WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 10, 404-422. Review Article ISSN 2277–7105

RECENT TRENDS IN GASTRORETENTIVE FLOATING DRUG DELIVERY SYSTEM-A REVIEW

Rukhsar Khan[1], Anup Ojha[1], Ritika Arora[1], Kumud Upadhyay[1]* and Himansu Chopra[2]

[1]Faculty of Pharmacy, Kumaun University, Bhimtal, Nainital.

[2]Faculty of Pharmacy, Gyani Inder Singh Institute of Professional Studies, Dehradun.

Article Received on
16 July 2017,

Revised on 04 August 2017,
Accepted on 25 August 2017

DOI: 10.20959/wjpr201710-9424

***Corresponding Author**
Dr. Kumud Upadhyay
Faculty of Pharmacy,
Kumaun University, Bhimtal,
Nainital.

ABSTRACT

Gastro retentive drug delivery system have been a significant approach over the past few years to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract for local or systemic effect. Conventional oral dosage forms having low bioavailability problems due to their rapid gastric transition from stomach, in case of drugs which are less soluble at alkaline pH of intestine. Further drugs which produce their local action in stomach, get rapidly emptied do not get enough residence time in stomach. Hence, the frequency of dose administration in such cases is increased. To avoid these problems, various efforts have been made to prolong the retention time of drug in stomach. Floating system has been considered as imperative categories of drug delivery system which has gastric retentive behaviour. FDDS is low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach for a prolonged period of time without affecting the gastric emptying rate. The review article explain the various floating drug delivery system that are formulated in order to enhance the drug bioavailability, reduce drug wastage & provide controlled drug delivery & better patient compliant. Several approaches & techniques were developed in recent years for FDDS are discussed.

KEYWORDS: Floating Drug delivery system, Gastro retentive.

INTRODUCTION

Oral drug delivery is the most desirable and preferred route of administration for their systemic effects to provide high level of patient compliance in taking oral dosage forms is

due to the ease of administration, flexibility in formulation & handling of these forms.[1] To modify the gastric retention time is one of the main challenge in the development of oral controlled drug delivery system (OCDDS). Gastric emptying of the dosage forms is the most prominent process & ability to prolong & control the gastric emptying time is valuable asset for dosage forms, which reside in the stomach for a long period of time than conventional dosage forms.[2] Formulation of floating drug delivery was useful approach to avoid this variability like; unpredictable gastric emptying and degradation of the drug due to highly reactive nature of GI content, with increased gastric retention time of the drug delivery system.[3,4]

Designing controlled released systems several difficulties are faced for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. The relatively brief gastric emptying time (GET) in humans which normally averages 2-3 hr through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system which leads to reduced efficacy of the administered dose. Sustained releases are dosage forms that provide medication over an extended period of time.[5]

Several approaches are formed to enhance the gastric residence time of gastro retentive dosage forms (GRDF) and majority of the work is carried out by introducing low- density polymeric substances which can float in the gastric juice. Studies have shown that these floating units which remain buoyant on gastric juice cannot be easily expelled out from the stomach when compared with the non-floating units which stay in antrum region and are easily moved by the peristaltic waves. Hence lots of research of floating drug delivery system is carried out with organic substances as a matrix to load a drug with different low- density.[6] Gastric emptying is a complex process and makes uncertain in vivo performance of drug delivery system. To avoid this variability with increased gastric resident time of drug delivery system the formulation of floating drug delivery systems is a useful approach.[7]

Advantages of Floating drug delivery system

1. The gastroretentive systems are advantageous for drugs absorbed through the stomach.
2. Irritation on the stomach wall caused by acidic substances like aspirin can be avoided by using floating drug delivery system.
3. Administration of floating dosage forms will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid and would be available for absorption in the small

intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.

4. The gastroretentive systems are advantageous for drugs meant for local action in the stomach.
5. When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhoea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

Disadvantages of floating drug delivery system

1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.

2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.

3. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.

4. Some drugs present in the floating system causes irritation to gastric mucosa.

Applications of floating drug delivery systems

1. Site-Specific Drug Delivery: These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine.

2. Absorption Enhancement: Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

3. Sustained Drug Delivery: These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.[8]

Basic gastrointestinal tract physiology

Stomach is a J- shaped enlargement of the GI tract.[9] It is a saclike organ located between the oesophagus & the small intestine.[10] It was filled with food that comes from the oesophagus. The cell lining of the stomach secrete 3 important substances: Mucus, HCL, Pepsinogen (precursor of pepsin).[11]

1. Mucus: - Protects gastric cells from injury.

2. HCL: - Provide acidic medium to kill pathogens as well as to promote the protein breakdown by the pepsin.

3. Pepsin: - Protein –digesting enzyme.[12]

The stomach has 4 main areas.

1. Cardia 2. Fundus 3. Body 4. Pylorus.

- The rounded portion superior to & to the left of the cardia is the fundus.
- Inferior to the fundus is the large central portion of the stomach called the body.
- The region of the stomach that connects to the duodenum is the pylorus (Pyle = gate, ouros = guard).

Functions of the stomach

Stomach mixes saliva, food & gastric juice to form chime. It serves as a reservoir for holding food before release into small intestine. Its secrets gastric juice, which contain HCL, Pepsin, Intrinsic factor & Gastric lipase. Intrinsic factor aids absorption of vit. B_{12}, Gastric lipase aids digestion of triglycerides. It also secret gastrin into blood.[13]

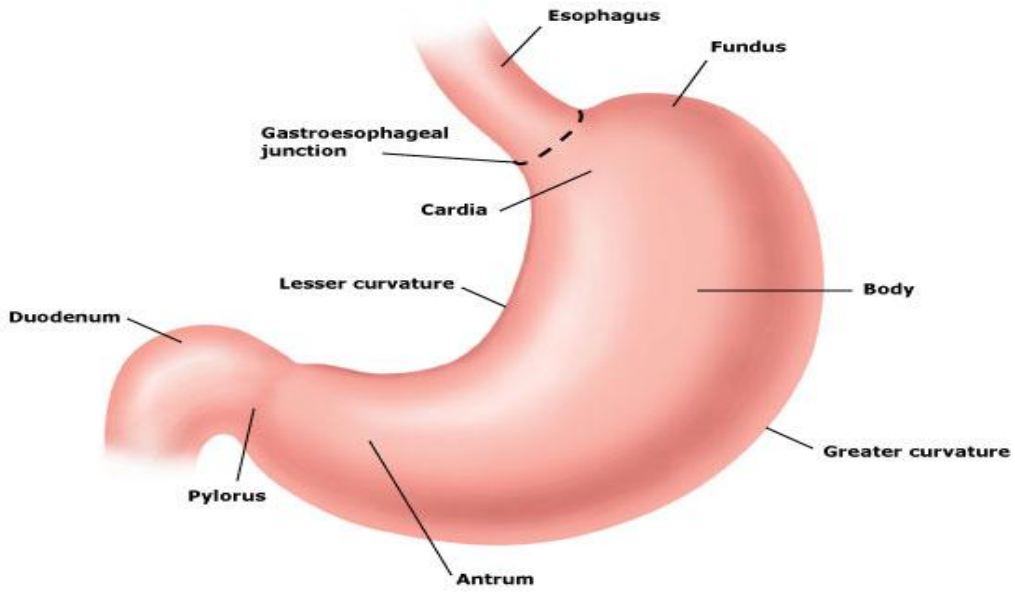

Figure 1: Anatomy & Physiology of stomach[14]

Hormones & Hormone like products that act in digestion[15]

Hormone	Source	Stimulus for secretion	Action
Gastrin	Stomach	Food in stomach (chemical stimulus)	Stimulates release of gastric juice. Stimulate mobility of small intestine.
Histamine	Stomach	Food in stomach	Activates parietal cells to secrete HCL.
Somatostatin	Stomach	Food in stomach	Inhibits secretion of gastric juice & pancreatic juice. Inhibits emptying of stomach & gallbladder.

Gastric Emptying: It was occurs during fasting as well as fed states. The two modes state of continuous motility consisting in GI tract are; Inter-digestive motility pattern & Digestive motility pattern.[16-19]

In the fasted states, it is characterized by an interdigestive series of electrical events, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC) **[figure2],** which is further divided into following four phases.

Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions. It is characterized by lack of any secretary, electrical activity and contractile motions.

Phase II (preburst phase) lasts for 20 to 40 minutes with intermittent action potential and contractions. Bile enters the duodenum during this phase, while the gastric mucous discharge occurs during the later part of phase I and throughout the phase III.

Phase III (burst phase) lasts for 10 to 20 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the "housekeeper wave".

Phase IV (transition period) lasts for 0 to 5 minutes and occurs between phase III and phase I.

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.[20]

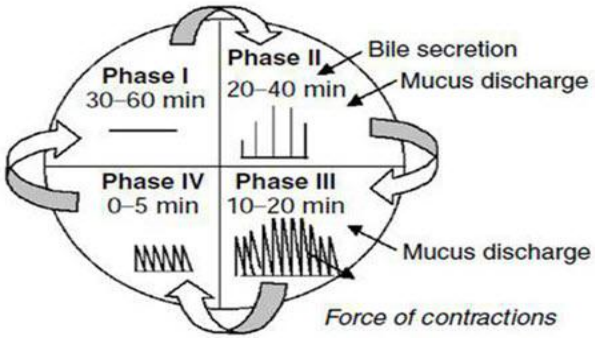

Figure 2: Motility patterns of the GIT in the fasted state.[21]

Mechanism of floating system

Floating drug delivery systems (FDDS) have prolonged the gastric emptying rate for a long period of time and remain buoyant in the stomach due to low density as compared to gastric fluid. Drug released slowly at the desired rate from the system while the system is floating on the gastric content (image). The residual system is emptied from the stomach, after release of drug. This results in an increased GRT and a better control of the fluctuation in plasma drug concentration. However, a minimum level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of meal beyond a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle. A novel apparatus for determination of resultant weight has been reported in the literature, to measure the floating force kinetics. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to submerged object. If F is on the higher positive side the object floats better (image). To prevent the drawbacks of unforeseeable intra gastric buoyancy Capability variations this apparatus helps in optimizing FDDS with respect to stability & durability of floating forces produced.[22]

F = F buoyancy - F gravity = (Df – Ds) g* v

Where,

F= total vertical force, Df = fluid density, Ds = object density,

v = volume and g = acceleration due to gravity

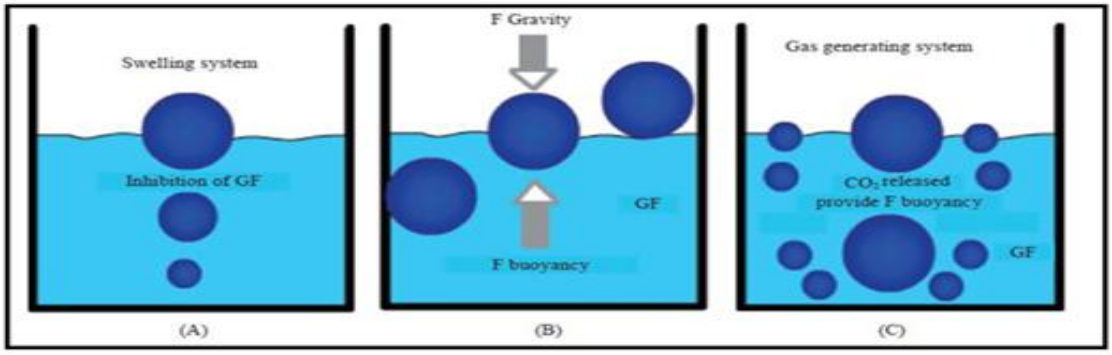

Figure 3: Mechanism of floating systems, GF= Gastric fluid.[23]

Factors affecting gastric retention

Physicochemical factors

Density: In gastric region location of the particular gastro retentive dosage form is depends on the density. Low density tends to float on the gastric fluid while high density systems sink to the bottom of the stomach.

Size of dosage form: Dosage forms having greater diameter than the diameter of pyloric sphincter escape from gastric emptying & remain within gastric region.

Shape of dosage form: round or ring shaped dosage form reported to have better floating, 90% to 100% retention at 24 hrs compared with other shapes.[24-25]

Biological factors

Age: Neonates & children have low gastric retention time while geriatric patient show a longer gastric retention time, in compare to a normal adults.

Gender: Gastric retention time in male (3-4 hrs) is lesser than the female (4-6 hrs).

Fed or unfed state: Gastric motility under fasting condition is higher which depicts lesser GRT.

Nature of meal: Feeding of indigestible polymers or high amount of fatty acids generally decreases the GRT by altering gastric motility.

Disease condition: during the various gastric diseases like Crohn's disease etc, altering the GRT.

Idiosyncratic factor

Concomitant drug administration: Gastric retention time affect when administration of certain drugs (metoclopramide, cisapride) or depressants (atropine), which enhance gastric motility and hence absorption of stomach specific absorbing drugs.[26]

APPROACHES TO GASTRIC RETENTION

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 include.

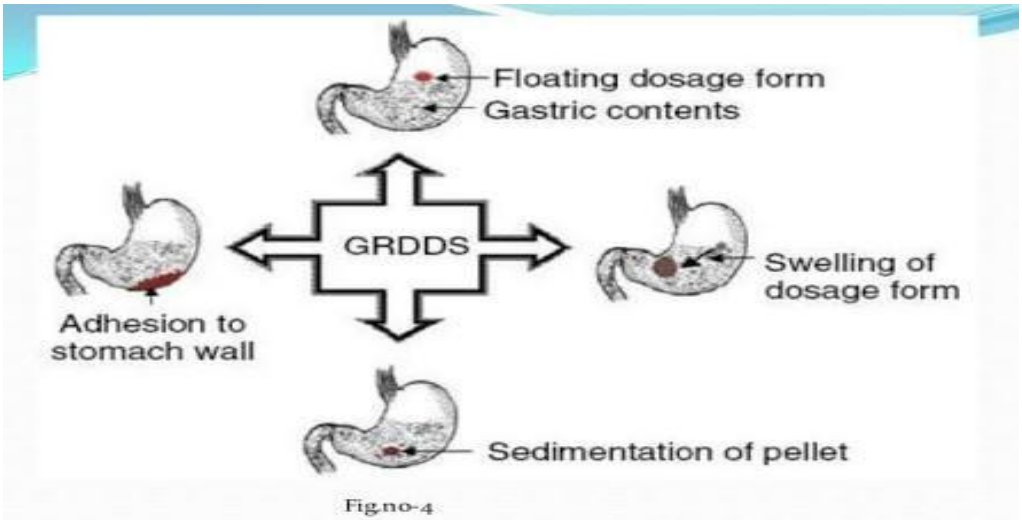

Fig.4: Illustration of types of gastroretentive drug delivery systems.[27]

a) Floating Systems[28-29]

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, non-effervescent and effervescent systems.

b) Bio/Muco-adhesive Systems[30-31]

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:–

- Hydration-mediated adhesion.
- Bonding-mediated adhesion.
- Receptor-mediated adhesion.

c) Swelling and Expanding Systems[32-29]

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 logged at the pyloric sphincter.

d) High Density Systems[33-34]

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.

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM

Two distinctly different technologies that have been utilized in the development of FDDS, are based on the mechanism of buoyancy. These are.

1. Non-Effervescent FDDS.[35-38]

These systems are various types as

i) Single Layer Floating Tablets

ii) Bi-layer Floating Tablets

iii) Alginate Beads

iv) Hollow Microspheres

2. Effervescent FDDS: Two types.

i) Volatile liquid containing system

ii) Gas-generating Systems

3. Raft Forming systems

1. Non-Effervescent FDDS:- These systems are based on mechanism of swelling of polymer or bioadhesion with mucosal layer of git. These non-effervescent FDDS mostly use gel

forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as Chitosan and carbopol for single-unit dosage forms.

The various types of this system are as

a) Single Layer Floating Tablets: They are formulated by intimate mixing of polymer like gel-forming hydrocolloid with drug, which erosion in contact with gastric fluid and maintained its bulk density of less than unity. The enteric materials for low density, HPMC were used.

b) Bi-layer Floating Tablets: A bi-layer tablet contain two layer one immediate release layer and another one is sustained released layer. One released initial dose while another layer absorbs gastric fluid. These layers formed an impermeable colloidal gel barrier on its surface, and maintained a bulk density of less than gastric fluid & thereby it remains buoyant in the stomach.

c) Alginate Beads: Freeze-dried calcium alginate was developed from Multi-unit floating dosage forms. Spherical beads can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, approximately 2.5 mm diameter of beads causing precipitation in calcium alginate leading to formation of porous system, which can maintain 12 hr floating force. These floating beads gave a prolonged residence time of more than 5.5 hrs as compared with the solid beads.

d) Hollow Microspheres: Hollow microsphere containing a core substance in real sense, spherical empty particles. The dried microspheres form a free-flowing powder. They consist of protein or synthetic polymer, which biodegrade and ideally have a size range less than 200 µm. Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. The solid biodegradable microspheres have a potential for controlled release of drugs by incorporating a drug dispersed or dissolved throughout particle matrix. Gastro-retentive floating microspheres have sufficient buoyancy due to low density system which helps to float over gastric content & retain in the stomach for prolonged period. As the floating system the drug float over gastric content & the drug releases slowly at desired rate resulting in enhanced gastric retention with reduced plasma drug concentration fluctuations.[39]

2. Effervescent FDDS

a) Volatile liquid containing system: A volatile liquid is incorporated in an inflatable chamber which increases the GRT. This happens because the volatile liquid at body temperature starts to gasify and thus causing inflatation of the chamber in the stomach. E.g. of volatile liquid ether, cyclopentane. It may also consist bioerodible plug made up of Poly vinyl alcohol, Polyethylene, etc, which dissolves gradually causing the release of gas from the inflatable chamber & further spontaneous ejection of the system from the stomach by collapsing after a predetermined time.[40]

b) Gas-generating System: These buoyant delivery systems, the gellified hydrocolloid layer of the system covered by carbonate/bicarbonate salts and citric/tartaric acid, then the effervescent reaction occur between the systems, which liberate CO2 thus decreases its specific gravity and making it to float over chyme.[41]

3. Raft systems

It incorporates alginate gels that have a carbonate component and upon reaction with gastric acid, bubbles form in the gel enabling floating.[42]

EVALUATION OF FLOATING DOSAGE FORMS

1. For Single Unit Dosage Forms[43] (Eg: tablets)

i) Floating lag time: It is expressed in seconds or minutes. The floating lag time is the time taken by the tablet to emerge onto the surface of the dissolution medium.

ii) *In vitro* drug release and duration of floating: By using USP II apparatus (paddle) stirring at a speed of 50 or 100 rpm at 37 ± 0.2 °c in simulated gastric fluid (pH 1.2 without pepsin) it is determined. Collected the aliquots of the sample & analysed for the drug content. The time (hrs) for which the tablets remain buoyant on the surface of the dissolution medium is the duration of floating and is visually observed.

iii) *In vivo* evaluation for gastro-retention: By means of X-ray or Gamma scintigraphic monitoring of the dosage form transition in the GIT is carried out. The tablets are also evaluated for hardness, weight variation, etc.

2. For Multiple Unit Dosage Forms[44] (Eg: microspheres)

Apart from the In vitro release, duration of floating and in vivo gastro-retention tests, the multiple unit dosage forms are also evaluated for.

i) Morphological and dimensional analysis: It is examined by scanning electron microscopy (SEM). The size can also be measured using an optical microscope.

ii) % yield of microspheres: This is calculated by the formula.

$$\frac{\text{Weight of microspheres obtained}}{\text{Total weight of drug and polymer}} \times 100$$

iii) Entrapment efficiency: The drug is extracted by a suitable method, analysed and is calculated from.

$$\frac{\text{Practical amount of drug present}}{\text{Theoretical drug content}} \times 100$$

iv) In vitro floating ability (Buoyancy %): A known quantity of microspheres are spread over the surface of a USP (Type II) dissolution apparatus filled with 900 ml of 0.1 N HCl containing 0.002% v/v Tween 80 and agitated at 100 rpm for 12 hours.

After 12 hours, the floating and settled layers are separated, dried in a dessicator and weighed. The buoyancy is calculated from the following formula.

Buoyancy (%) = Wf / (Wf + Ws) x 100.

Where Wf and Ws are the weights of floating and settled microspheres respectively.

v) Drug-excipient (DE) interactions: This is done using FTIR. Appearance of a new peak, and/or disappearance of original drug or excipient peak indicates the DE interaction. Apart from the above mentioned evaluation parameters, granules are also evaluated for the effect of ageing with the help of Differential Scanning Calorimeter or Hot stage polarizing microscopy.

Drugs used in the formulations of stomach specific floating dosage forms.

S. No.	Dosage Forms	Drugs Explored In Floating Dosage Forms
1.	Microspheres Tablets/ Pills	Aspirin, Chloropheniramine malate, Griseofulvine[45], p-nitroaniline[46], Ibuprofen[47], Terfenadine[48], Tranilast[49], Verapramil HCL.[50] Acetylsalicylic acid[51], Ibuprofen, Amoxycillin trihydrate[52], Ampicillin[53], Sotalol[54], Isosorbidemononitrate[55], Tranilast[56], Captropril[57], Ciprofloxacin[58], Qunidine[59], Acetaminophen[60], Diltiazem.[61]
2.	Granules	Cinnarizine[62], Diclofenac sodium[63], Isosorbide dinitrate[64], Isosorbide mononitrate[65], Diltiazem, Indomethacin[66], Fluorouracil[67], Prednisolone.[68]
3.	Films	Cinnarizine[69], p-Aminobenzoic[70], Prednisolone[71], Piretanide[72], Quinidine gluconate.[73]
4.	Powders	Sotalol[74], Theophylline[75], Riboflavin-60-phosphate.[76]
5.	Capsules	Chlordiazepoxide HCL[77], Furosemide[78], Misoprostol[79], Verapramil HCL[80,81,82], L-Dopa and benserazide[83], Propranolol HCL[84], Ursodeoxycholic acid[85], Diazepam[86,87], Nicardipine.[88]

REFERENCES

1. Ansel HC, Allen LV, Popovich NG.," Pharmaceutical Dosage Forms and Drug Delivery System," Philadelphia, Lippincott Williams and Wilkins Chapter -3, 2003; 23-31.
2. Hirtz J.," The git absorption of drugs in an: a review of current concepts and methods of investigation," Br J Clin Pharmacol, 1985; 19: 77-83.
3. Mayavanshi A. V, Gajar SS,"Floating drug delivery system to increase gastric retention of drug: A Review". J. Pharm. Res, Oct -Dec. 2008; 1940: 345-348.
4. Vachhani savan R, Patel Dipen, Prajapati ST, Patel CN.; J Chem. Pharma Res., 2010; 2(2): 57-64.
5. Gupta Pooja, Gnanarajan, Kothiyal Preeti, "Floating Drug Delivery Systems: A Review," International Journal of Pharma Research & Review, Aug 2015; 4(8): 37-44, ISSN: 2278-6074.
6. Patel, A., Ray, S., Thakur, R.S.,"Invitro evaluation and optimization of controlled release Floating Drug Delivery System of metformin hydrochloride," 2006; Daru, 14(2): 57-64.
7. Ishak, R.A.H., Awad, G.A.S., Mortada, N.D., Nour, S.A.K.," Preparation, in vitro and in vivo evaluation of stomach-specific metronidazole-loaded alginate beads as local anti-Helicobacter pylori therapy", Journal of Controlled Release, 2007; 119(2): 207-214.
8. Ramesh Putheti R and Mahesh Patil C.," Pharmaceutical Formulation and Development of Floating and Swellable Sustained Drug Delivery Systems: A Review", e-Journal of Science and Technology, 2009; 4: 1-12.
9. Tortora Gerard.J, Grabowski Sandra Reynolds, "Principles of Anatomy & Physiology," Eighth edition, Harper Collins College Publication.
10. Dr. Bodhankar S.L., Vyawahare N.S.,"Pathophysiology ", Nirali Prakasan Page no- 6.1.
11. Luciano, Vander, Sherman," Human Physiology, The Mechanism of Body Function ", International Edition, Seventh edition Mc Graw Hill WCB Mraw-Hill, 553-554.
12. Sembulingam Prema, Sembuligam K,"Essentials of Medical Phtsiology," Third Edition.2005 Jaypee Brothers Medical Publishera (P) LTD New Delhi, 176-178.
13. Fox Stuart Ira,"Human Physiology", Ninth Edition, Mc Graw Hill, Higher Education, 589-594. 14.www.pharmatutor.org
14. Marieb Elaine N," International Edition Essentials of Human Anatomy & Physiology", Benjamin Cummings, Seventh Edition, 448-453.
15. Ramdas TD, Hosmani A, Bhandari A, Kumar B and Somvanshi S. Novel sustained release gastroretentive drug delivery system: A review, 2011; 2(11): 26-41.

16. Rocca G J, Omidian H and Shah K. Progresses in Gastroretentive Drug Delivery Systems. Business briefing. Pharmatech, 2003; 152-156.
17. Vinod K.R, Vasa S, Anbuazaghan S, Banji D, Padmasri A and Sandhya S. Approaches for gastrotentive drug delivery systems. IJABPT, 2010; 1(1): 589-60.
18. Jain N.K.,"Progress in Controlled and Novel Drug Delivery Systems", CBS Publishers & Distributors Pvt.Ltd.First edition, 2004; 79-81.
19. Mukund J.Y, Kantilal B.R, Sudhakar N," Floating Microspheres : A Review", BJPS, Vol.48, n.1, Jan/Mar, 2012.
20. www.pharmatutor.org
21. Suryawanshi A, Hiremath SP, "Floating Drug Delivery System - A Review", American Journal of Pharm Tech Research, 2012; 2(1): 138-153.
22. www.pharmatutor.org
23. Bhardwaj L, Sharma KP, Malviya R, "A Short Review on Gastro Retentive Formulations for Stomach Specific Drug Delivery: Special Emphasis on Floating In situ Gel Systems", African Journal of Basic & Applied Sciences, 2011; 3(6): 300-312.
24. Ichikawa M, Watanabe S, Miyake Y. A new multiple unit oral floating dosage systems. I: Preparation and in vitro evaluation of floating and sustained release kinetics. J Pharm. Sci, 1991; 8: 1062-1066.
25. Bhardwaj V, Nirmala, SL, Harikumar, "Floating Drug Delivery System: A Review", Pharmacophore, 2013; 4(1): 26-38.
26. www.pharmatutor.org
27. Singh BN, Kim KH. Floating drug delivery systems an approach to oral controlled drug delivery via gastric retention. J Control Rel, 2000; 63: 235-59.
28. Jain NK, Progress in controlled and novel drug delivery systems. Delhi; CBS Publishers, 2003; 76-97.
29. Ponchel G, Irache JM. Specific and nonspecific bioadhesive particulate systems for oral delivery to the gastrointestinal tract. Adv. Drug Del. Rev, 1998; 34: 191-19.
30. Chueh HR, Zia H, Rhodes CT. Optimization of Sotalol floating and bioadhesive extended release tablet formulations. Drug Dev. Ind. Pharm, 1995; 21: 1725-47.
31. Mathiowitz E. Encyclopedia of controlled drug delivery. USA: John Wiley and Sons Inc, 1999; Vol. II: 729-31.
32. Wab H, Robinson JR, Lee VHL. Design of oral controlled release drug delivery systems. In: Robinson VR, Lee VHL (editors). Controlled Drug Delivery Fundamentals and Applications. Second edition, New York: Marcel Dekker, 1987; 418-20.

33. Davis SS et al. The effect of density on the gastric emptying on single and multiple unit dosage forms. Pharm. Res, 1986; 3: 208-13.
34. Jain, N.K., Progress in Controlled and Novel Drug Delivery Systems, First Ed. CBS S.Gopalakrishnan et al / Journal of Pharmaceutical Science and Technology, 2011; 3(2): 548-554. Publishers and Distributors, New Delhi, Bangalore, 2004; 84-85.
35. Mojaverian, P., Vlasses, P. H, Kellner, P. E and Rocci, M.L., "Effects of gender, posture, and age on gastric residence time of an indigestible solid: pharmaceutical considerations", Pharm. Res, 1988; 10: 639–664.
36. Timmermans, J. and Moes, A. J., Measuring the resulting weight of an immersed tests material II: Examnples of kinetic determination applied for monolithic dosage forms, Acta. Pharma. Technol, 1990; 36: 176-180.
37. Yyas, S. P. and Roop, K. K., Controlled Drug Delivery Concepts and Advances, First Edition, New Delhi, 2002; 196-217.
38. Lieberman's/ Lachman, Khar k Roop, Vyas P S, Ahmad J Farhan, Jain K Gaurav," The Theory and Practice of Industrial Pharmacy", CBS Publishers & Distributors Pvt Ltd., Fourth Edition, 888-889.
39. Sangekar, S., Evaluation of effect of food and specific gravity of the tablets on gastric retention time. Int. J. Pharm, 1985; 35: 34-53.
40. Singh, B. N. and Kim, K. H., Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release, 2000; 63: 235-259.
41. Rocca JG, Omidian H, Shah K. Progress in gastroretentive drug delivery systems, 2003; [4 screens]. Available at: URL:http://bbriefings.com/pdf/17/ACF8D8E.pdf. Accessed May 20, 2004.
42. Jegadeesh Nagigoti and Shayeda., Floating Drug Delivery System. Int. J. Pharm.Scien. Nano, 2009; 2: 595-601.
43. Fell, J. T, Whitehead, L. and Collet, H., Prolonged gastric retention using floating dosage forms. Pharm Technol, 2000; 24: 82-90.
44. Thanoo BC, Sunny MC, Jayakrishnan A, "Oral sustained-Smith, Floating dosage forms:an in vivo study demon- release drug delivery systems using polycarbonate microstrating prolonged gastric retention", J. Pharm. Pharmacol, 1993; 45: 21–24.
45. Kawashima, YN, Takeuchi TH, Hino, Ito TY, "Preparation of multiple unit hollow microspheres (microbaloons) with acrylic resin containing tranilast and their drug release characteristics (in vitro) and floating behavior (in-vivo)", J. Control. Release, 1991; 16: 279-290.

46. Miyazaki S, Yamaguchi H, Yokouchi C, Takada M, Hou WM, "Sustained –release and intragastric-floating granules of indomethacin using chitosan in rabbits", Chem. Pharm. Bull, 1988; 36: 4033-4038.
47. Ichikawa M, Kato T, Kawahara M, Watanabe S, Kayano M, "A new multiple unit oral floating dosage system. II: In vivo evaluation of floating and sustained-release characteristics with p-aminobenzoic acid and isosorbide dinitrate as model drugs", J. Pharm. Sci, 1991; 80: 1153–1156.
48. Rouge N, Cole ET, Doelker E, Buri P, "Buoyancy and drug release patterns of floating minitablets containing piretanide and atenolol as model drugs", Pharm. Dev. Technol, 1998; 3: 73–84.
49. Bhushan S. Gulecha Sandhna Shahi Vivek B. Rajendra; Formulation and Optimization of Biphasic Floating Drug Delivery System of Verapamil Hydrochloride; International Journal of Pharmacy and Pharmaceutical Sciences, 2012; 4(5).
50. Biju SS, Saisivam S, Maria NS, Gerald R, Mishra PR, "Dual coated erodible microcapsules for modified release of Diclofenac Sodium", European Journal of Pharmaceutics and Biopharmaceutics, 2004; 58: 61-67.
51. Inouye K, Machida Y, Sannan T, Nagai T, "Buoyant sustained release granules based on Chitosan", Drug Des. Del, 1989; 4: 55-42.
52. Ichikawa M, Watanabe S, Miyake Y, "A new multiple-unit oral floating dosage system. I: Preparation and in vitro evaluation of floating and sustained-release characteristics", J. Pharm. Sci, 1991; 80: 1062–1066.
53. Chueh HR, Zia H, Rhodes CT, "Optimization of sotalol floating and bioadhesive extended release tablet formulaltions", Drug Dev. Ind. Pharm, 1995; 21: 1725–1747.
54. Ichikawa M, Kato T, Kawahara M, Watanabe S, Kayano M, "A new multiple unit oral floating dosage system. II: In vivo evaluation of floating and sustained-release characteristics with p-aminobenzoic acid and isosorbide dinitrate as model drugs", J. Pharm. Sci, 1991; 80: 1153–1156.
55. Rouge N, Cole ET, Doelker E, Buri P, "Buoyancy and drug release patterns of floating minitablets containing piretanide and atenolol as model drugs", Pharm. Dev. Technol, 1998; 3: 73–84.
56. Nur AO, Zhang JS, "Captopril floating and/or bioadhesive tablets: design and release Kinetics", Drug Dev Ind Pharm, 2000; 26: 965-969.
57. Bhalchandran M. Habade*[1].Vidya shrri kamble, K.Ramesh, Milind P.Wagh; Formulation and Evaluation of Floating Drug Delivery System of Ciprofloxacin; IJPRD, 2011; 3(11).

58. Agyilirah GA, Green M, DuCret R, Banker GS, "Evalua tion of the gastric retention properties of a cross-linked polymer coated tablet versus those of a non-disintegrating tablet",Int. J. Pharm, 1991; 75: 241–247.
59. Kawashima YN, Takeuchi T, Hino H, Itoh TY, "Gravity and eating on gastric emptying of slow-release Hollow microspheres for use as a floating controlled drug capsules", New Engl. J. Med, 1981; 304: 1365–1366.
60. Gu TH, Chen SX, Zhu JB, Song DJ, Guo JZ, Hou HM, "Pharmacokinetics and pharmacodynamics of diltiazem floating tablets", Chung Kuo Yao Li Hsueh Pao, 1992; 13: 527–531
61. Machida Y, Inouye K, Tokumura, T, Iwata M, Nagai T, "Preparation and evaluation of intragastric buoyant preparations", Drug Des. Del, 1989; 4: 155–161.
62. Yuasa H, Takashima Y, Kanaya Y, "Studies on the development of intragastric floating and sustained release preparation. I. Application of calcium silicate as a floating carrier", Chem. Pharm. Bull, 1996; 44: 1361–1366.
63. Dinarvand R, Mirfattahi S, Atyabi F, "Preparation, characterization and in vitro drug release of isosorbide dinitrate microspheres", J Microencapsul, 2002; 19(1): 73-81.
64. Ichikawa M, Kato T, Kawahara M, Watanabe S, Kayano M, "A new multiple unit oral floating dosage system. II: In vivo evaluation of floating and sustained-release characteristics with p-aminobenzoic acid and isosorbide dinitrate as model drugs", J. Pharm. Sci, 1991; 80: 1153–1156.
65. Miyazaki S, Yamaguchi H, Yokouchi C, Takada M, Hou WM, "Sustained-release and intragastric-floating granules of indomethacin using chitosan in rabbits", Chem. Pharm. Bull, 1988; 36: 4033–4038.
66. Watanabe K, Machida Y, Takayama KI, Nagai MT, "Preparation and evaluation of intragastric floating tablet having pH independent buoyancy and sustained release Property", Arch. Pract. Pharm, 1993; 53: 1–7.
67. Inouye K, Machida Y, Sannan T, Nagai T, "Buoyant sustained release granules based on Chitosan", Drug Des. Del, 1989; 4: 55–67.
68. Machida Y, Inouye K, Tokumura, T, Iwata M, Nagai T, "Preparation and evaluation of intragastric buoyant preparations", Drug Des. Del, 1989; 4: 155–161.
69. Ichikawa M, Kato T, Kawahara M, Watanabe S, Kayano M, "A new multiple unit oral floating dosage system. II: In vivo evaluation of floating and sustained-release characteristics with p-aminobenzoic acid and isosorbide dinitrate as model drugs", J. Pharm. Sci, 1991; 80: 1153–1156.

70. Inouye K, Machida Y, Sannan T, Nagai T, "Buoyant sustained release granules based on Chitosan", Drug Des. Del, 1989; 4: 55–67.
71. Rouge N, Cole ET, Doelker E, Buri P, "Buoyancy and drug release patterns of floating minitablets containing piretanide and atenolol as model drugs", Pharm. Dev. Technol, 1998; 3: 73–84..
72. Agyilirah GA, Green M, DuCret R, Banker GS, "Evalua tion of the gastric retention properties of a cross-linked polymer coated tablet versus those of a non-disintegrating tablet", Int. J. Pharm, 1991; 75: 241–247.
73. Chueh HR, Zia H, Rhodes CT, "Optimization of sotalol floating and bioadhesive extended release tablet formulaltions", Drug Dev. Ind. Pharm, 1995; 21: 1725–1747.
74. Desai S, Bolton S, "Floating controlledrelease drug delivery systems: in vitro–in vivo Evaluation", Pharm. Res, 1993; 10: 1321–1325.
75. Deshpande AA, Shah NH, Rhodes CT, Malick W, "Development of a novel controlled-release system for gastric retention", Pharm. Res, 1997; 14: 815–819.
76. Sheth PR, Tossounian J, "The hydrodynamically balanced system (HBSE): a novel drug delivery system for oral use", Drug Dev. Ind. Pharm, 1984; 10: 313–339.
77. Menon A, Ritschel WA, Sakr A, "Development and evalua tion of a monolithic floating dosage form for furosemide", J. Pharm. Sci, 1994; 83: 239–245.
78. Oth M, Franz M, Timmermans J, Mo¨es A, "The bilayer floating capsule: a stomach directed drug delivery system for misoprostol", Pharm. Res, 1992; 9: 298–302.
79. Asrani K, "Evaluation of bioadhesive properties of poly (acrylic acid) polymers and design of a novel floating bioadhesive drug delivery system", Doctoral thesis, St. John's University, Jamaica, NY, 1994.
80. Sawicki W, Janicki S, Pietkiewicz P, "Method of obtaining floating tablets with verapamil hydrochloride", Farm. Pol, 1997; 53: 698–701.
81. Chen GL, Hao WH, "In vitro performance of floating sustained-release capsule of Verapamil", Drug Dev. Ind. Pharm, 1998; 24: 1067–1072.
82. Erni W, Held K, "The hydrodynamically balanced system: a novel principle of controlled drug release", Eur. Neurol, 1987; 27: 21S–27S.
83. Khattar D, Ahuja A, Khar RK, "Hydrodynamically balanced systems as sustained release dosage forms for propran formulaolol hydrochloride", Pharmazie,1990; 45: 356–358.
84. Simoni P, Cerre C, Cipolla A, Polimeni C, Pistillo A, Ceschel G, Roda E, Roda A, "Bioavailability study of a new, delivsinking, enteric-coated ursodeoxycholic acid Formulation", Pharmacol. Res, 1995; 31: 115–119.

85. Sheth PR, Tossounian J, "The hydrodynamically balanced system (HBSE): a novel drug delivery system for oral use", Drug Dev. Ind. Pharm, 1984; 10: 313–339.
86. Gustafson JH, Weissman L, Weinfeld RE, Holazo AA, Khoo KC, Kaplan SA. "Clinical Bioavailability Evaluation of A Controlled Release Formulation of Diazepam, J. Pharmacokinetic", Biopharm, 1981; 9: 679–691.
87. Coupe AJ, Davis SS, Wilding IR, "Variation in Gastroin Behavior Intestinal Transit of Pharmaceutical Dosage Forms In Healthy Subjects", Pharm. Res, 1991; 8: 360–364.