Review Article

Gastro Retentive Drug Delivery System: A Novel Approach for Prolong Therapeutic Activity

Pratiksha Kaikade*, Sheelpriya Walde, Shital Chavan, Anand Purohit
Department of Quality Assurance, Gurunanak College of Pharmacy, Nagpur, India.
***Corresponding author's E-mail:** pratikshakaikade0@gmail.com

Received: 11-03-2023; **Revised:** 23-05-2023; **Accepted:** 30-05-2023; **Published on:** 15-06-2023.

ABSTRACT

Gastro-retentive drug delivery systems have a particular emphasis on oral controlled release and site-specific drug delivery systems, which have generated a significant amount of interest in the pharmaceutical industry in an effort to improve therapeutic action. The idea for a revolutionary drug delivery system emerged as a means of resolving issues with formulations and drug molecules' physicochemical qualities. Gastro retentive drug delivery system aims to target site-specific drug release for local or systemic effects in the stomach by extending the duration, or gastric residence time, of any therapeutic ingredients or drug. This method is particularly helpful for drugs with a narrow window of absorption in the upper Gastro Intestinal Tract. Several gastro-retentive drug delivery methods, including floating and non-floating systems, have been covered in this review.

Keywords: Floating system, non-floating system, gastric residence time, evaluation parameter, Gastric retention, Oral controlled release.

QUICK RESPONSE CODE →

DOI: 10.47583/ijpsrr.2023.v80i02.002

DOI link: http://dx.doi.org/10.47583/ijpsrr.2023.v80i02.002

INTRODUCTION

The ability to delay, prolong, and control the emptying time is a crucial asset for dosage forms that remain in the stomach longer than conventional dosage forms since gastric emptying is a highly variable process. Designing a controlled release system involves many challenges in order to improve bioavailability for improved absorption. One of these challenges is the inability to keep the dosage form in a certain region of the digestive system. Drug absorption from the gastrointestinal system is a complex process that depends on a number of factors. It is commonly accepted that the period of the drug remaining in contact with the small intestine influences how much of it gets absorbed.[1]

The most feasible and preferable method of distribution to systemic circulation is oral administration. The pharmaceutical industry has recently shown a raise interest in oral controlled release drug delivery to achieve better therapeutic benefits such convenience of dosage administration, patient compliance, and formulation flexibility. Drugs with short biological half-lives and fast absorption from the Gastro Intestinal Tract (GIT) are removed from the bloodstream rapidly. These drugs must be dosed frequently to have a therapeutic effect. To get around these restrictions, oral sustained controlled release formulations have been developed in order to release the drug gradually into the gastrointestinal tract and sustain a stable drug concentration in the systemic circulation for an extended period of time. Such a drug delivery would remain in the stomach after oral administration and release the drug under controlled environments so that the drug could be constantly given to its absorption site in the GIT.[2]

By employing the mechanisms of mucoadhesion[3] flotation, sedimentation, expansion, changed shape systems, or concurrently implementing pharmacological agents[4-6] that prolong stomach emptying, solid dosage forms can be regulated gastric retention. These methods have led to a detailed description of the classification of floating drug delivery systems (FDDS). Scientists have talked about evaluating FDDS in vivo and in vitro to determine how effective the system is. There have been a number of recent contexts published demonstrating the effectiveness of such approaches for drugs with bioavailability issues. Due to the demand for gastro-retentive dosage forms (GRDFs), there have been significant efforts made in both academia and industry to create such a drug delivery mechanism. The gastric emptying rate is unaffected by the buoyancy of floating drug delivery systems since their bulk density is lower than that of gastric fluids. The drug is released from the stomach gradually and at the desired pace while the system is floating on the gastric content. As a result, the GRT rises and the variation in plasma drug concentrations is effectively controlled. Several FDDS utilizing development and sustainability, with their own benefits and drawbacks, has been designed. Examples are hollow microspheres, raft-forming systems, single- and multiple-unit hydrodynamically balanced systems (HBS). The development of GRDDS using natural polymers, which has lately emerged as the industry's preferred methodology, is the subject of the current review. Natural

polymers are a reliable choice for drug administration in the oral cavity. Biological characteristics including non-toxicity, biocompatibility, and biodegradability are also important.[7]

PHYSIOLOGY OF THE STOMACH

The stomach, esophagus, duodenum, jejunum, and ileum comprise up the small intestine, which is a nine-meter-long tube that travels through the centre of the body from the mouth to the anus. The large intestine is also a part of the intestinal mucosa (consisting of the cecum, appendix, colon, and rectum). The majority of the gastrointestinal tract's length, from the esophagus to the anus, is covered by the same general structure, with some changes for each specific area. An organ having storage and mixing capabilities is the stomach. The antrum is where the contents of the stomach are mixed and crushed. The duration of the phases is determined by the amount of the hormone motilin in the blood. Every 90–120 minutes during the inter-digestive or fasting stage, an MMC wave travels from the stomach throughout the GI system. Four phases compose a complete cycle; they start at the lower esophageal sphincter/gastric pacemaker, spread over the entire stomach, the duodenum, and jejunum, and end at the ileum. Phase III is known as the "housekeeper wave" because the strong contractions during this phase tends to clear the stomach of its indigestible waste and fasting contents. The MMC cycle is abruptly broken by the administration and subsequent consumption of food, allowing the digestive phase to proceed. The undigested food is initially stored in the upper section of the stomach, where it is gradually compacted by phasic contractions. In addition to a meal being consumed, the digesting or fed state is shown. As long as the food remains within the stomach, it is continuous and resembles the fasting Phase II.

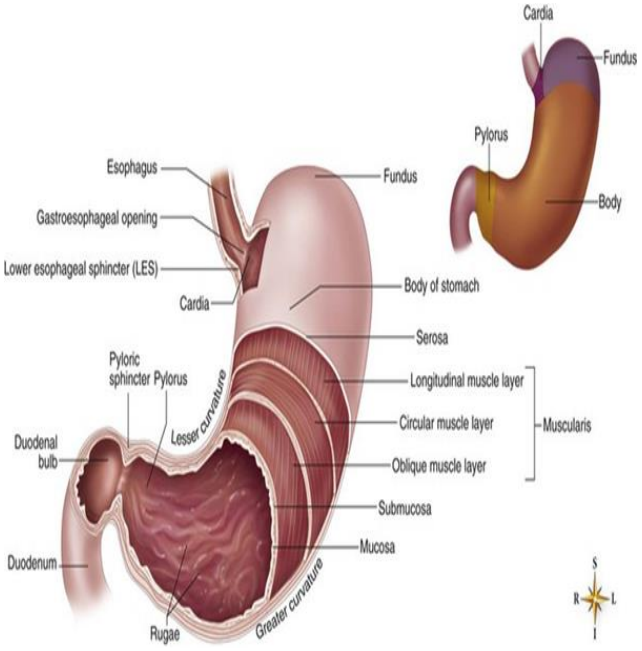

Figure 1: Physiology of stomach[9]

During the feeding pattern, the stomach retains massive things, but Phase III of the inter-digestive MMC allows them to pass. It is believed that the feeding pattern or the presence of food improves the stomach's screening efficiency (i.e., its capacity to crush food into smaller pieces).[8] (fig1 & fig2)

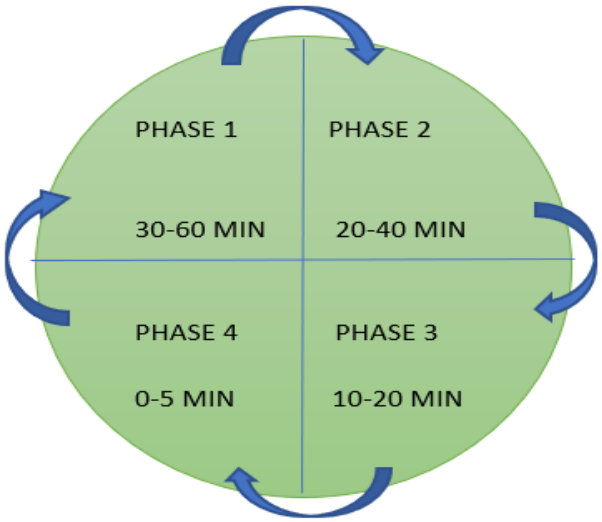

Figure 2: Motility pattern of GIT

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM: [10-18]

A) EFFERVESCENT SYSTEMS:-

These are manufactured using swellable polymers like methylcellulose and chitosan, as well as different effervescent agents like sodium bicarbonate, tartaric acid, and citric acid. When these materials are combined with the stomach's acid, co2 is released and gas is trapped in the swollen hydrocolloids, offering the dosage form buoyancy. (fig 3).

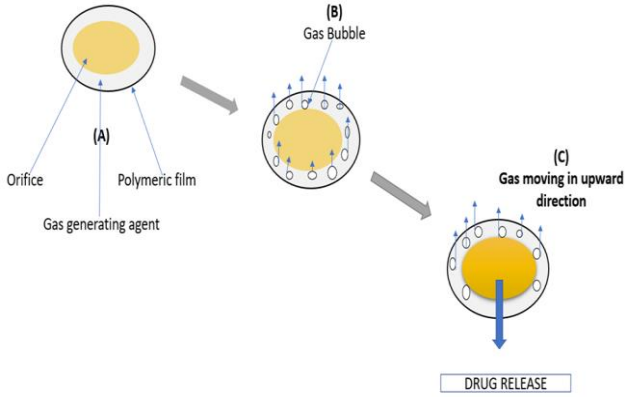

Figure 3: Effervescent floating drug delivery system

1) Volatile Liquid Containing System:

By including an inflatable chamber with a liquid (ether, cyclopentane) that gasifies at body temperature to induce the inflammation of the chamber in the stomach, a drug delivery system's GRT can be maintained. The apparatus might additionally include a bio-erodible plug consisting of PVA, polyethylene, or another material that eventually

dissolves and causes the inflatable chamber to release gas and collapse after a set amount of time, allowing the inflatable systems to instantaneously eject from the stomach.

Intragastric Floating Gastrointestinal Drug Delivery System

Because of the floating chamber, which may be a vacuum or filled with air or a harmless gas, and the drug reservoir being enclosed inside a microporous compartment, this system can be designed to float in the stomach.

Inflatable Gastrointestinal Delivery System

These systems include an inflatable chamber filled with liquid ether that, when heated to body temperature, gasifies and causes the chamber to inflate in the stomach. These systems are made by filling the chamber with the drug reservoir, which may be a polymeric matrix that has been impregnated with the drug, and then encasing it in a gelatin capsule. Upon oral administration, the capsule dissolves and the drug reservoir and inflated chamber are released. The drug reservoir is automatically retained and inflated into the stomach fluid by the inflatable chamber.

2) Gas Generating System:

In these systems, carbonates/bicarbonates salts and citric/tartaric acid undergo effervescent reactions that release CO2, which is then retained in the gelling matrix of the systems. Hence, it will have a lower specific gravity and will float above the gastric juice.

***I) Floating Pills*:**

These systems are composed of two layers: an outside swellable polymeric membrane and an inside effervescent layer containing tartaric acid and sodium bicarbonate. To prevent tartaric acid and sodium bicarbonate from coming into contact physically, the inner layer is further split into two sublayers. This pill sinks to the bottom of the buffer solution when submerged in it at 37 °C, and the buffer solution enters the effervescent layer through the outer swellable membrane. When tartaric acid and sodium bicarbonate combine, carbon dioxide is produced, which causes swollen pills or balloons to form. The delivery mechanism traps the carbon dioxide produced, which causes the device to float. These systems were reported to entirely float within 10 minutes, and exhibit good flotational properties irrespective of pH, medium viscosity, and controlled drug release.

***II) Floating Capsules*:**

A mixture of sodium alginate and sodium bicarbonate is used to make floating capsules, which float when exposed to an acidic environment because the carbon dioxide they produce becomes trapped in the hydrating gel network.

***III) Floating Systems with Ion Exchange Resins*:**

By combining the beads with sodium bicarbonate solution, ion exchange resin that is loaded with bicarbonate is used to create these systems. To prevent the abrupt loss of carbon dioxide, a semi-permeable barrier was placed around these loaded beads. When in contact with gastric contents, resin beads exchange chloride and bicarbonate ions, which produces carbon dioxide and lifts them to the surface where they form a floating layer that releases the medicine at a predetermined time.

IV) Tablet

A) Intragastric Single Layer Floating Tablets or Hydrodynamically Balanced System

Because these formulations float in the stomach due to their lower bulk density than gastric fluids, the gastric emptying rate is increased for a longer time. They are created by thoroughly combining the medication and gas (CO2) producing agents in the matrix tablet. After the medication has been completely freed from the floating system and the residual system has been emptied from the stomach, the drug is released slowly and at the chosen rate. As a result, the stomach residence duration lengthens and is increased, and fluctuations in plasma drug concentration are better managed.

B) Bi-Layer Tablet

Bilayer tablets can also be created by placing a gas-generating matrix in the first layer and placing the medicine in the second layer for a prolonged release.

C) Triple Layer Tablet

A three-layer tablet also has a first swellable floating layer, a second layer that releases two medications over time, and a third layer that dissolves quickly.

B) NON-EFFERVESCENT SYSTEMS:

After swallowing, this type of system swells uncontrollably due to the ingestion of gastric fluid to the point where it hinders its exit from the stomach. Since they tend to stay ensconced near the pyloric sphincter, these systems may be referred to as "plug-type systems." One of the processes used to create these dosage forms involves mixing the drug with a gel that, when combined with the drug after oral administration, swells in contact while maintaining a bulk density of less than 1. This is based on the polymer swelling process or bio adhesion to the mucosal layer of the gastrointestinal tract. This is based on the polymer swelling process or bio adhesion to the mucosal layer of the gastrointestinal tract. The excipients that create gels the most frequently are those made of polycarbonate, polyacrylate, polystyrene, etc. At the surface of the dosage form, a gel first forms when the hydrocolloid begins to hydrate. The rate of solvent and drug diffusion into and out of the dosage form is then controlled by the resulting gel structure. The following are the different types of this system:

Single Layer Floating Tablets

This can be created by combining the drug closely with a hydrocolloid that forms a gel when it comes into contact with stomach juice and maintains a bulk density of less

than 1. These dose forms float due to the air trapped by the inflated polymer.

Bilayer Floating Tablets

A bilayer tablet has two layers: an immediate release layer that releases the first dosage from the system and a sustained release layer that absorbs gastric fluid and keeps the bulk density below 1, keeping the bilayer buoyant in the stomach (Fassihi and Yang developed a zero-order controlled release). One medication layer and at least two barrier layers make up a multilayer tablet. The tablet swells when it comes into contact with the aqueous medium, and all of the layers are constructed of erodible, swellable polymers. The barrier layers on the pill dissolved, exposing more of the medication as a result. If a gas developing agent is applied to either of the barrier layers, the pill will float, which will increase its retention in the patient's stomach.

Colloidal Gel Barrier Systems

It comprises medication made with hydrocolloids that form a gel and are designed to float on stomach contents. This system contains a significant amount of one or more hydrocolloids of the cellulose type that create highly swellable gels. The hydrocolloids in the system hydrate and create a colloidal gel barrier around the gel surface when they come into touch with stomach fluid. A density less than unity is maintained by the air retained by the inflated polymer, giving the dose forms buoyancy.

Microporous Compartment System

The establishment of this technology is the encapsulation of the drug reservoir inside a microporous compartment with an opening running along the top and bottom walls. To avoid any unintentional direct contact of the undissolved drug with the gastric mucosal surface, the peripheral walls of the drug reservoir compartment are totally sealed. The delivery system floats over the gastric contents of the stomach due to the air-filled flotation chamber. Via the holes, gastric fluid enters, dissolves the medication, and transports it continuously across the intestine for absorption.

Alginate Beads

The use of freeze-dried calcium alginate has allowed for the creation of multi-unit floating dosage forms. By dripping sodium alginate solution into an aqueous solution of calcium chloride, calcium alginate can be precipitated to form spherical beads that are about 2.5 mm in diameter. The beads are split into individual pieces, quickly frozen in liquid nitrogen, and then freeze dried at -40°C for 24 hours. This creates a porous structure that can sustain a floating force for up to 12 hours. Yet, multiple-unit dosage forms seem to be more appropriate because they are said to lessen the variability in absorption across individuals and the likelihood of dose-dumping.

Hollow Microspheres

Hollow microspheres with drug-loaded exterior polymer shelves were created using a unique emulsion solvent diffusion technique. In an agitated aqueous solution of PVA that was thermally regulated at 40°C, the drug's ethanol: dichloromethane solution and enteric acrylic polymers are added. Dichloromethane's evaporation created the gas phase in the dispersed polymer droplet, which then established an interior cavity in the drug-filled polymer microspheres. For more than 12 hours, the micro balloons floated constantly over the surface of an acidic dissolving medium that contained surfactant. The medication that was discharged had a higher pH of 7.2 than pH 6.8. Ibuprofen-loaded hollow microspheres (micro balloons) were created using a brand-new emulsion-solvent diffusion technique.

FACTORS AFFECTING GASTRIC RETENTION: [19]

1) Physiological Factors:-

A) Density:

The dosage form buoyancy, which depends on the density, determines how long food remains in the stomach. Because it is floating away from the pyloric sphincter and has a density lower than that of gastric fluids, the dose unit is kept in the stomach for a long time. It has been reported that the density is less than 1.004g/ml, or less than the density of gastric contents.

B) Size:

According to reports, dosage form units with a diameter of more than 7.5mm have a higher GRT than those with a diameter of 9.9mm.

C) Shape of Dosage Form:

When compared to other designs, tetrahedron and ring-shaped devices with flexural moduli of 48 and 22.5 kilo pounds per square inch (KSI) exhibit greater GRT 90% to 100% retention at 24 hours.

2) Biological Factors:

Fed or Unfed State: The migrating myoelectric complex (MMC), which happens every 1.5 to 2 hours, or times of intense motor activity are what defines GI motility under fasting settings. The undigested matter is removed from the stomach by the MMC. Yet, MMC is delayed and GRT takes much longer in the federal state.

Nature of Meal: Feeding the stomach with indigestible polymers or salts of fatty acids might cause the stomach's motility pattern to change to a fed state, slowing down gastric emptying and extending medication release.

Caloric Content: A meal rich in proteins and lipids can extend GRT by 4 to 10 hours.

Frequency of Feed: Due to the low frequency of MMC, the GRT can increase by more than 400 minutes when multiple meals are given instead of only one.

Gender: Regardless of weight, height, or body surface, the mean ambulatory GRT in males (3.40.6 hours) is lower than that in their age- and race-matched female counterparts (4.61.2 hours).

Age: In comparison to younger participants, older people had lower stomach emptying times. Transit times through the stomach and intestines can vary both within and across subjects. Elderly persons, particularly those over 70 years old, have GRTs that are much longer.

Posture: Depending on the patient's ambulatory position—lying down or standing up—GRT can change. Due to the floating form's ability to stay above the gastric contents, regardless of size, it is protected from postprandial emptying when it is in an upright position. During prolonged retention in supine individuals, bigger dosage forms are used. Somewhere between the stomach's smaller and larger curvature, the gastric retention of floating forms seems to remain buoyant. The peristatic movements that push the stomach's contents towards the pylorus when these units move distally may sweep them away, significantly lowering GRT in comparison to upright people.

Concomitant Drug Administration: An oral dose form's stomach residence duration is impacted by anticholinergic drugs like atropine and propantheline, opioids like codeine, and prokinetic drugs like metoclopramide and cisapride.

Table 1: Gastro-Retentive Products Available in the Market

Marketed product (brand names)	Active pharmaceutical ingredient	Developed products
Prazopress xl	Prazosin hydrochloride	Effervescent and swelling based floating system
Tramadol LP	Tramadol	Floating system
Madopar	Levodopa and benserazide	Floating capsule
Xifaxan	Rifaximin	Bio-adhesive tablets
Coreg CR	Carvedilol	Gastro retentive with an osmotic system
Glumetza	Metformin hydrochloride	Polymer based swelling technology
Gabapentin GR	Gabapentin	Polymer based swelling technology

Merits of Gastro Retentive Drug Delivery System[20]

1. Improved drug absorption because of increased GRT.
2. Controlled drug delivery
3. Enhanced bioavailability
4. Reduced dosing frequency
5. Better patient compliance
6. Minimizing fluctuations of drug concentration

Demerits of Gastro Retentive Drug Delivery System [20]

1. The drugs which cause gastric irritation in the stomach is not desirable. eg; NSAIDS.
2. The drugs having limited acid solubility eg; phenytoin.
3. The drugs which degrade in an acidic environment of the stomach eg : Insulin
4. The drugs go through significant first pass metabolism. eg; Nifedipine.
5. For drug delivery to float on the surface & work efficiently in the stomach requires a high level of fluid.

CONCLUSION

To achieve prolonged release and limit the region of drug release to the stomach, numerous medications have recently been designed and developed as floating drug delivery systems. The concept of buoyant preparation offers an efficient method for extending the dosage form's remains in the stomach and ensuring prolonged medication release. The currently available polymer mediated non-effervescent and effervescent FDDS, which were developed using delayed stomach emptying and buoyancy principles, seem to be a very useful method for modifying controlled oral drug delivery. The most crucial factor that must be taken into consideration when creating a floating drug delivery system is that the dosage form's density must be lower than that of stomach fluid.

ACKNOWLEDGEMENT: The author is thankful to all the contributors in compiling and preparing a manuscript for this article.

REFERENCES

1. Hirtz J. The git absorption of drugs in man: a review of current concepts and methods of investigation. Br J Clin Pharmacol. 1985;19:77SY83S.

2. Streubel A, Siepmann J. Bodmeier R. Multiple unit Gastroretentive drug delivery: A new preparation method for low density microparticles. J Microcapsule 2003;20:329-47.

3. Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage forms. J control Release 2003:90:143-62.

4. Deshpande AA, Shah N, Rhodes CT, Malik W. Development of novel controlled release system for gastro retention. Pharm res 1997:14:815-19.

5 . Park K. Enzyme digestible swelling as platforms for long term oral drug delivery: synthesis and characterization. Biomaterials 1988:9:435.

6. Radi Hejazi, Mansoor Amiji. Chitosan based gastrointestinal delivery systems. Journal of Controlled Release 2023;89:151-165.

7. Mojaverian P, Ferguson RK, Vlasses PH. Estimation of gastric residence time of the Heidelberg capsules in humans: effect of varying food composition, gastroetrenology.1885;89:392Y397.

8. Y. Madhusudan Rao, A. V. Jithan, Advances in Drug Delivery, Vol. II, Pharma. Med. Press, Hyderabad (2011).

9.https://www.google.com/search?q=physiology+of+stomach&rlz=1C1RXQR_enIN1022IN1022&source=lnms&tbm=isch&sa=X&ved=2ahUKEwi51vyZv5L-AhUbTWwGHYx-B4cQ_AUoAXoECAIQAw&biw=1536&bih=746&dpr=1.25#imgrc=R6A0FtcRV8LyZM

10. Chawla G, Gupta P, Koradia V and Bansal AK. Gastro retention: A Means to Address Regional Variability in intestinal drug Absorption, Pharmaceutical technology. 2003; 27(2):50-68.

11. Chandel A, Chauhan K, Parashar B, Kumar H and Arora S Floating drug delivery systems: A better approach. International Current Pharmaceutical Journal. 2012; 1(5):110-118.

12. Rubinstein A and Friend DR. Specific delivery to the gastrointestinal tract, in: A. J. Domb (Ed.), Polymeric sitespecific Pharmacotherapy, Wiley, Chichester. 1994; 282-283.

13. Vyas SP and Roop KK. Controlled Drug Delivery Concepts and Advances, First Edition, New Delhi. 2002; 196- 217.

14. Jain NK. Progress in Controlled and Novel Drug Delivery Systems. First Ed. CBSS. Gopalakrishnan. Journal of Pharmaceutical Science and Technology. Publishers and Distributors, New Delhi, Bangalore. 2004; 3(2):84-85.

15. Goyal M, Prajapati R, Purohit KK and Mehta SC. Floating drug delivery system, Journal of current pharmaceutical research. 2011; 5(1): 7-18.

16. Klausner EA, Sara E, Lavy E, Friedman M and Hoffman A. Novel levodopa gastro-retentive dosage form: *in-vivo* evaluation in dogs. J. Control. Release. 2003; 88:117-126.

17. Kale RD and Tayade PT. A multiple unit floating drug delivery system of Piroxicam using Eudragit polymer. Indian J PharmScie. 2007; 69(1):120- 123.

18.Sangekar S. Evaluation of effect of food and specific gravity of the tablets on gastric retention time. Int J Pharm. 1987; 35(3):34-53.

19. Kamalakkannan V, Pyratchikody A, Viswanadhan VP, "Enhancement of Drugs bioavailability by Floating Drug Delivery System-A Review.'' Int. J. Drug Delivery. 2011;3(4): 558-570.

20.Geetha A, Rajendra kumar J. A Review on floating drug delivery system. Int. J. Pharmaceutical Research & Biomedical Analysis, 2012;1(1):1-13.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.