sodium carboxy methylcellulose, and sodium and polyacrylic acid can be used for complex coacervation with Chitosan to form microspheres. These microparticles are formed by the inter-ionic interaction between oppositely charged polymers solution and potassium chloride and calcium chloride solutions. The acquired micro capsules were hardened in the counter particle arrangement before washing and drying [38].

Ionotropic gelation method: In this technique (Fig 1), cross-connecting of the polyelectrolyte happens within the sight of counter particles to form gel lattice. Polyelectrolyte, for example, sodium alginate having a property of covering on the medication core and goes about as delivery rate retardant contains certain anions in their compound structure. These anions form meshwork structure by connecting with polyvalent cations inducing gelation. Microspheres are prepared by dropping drug loaded polymeric solution using syringe into the solution of polyvalent cations. The cations diffuse into the drug loaded lymeric drops, forming a three-dimensional lattice of ionically cross-linked moiety. Microspheres formed left into the first solution for sufficient period of time for internal gelification and that they are separated by filtration. Natural polymers like alginates are

often used to improve drug entrapment and are widely utilized in the event of floating microspheres [39-41]

List of Some Polymers Employed in the Formulation of the Floating Microspheres: Various biodegradable polymers both of natural and synthetic origins have been found to have applications in formulating floating microspheres [42] (Table 1).

Table 1: Different types of polymers employed in the formulation of floating microspheres

Hydrophilic polymers	Hydrophobic polymers	Biodegradable polymers	Non-biodegradable Polymers
Examples: gelatine, agar, starch, chitosan.	Examples: ethyl cellulose, poly lactic corrosive, acrylic acid esters.	Examples: poly(lactic-co-glycolic acid) poly (glycolic acid), Poly-ε-caprolactone	Examples: ethyl cellulose, poly vinyl chloride, poly ethylene.

Various Parameters Employed for the Evaluation of Floating Microspheres:

In general, floating microspheres are critically evaluated using the following parameters:

1. **Particle size:** Particle size of floating microspheres is determined by utilizing optical microscopy and size distribution is determined by sieving technique. This is required for the analysis of mean particle size with the help of a calibrated ocular micrometer [44].
2. **Percentage yield:** The formulated floating microspheres were collected and weighed. Yield percentage is calculated by dividing actual weight of product to total amount of all non-volatile components, which will be utilized in the preparation of floating microspheres [45].

Percentage yield = actual weight of microspheres / total weight of excipient and drug × 100

Drug capture effectiveness: The weighed and powdered microspheres should be dissolved in ethanol (5ml) in a volumetric flask (100ml) and made the volume up with 0.1 N Hydrochloric acid (HCl). Whatmann filter paper is used to filter the above solution. After that absorbance should be measured using Ultraviolet (UV) spectrophotometer against 0.1 N HCl as a blank. The percentage drug capture should be calculated using the formula below [46].

% drug capture efficiency = Calculated drug concentration / theoretical drug concentration × 100

Surface morphology: Scanning electron microscopy is used for determining the surface characteristics of floating microspheres. Before the observation samples should be coated with gold dust. To observe the core and internal structure of the microspheres cross-section should be made. The Internal and external morphology of floating microspheres can be understood by these studies [47-48].

In-vitro drug release: The amount of drug delivered from floating microspheres is estimated utilizing United States Pharmacopeia (USP) dissolution apparatus type I or type II at 37±0.5 ℃. The disintegration test is performed utilizing 900 mL of 0.1 N HCl dissolution medium at 100 revolutions per minute (rpm) for the recommended duration of time. At proper intervals known volumes should be aliquoted and restored with an equal volume of new dissolution medium to maintain the steady dissolution medium volume. The individual solutions should be filtered through Whatman filter paper and studied using a UV spectrophotometer in order to understand the amount of drug released into the medium [49-50].

Floating time: In vitro floating tests can be performed as per the USP type II dissolution test mechanical assembly by spreading the floating microspheres on a stimulated gastric liquid (pH 1.2) containing the suitable

surfactant. The media should be mixed at 100 rpm at 37± 0.5°C. After distinct intervals of time, both floating and settled microspheres should be collected and the buoyancy of the floating microspheres is calculated by the formula [51].

Floating time % = Qf/Qf + Qs x 100

(Where, Qf and Qs are the majorities of floating and settled floating microspheres, individually)

In vivo **studies:** *In vivo* studies are generally performed on healthy albino rats weighing 500–600 gm was treated with optimized formulation and monitored through radiological method with modification. Animals are housed individually in polypropylene cages and maintained under standard conditions (12-h light and 12-h dark cycle; 25–30°C). The animals would be fasted for 12 h and initially X-ray should be taken to make sure the absence of radio opaque material within the stomach. During the study animals weren't allowed to eat food but water was provided spontaneously. Radiopaque microspheres would be prepared by incorporating 500 mg of barium sulphate into polymeric solution as like the procedure mentioned above. At varying time intervals X-ray photographs (Sire graph-B, Siemens, Karlsruhe, Germany) of gastric region would be taken for monitoring the floating behavior of microspheres [52].

Examples of Some Important Drug Candidates Formulated as Floating Microspheres:

These are few important drug candidates which has been formulated and the list of the some drugs which have been formulated floating microspheres till date (Table 2)

Dexrabeprazole Sodium Floating Microspheres: Floating microsphere containing dexrabeprazole have been prepared by emulsion solvent diffusion technique using different proportions of drug and polymer, such as hydroxypropyl methylcellulose and ethyl cellulose. A drug to polymer ratio of 1:7 has been used to prepare different formulations. The prepared microspheres showed satisfactory results related to various evaluation parameters like particle size determination, floating behavior, drug entrapment, and in-vitro release studies among various batches. Dexrabeprazole sodium floating microspheres help in treating pregnancy related complications [53].

Meclizine Hydrochloride Floating Microspheres: In this study, meclizine hydrochloride (MCZ) floating microspheres were formulated, characterized, and evaluated for their effectiveness in prolonging the drug action. In-vitro drug release studies concluded the ability of floating microspheres to sustain the drug release up to 24 h in the dissolution medium with more than 70% of entrapped drug released has been found among various formulations reported. In addition, pharmacokinetic studies confirmed that the optimized formula (Eudragit RS100: HPMC) of MCZ floating microspheres was found to prolong the drug release leading to enhanced bioavailability when compared to the plain drug. Collectively, these results suggest that floating microspheres might represent a viable alternative to the conventional oral dosage forms in terms of the dosing frequency, improving patient compliance, and more importantly the therapeutic efficiency of MCZ especially during pregnancy [54].

Metformin hydrochloride Floating Microspheres: In this study, gastro retentive floating microspheres of metformin hydrochloride (an anti-diabetic agent) which have been prepared by oil in oil emulsion solvent evaporation technique using ethyl cellulose, methacrylic acid copolymer (Eudragit RS100, Eudragit RSPO, and Eudragit RLPO). Prepared floating microspheres of metformin HCl may prove to be safe and effective delivery system over an extended period which in turn minimizing the dosing frequency. Microspheres were evaluated by various parameters like percentage yield, drug entrapment efficiency, Further, the evaluated microspheres showed prolonged drug release in the stomach for at least 8in turn improving bioavailability and patience compliance [55].

Table 2: General list of some drugs which have been formulated floating microspheres till date

Name of the drug	Pharmacological class	References
Acyclovir	Antiviral	[56]
Ranitidine HCl	Histamine receptor (H_2) blocker	[57]
Ketoprofen	Non-steroidal anti-inflammatory agent	[58]
Aceclofenac	Non-steroidal anti-inflammatory agent	[59]
Nitrendipine	Calcium-channel blocker	[60]
Cefpodoxime proxetil	Beta-lactam Antibiotic	[61]
Rosiglitazone	2,4-Thiazolidinedione	[62]
Cimetidine	Histamine2 blockers	[63]
Ibuprofen	Non-steroidal anti-inflammatory agent	[64]
Aluminium hydroxide	Antacid	[65]

CONCLUSION AND FUTURE DIRECTIONS:

Floating microspheres are known for their high potential for the gastro-retention and would be a reliable option for upgrading bioavailability and controlling the release of numerous drugs. They are known to precisely control the drug release at the target site. These models also provide tremendous opportunities for designing certain advanced oral delivery systems in turn opening new avenues in the pharmaceutical development. Importantly, certain typical drug classes (especially anti-cancer, anti-viral, anti-diabetic, and anti-hypertensive agents) that are employed for chronic therapy could be efficiently developed as floating formulations thereby limiting poor patient compliance, erratic bioavailability, and dose related side effects respectively.

Acknowledgements: We express our deepest gratitude to the students, teaching, and, the non-teaching faculty of S V University College of Pharmaceutical Sciences, S V University, Tirupati, India, for their constant support and encouragement.

REFERENCES:

1. Soppimath KS, Kulkarni AR, Rudzinski WE, Aminabhavi TM, Microspheres as floating drug delivery systems to increase gastric retention of drugs, Drug Metabolism Reviews, 2001; 33 (2): 149-160
2. Shwetha A, Javed A, Alka A, Roop KK, Sanjula B, Floating drug delivery systems: a review, American Association of Pharmaceutical Scientists, 2005; 6 (3): 372-390
3. HirtzJ, The GIT absorption of drugs in man: a review of current concepts and methods of investigation, British Journal of Clinical Pharmacology, 1985; 19 (Suppl 2)77-83
4. Franz Michel R, Oth Marianne P, Sustained release bilayer buoyant dosage form, US Patent, 1993; 5, 232, 704
5. Hilton AK, Deasy PB, In vitro and in vivo evaluation of an oral sustained-release floating dosage form of Amoxycillin trihydrate, International journal of pharmaceutics, 1992; 86 (1): 79-88
6. AvachatM, Dhamne A, Gastric floating system, WO Patent, 2002; 02, 102, 415
7. Sheth PR, Toussounian JL, Novel sustained release tablet formulations, US Patent, 1979; 4, 167, 558.
8. Desai S, BOLTON S, Floating sustained release therapeutic compositions, US Patent, 1989; 4, 814, 179
9. Dave BS, Amin AF, & MM Patel, Gastro retentive drug delivery system of ranitidine hydrochloride: formulation and in vitro evaluation, American Association of

Pharmaceutical Scientists, 2004; 5 (2): 77-82
10. Wilson CG, Washington N, The stomach: its role in oral drug delivery, In: Rubinstein M.H., (Ed.) Physiological pharmaceutical: biological barriers to drug absorption, Chichester UK, Ellis Horwood, 1989: 47-70
11. Griffith GH, Owen GM, Kirkman S, Shields R, Measurement of the rate of gastric emptying using Chromium-51, Lancet, 1966; 1 (7449): 1244-1245
12. Kagan L, Lapidot N, Afargan M, Kirmayer D, Moor E, Mardor Y, Friedman M, Hoffman A, Gastroretentive Accordion Pill: enhancement of riboflavin bioavailability in humans, Journal of Control Release, 2006; 113 (3): 208–215
13. Murphy CS, Pillay V, Choonara YE, Du Toit LC, Gastroretentive drug delivery systems: current developments in novel system design and evaluation, Current Drug Delivery, 2009; 6 (5): 451–460
14. Chawla G, Gupta P, Koradia V, Bansal AK, Gastroretention: a means to address regional variability in intestinal drug absorption. Journal of Pharmaceutical technology, 2003; 27(7): 50–68
15. Hoffman A, Stepensky D, Lavy E, Eyal S, Klausner E, Friedman M, Pharmacokinetic and pharmacodynamic aspects of gastroretentive dosage forms, International journal of pharmaceutics, 2004; 277 (1-2): 141–153
16. Klausner EA, Lavy E, Friedman M, Hoffman A, Expandable gastroretentive dosage forms, Journal of controlled release, 2003; 90 (2): 143–162
17. Singh BN, Kim KH, Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention, Journal of controlled release, 2000; 63 (3): 235–259
18. Sharma D and Sharma A, Gastro-retentive drug delivery system a mini-review, Asian Pacific Journal of Health Sciences, 2014; 1 (2): 80-89
19. Rathod HJ, MehataDP, and Yadav JS, A review on gastroretentivedrugdeliverysystems, PharmTutor,20(7)0
20. Aslam R, Mehmood Y, Khan S and Yousaf H, Techniques and Polymers used to design gastro-retentive drug delivery systems-a review, World Journal of Pharmacy and Pharmaceutical Sciences, 2014; 3 (12): 97-110
21. More S, Gavali K, Doke O, and Kasgawade P, Gastroretentive drug delivery system, Journal of Drug Delivery & Therapeutics, 2018; 8 (4): 24-35
22. Sharma AR and Khan A, Gastro-retentive drug delivery system, an approach to enhance gastric retention for prolonged drug release, International Journal of Pharmaceutical Sciences and Research, 2014; (5): 1095- 1106
23. Sawant K, Patel M, Patel et al, Formulation, Optimization, Characterization and in Vivo Antiulcer Activity of Esomeprazole Magnesium Trihydrate Gastro-resistant Microspheres, International Journal of Pharmacy and Pharmaceutical Sciences, 2017; 9 (1): 273-282
24. **[24]** Begum SK, Basava RD, Design and evaluation of microspheres using anti-ulcer agent Roxatidine, Der Pharmacia Lettre, 2016; 8 (4): 371-380
25. **[25]** Kallepu S, Harika M, Kandala S, Bakshi V, Formulation and Evaluation of Gastro Retentive Floating Microspheres of Nimodipine, Asian Journal of Pharmaceutics, 2016; 10(4); S628
26. Jain NK, Progress in controlled and novel drug delivery systems, 2009; 1st Edition, CBS Publishers & Distributors New Delhi

27. Chowdary KPR and ChaitanyaCHKL, Recent research floating drug delivery system-A review, Journal of Global Trends in Pharmaceutical Sciences, 2014; 5 (1) 1361-1373
28. Sudheer P, Kumar H, Thomas L, and Nethradevi DR, Floating microspheres an excellent approach of gastric retention, Journal of Pharmaceutical Researchh, 2015; 14 (4): 71-80
29. Grabowski SR, Principles of anatomy and physiology, 2000, 10th edition, 2000, John Willey and Sons, New York
30. Gholap SB, Bannerjee SK, Gaikwad DD, Jadhav SL, and Thorat RM, Hollow Microsphere: A Review International Journal of Pharmaceutical Sciences Review and Research, 2010; 1 (1): 74-79
31. Somwanshi SB, Dolas RT, Nikam VK, Gaware VM, Kotade KB, Dhamak KB, and Khadse A N, Floating Multi particulate Oral Sustained Release Drug Delivery System, Journal of Chemical and Pharmaceutical Research,2011, 3(1): 536-547
32. Whateley TL. In Microencapsulation: methods and industrial applications (Benita, S., ed.). Marcel Dekker, New York. Wick, R. & Luisi, PL (1996).. Chem Biol. 1996; 3(4):277-285
33. Okada H, Toguchi H, Biodegradable microspheres in drug delivery, Critical Reviews in Therapeutic Drug Carrier Systems, 1999; 12(1): 1-99.
34. Vyas, In Jain, NK, Pharmaceutical Product Development, 2006; 1st edition, CBS Publishers, New Delhi 419-424
35. Watts PJ, Davis MC, Melia CD, Microencapsulation using emulsification/solvent evaporation: an overview of techniques and applications, ―Critical Reviews in Therapeutics Drug Carrier Systems, 1990; 7(3): 235-259
36. Patel G, Tiwari A, Rabadia N, Floating microspheres as a novel tool for H2 receptor blocker, International Research Journal of Pharmacy,2012; 3 (2): 45-52
37. Kapil K and Rai AK, Floating Microsphere: An Innovative Approach for Gastro retention, Journal of Pharmacy Research, 2012; 5(2): 883-886
38. Ma N, Xu L, Wang Q, Zhang X, Zhang W, Li Y, Jin L, Li S, Development and evaluation of new sustained-release floating microspheres, International Journal of Pharmaceutics, 2008; 358 (1-2): 82-90
39. Patil JS, Kamalapur MV, Marapur SC, Kadam DV, Ionotropic gelation and polyelectrolyte complexation: the novel techniques to design hydrogel particulate sustained, modulated drug delivery system: a review, Digest Journal of Nanomaterials and Bio structures, 2010; 5(1): 241-248
40. Lim F, Sun AM, Microencapsulated islets as the bio artificial endocrine pancreas, national library of medicine, 1980; 210 (4472): 908-910
41. Anamika Saxena, Kalpesh Gaurl, Virendra Singh, Rajneesh Kant Singh, and Ashok Dashora, floating microspheres as drug delivery system, American Journal of Pharmacy and Pharmaceutical Sciences, 2014; 1 (2): 27-36
42. Rajkumar K, Goud R S, Sowjanya P, Lavanya AP, Adavi S, Reddy ER, Floating Microspheres: A Novel Approach in Drug Delivery, Journal of Drug Delivery Research, 2012; 1(4): 1-20
43. Yasunory S, Yoshiaki K, Hirofumi T and Hiromitsu Y, In vitro evaluation of floating and drug-releasing behaviors of hollow microspheres (micro balloons) prepared by the emulsion solvent diffusion method, European Journal of Pharmaceutics,

and biopharmaceutics, 2004; 57(2): 235-243
44. Pahwa R, Neeta, Bhagwan S, Kumar V, Kohli K, Floating microspheres, An innovative approach for gastric retention. Pharmacia Lettre, 2010; 2 (4): 461-475
45. Pandya N, Pandya M, Bhaskar VH, Preparation and In-vitro Characterization of Porous Carrier-Based Glipizide Floating Microspheres for Gastric Delivery,Journal of Young Pharmaci sts, 2011; 3(2): 97–104.
46. Stithi S, Chen W, Price JC, Development and characterization of buoyant theophylline microspheres with near zero-order release kinetics, Journal of of Microencapsulation, 1988; 15(6): 725-737
47. El-Gibaly, Development and in-vitro evaluation of novel floating chitosan microcapsules for oral use: comparison with non-floating chitosan microspheres, International Journal of Pharmaceutics, 2002; 249(1-2)7-21
48. Junyaprasert VB, Pornsuwannapha S, Floating Properties and Release Characteristics of Hollow Microspheres of Acyclovir, Drug Delivery, 2008; 15 (5): 331-341
49. Furtado S, Abraham S, Bharath S, Deveswaran R, Basavaraj BV, Madhavan V, Hollow microspheres of Diclofenac sodium, A gastroretentive controlled delivery system, Pakistan Journal of Pharmaceutical Sciences, 2008; 21(4): 451-454
50. Joseph N, Lakshmi S, Jayakrishnan A, A floating-type oral dosage form for piroxicam based on hollow polycarbonate microspheres: in vitro and in vivo evaluation in rabbits, Journal of controlled Release, 2002; 79: 71-79
51. Wei Y, Zhao L, In vitro and in vivo evaluation of ranitidine hydrochloride loaded hollow microspheres in rabbits, Archives of Pharmacal Research, 2008; 31 (10): 1369-1377
52. Tanwar Y S, Naruka P S, Ojha G R, Development and evaluation of floating microspheres of verapamil hydrochloride, Brazilian Journal of Pharmaceutical Sciences, 2007; 43: 529-534
53. Krishna Kumar Kashyap, Anjana Bharadwaj, Fabrication and characterization of floating microspheres of Dexrabeprazole Sodium to improve bioavailability, Advance Pharmaceutical Journal, 2020; 5 (4): 134-138
54. Husseiny RA, Abu Lila AS, Abdallah MH, Hamed EE, El-ghamry HA, Design, in vitro/in vivo evaluation of meclizine HCl-loaded floating microspheres targeting pregnancy-related nausea and vomiting, Journal of Drug Delivery Science and Technology, 2018; 47: 395-403
55. Ansary J, Chaurasiya AK, Huq KB, Formulation and evaluation of metformin HCl floating microspheres, Asian Journal of Medical and Biological Research, 2015; 1 (3): 396-405
56. Patil MP, Patil HS, Bharat WT, Vinod MT, Patil VR, Formulation and in-vitro evaluation of floating microspheres of acyclovir, Archives Pharmacal Sciences Reserch, 2009; .1: 194-198
57. Wei Y, Zhao L, In vitro and in vivo evaluation of ranitidine hydrochloride loaded hollow microspheres in rabbits, Archives Pharmacal Research, 2008; 31(10):1369-1377
58. El-kamel AH, Sokar MS, AL Gamal SS, Naggar VF, Preparation and evaluation of ketoprofen floating oral drug delivery system, International Journal of Pharmaceutics, 2001; 220(1-2):13-21
59. Gattani YS, Kawtikwar PS, Sakarkar DM, Formulation and evaluation of gastro retentive multi particulate

drug delivery system of aceclofenac, International Journal of Chemtech Research, 2009;1 (1): 1-10

60. Cui F, Wang J, Shi KY, Wang S, Zhang L. In vivo evaluation of a sustained-release multiple-unit floating system containing nitrendipine, Asian Journal of Pharmaceutical Sciences, 2008;3: 151-157
61. Karthikeyan DM, Ramasamy C, Effect of different viscosity grades of Hydroxy methyl cellulose on drug release profile, Journal of pharmacy research, 2008; 1(1): 23-28
62. Kamila MM, Mondal N, Ghosh LK, Gupta BK, Multiunit floating drug delivery system of rosiglitazone maleate: development, characterization, statistical optimization of drug release and in vivo evaluation, American Association of Pharmaceutical Scientists, 2009; 10(3): 887-899
63. Srivastava AK, Ridhurkar DN, Wadhwa S, Floating microspheres of cimetidine: Formulation, characterization and in vitro evaluation, Acta Pharmaceutica sciencia, 2005; 55 (3): 277-285
64. Kawashima Y, Niwa T, Takeuchi H, Hino T, Itoh Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. Journal of Pharmaceutical Sciences, 1992 ;81 (2):135-140
65. Aubert J, Bejan-Angoulvant T and Jonville-Bera A P, Pharmacology of misoprostol (pharmacokinetic data, adverse effects and teratogenic effects), Journal deGynécologie Obstétrique et Biologie de la Reproduction, 2014; 43(2): 114–122