



Gastro-Floating Drug Delivery Systems - A Review

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ABSTRACT

Sustained release and site targeted drug delivery system have been an interesting research topic in pharmaceutical sector to maximize therapeutic benefits and patient adherence to therapy. Gastro-Floating Drug Delivery System (GFDDS) is one of the numerous mechanisms to prolong gastric residence time, thereby achieving site-targeted drug release in the stomach for local or systemic effects. This method is useful for medications with narrow absorption window in the upper part of gastro intestinal tract (GIT). Several approaches to GFDDS, including effervescent and non-effervescent methods including the sublimation and sintering techniques used in the formulation of GFDDS with no floating lag time have been discussed in this review. This update also gives an overview of advantages, disadvantages and commercial products of GFDDS.

Introduction

Gastro-floating drug delivery systems (GFDDS) are low-density formulations with adequate buoyancy to float over gastric contents and remain buoyant in the stomach for prolonged periods without interfering with gastric emptying rate.¹ They have a lower bulk density than the gastric content so the system remains afloat in the stomach over a long period of time without interfering with the gastric contents.² They are also known as low-density systems and are indicated for medications with Narrow Absorption Window (NAW) in the upper part of alimentary canal, medications that exert local action in the stomach and duodenum, drugs that are not soluble/stable at alkaline *pH*, medications that exert their pharmacological actions in the stomach, e.g., antibiotics used for *Helicobacter pylori* eradication in the management of peptic ulcer and medications that are not stable in the intestine or colonic environment.³ GFDDS, which are formulated to exhibit an increased gastric retention time, have been a subject of interest in terms of their suitability for controlled drug delivery.⁴ Several efforts have been made to formulate a floating system that could extend gastric residence time, thereby aiming at site-specific drug release in the stomach and duodenum for local or systemic effects. The dosage form floats in the gastrointestinal fluid due to its less bulk density compared to that of the aqueous medium.⁵ Various methods have been applied to levitate the drug delivery system, such as gas-generating, gas-filled floatation, and raft-forming systems.⁶ However, the available GFDDS have some limitations such as the fact that the gas-generating mechanism takes time to float (floating lag time). Besides, the formulation process of the pre-gas-filled system is complicated.⁷ Consequently, a novel and non-complicated technique offering short or no floating lag time has been developed^[8]. Oh *et al.*⁸ prepared highly porous gastrofloating metformin tablets from sublimation technique by using camphor as a sublimation material. They found that the formulated

floating tablets floated and remained buoyant for over 24 h and had zero floating lag time. However, as the quantity of camphor in the tablet matrix increased, the hardness of the tablet decreased after sublimation. The sublimation and sintering technique which are examples of a non-effervescent GFDDS are easy to formulate and the system can float instantaneously. Furthermore, these techniques also have the potential for industrial production due to the use of a few formulation steps and affordable pharmaceutical excipients.⁵

Sintering is the compaction of adjacent particle surfaces in a powder heap, by the use of heat.⁹ Conventional sintering technique involves the heating of solid material in a regulated environment at a temperature lower than its melting point under atmospheric pressure.¹⁰

Methodology

The search criteria used in this article include recent advances in gastrofloating drug delivery system, effervescent and non-effervescent floating drug delivery systems, the various methods of achieving gastroretention of dosage forms in the GIT, sintering technique, *in vitro* and *in vivo* analysis of floating dosage forms. The search was done by a thorough review of publications, journals and textbooks that covered this particular field of pharmaceutics and the search engine used in this study is Google Scholar.

Advantages of GFDDS

The GFDDS has the following advantages:

- i) It is appropriate for medications with pH dependent absorption from the stomach e.g. verapamil, diazepam, captopril, furosemide, etc.¹¹
- ii) Targeted delivery of drugs at the stomach and duodenum makes it appropriate for management of diseases of the region locally. Examples include anti-ulcer drugs, antacids and antibacterial for *Helicobacter pylori* infection.¹²
- iii) Controlled drug delivery and reduced dosing frequency enhance patient adherence to therapy.
- iv) It is suitable for medications that are degraded by enzymes in the small and large intestine e.g. ranitidine hydrochloride.¹³
- v) Increased bioavailability: The bioavailability of medications that their absorption occurs in the stomach and duodenum such as levodopa and riboflavin has been

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- significantly increased than that of the conventional dosage form.¹⁴
- vi) There is no fluctuation in plasma drug level and it maintains the maximum plasma and tissue therapeutic concentration over a prolonged time interval. This avoids sub-therapeutic as well as toxic concentrations hence minimising the risk of treatment failure and unwanted adverse effects.
 - vii) Easy to administer hence enhances patient adherence and easy to formulate using simple equipment and methods.⁴

Limitations of GFDDS

- i) It is not appropriate for medications that their absorption takes place in the intestine.
- ii) It is not appropriate for medications that are not stable in acidic environment.
- iii) It requires sufficiently high level of fluids (water) in the stomach to remain buoyant and work efficiently.
- iv) It is not appropriate for medications that irritate the gastric mucosa e.g. aspirin.
- v) It is not appropriate for medications that are not stable/soluble in the stomach.
- vi) Gastric retention is affected by several factors such as pH, gastric motility and presence of food. Hence, the formulation must be able to resist the grinding and churning force of peristaltic wave of the stomach.
- vii) Retrieval of medication from the system is difficult when toxicity, poisoning or hypersensitivity reaction occur.³

Factors affecting gastric residence time of GRDDS

Gastric emptying process is affected by several factors, which may adversely affect the rate of drug absorption and release; it is important to formulate a drug delivery system that displays an extended gastric retention time and a drug release kinetic that is not dependent on patient related variables.¹⁵

a) Formulation factors

- i) *Size of tablets*: Retention of floating dosage forms in the stomach is dependent on the size of the tablets. Tablets with small sizes are emptied from the stomach during the digestive phase, but large ones are swept away during the house keeping waves.¹⁶
- ii) *Density of tablet*: Density is the major factor influencing the gastric residence time of floating dosage forms. A buoyant dosage form having a density less than that of the gastric fluid floats, since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a long period of time.
- iii) *Shape of the Tablet*: The shape of the floating dosage form is one of the factors that affect its gastric retention time. Several shapes such as pellet, disk, ring, tetrahedron, string etc. have been investigated *in vivo* for their gastric retention ability. The tetrahedron rings displayed about 98% retention at 24 hours.¹⁷
- iv) *Viscosity Grade of polymer*: Drug release and floating properties of FDDS are greatly affected by the viscosity of polymers and their interaction. Polymers with low viscosity (e.g. hydroxypropylmethylcellulose K100LV) were found to be more useful than those with high viscosity (e.g. hydroxypropylmethylcellulose K4M) in improving floating properties. Also, a decrease in drug release was seen with an increase in polymer viscosity.¹⁸

b) Idiosyncratic factors

- i) *Gender*: Women have slower gastric emptying time than men. The average ambulatory gastroretention time in males is 3.4 ± 0.4 hours compared with that of females (4.6 ± 1.2 hours), irrespective of the height, weight and body surface.¹⁹
- ii) *Posture*:
 - a) *Upright position*: An upright position protects floating forms against postprandial emptying because the floating dosage form remains above the gastric content irrespective of its size.²⁰ Floating dosage forms display extended and more reproducible gastroretention while the conventional dosage forms sink to the lower part of the distal stomach from where they are expelled through the pylorus by antral peristaltic movement.²¹
 - b) *Supine Position*: This position does not offer any reliable protection against early and erratic emptying. In supine subjects, large dosage forms (both conventional and floating) stay in the stomach for prolonged period of time. The gastric retention of floating dosage forms remains buoyant anywhere between the less and greater curvature of the stomach. On

moving distally, these units may be expelled by the peristaltic movements that propel the gastric contents towards the pylorus, leading to significant decrease in gastroretention compared with upright subjects.²²

- iii) *Age*: The elderly experience low gastric emptying time compared to young subjects. Intra- and inter-individual differences are also observed in gastric and intestinal transit times. Elderly people (70 years and above) have a significantly longer gastroretention.²³
- iv) *Fasting or fed state of the stomach*: During the fasting state, an inter-digestive series of electrical events occur, which cycle both through stomach and intestine every 2 to 3 hours. In the fed state this cycle takes a longer time, hence the gastric emptying rate is reduced.^{23, 29}
- v) *Intake of food with drugs*: The nature of the food, calorie content and its frequency of intake have remarkable influence on the retention of drugs in the stomach.²⁴ Simultaneous administration of drugs such as anticholinergic agents (atropine, propantheline etc.) and the opioids delay the gastric emptying, while the prokinetic agents such as metoclopramide and cisapride increase the gastric emptying process.²⁵
- vi) *Feeding Regimen*: Gastric residence time increases in the presence of food, leading to enhanced drug dissolution of the dosage form at the optimal site of absorption. A gastroretention time of 4-10 h has been reported after a meal of fats and proteins. Biological factors such as gender, age, sleep, body mass index, posture, physical activity and disease states such as diabetes and Crohn's disease also affect GFDDS.^{26, 29}

Approaches to GFDDS

Gastro-floating drug delivery system can be divided into:

- a. Effervescent system
- b. Non-effervescent system which can be subdivided into:
 - i. Hydrodynamically balanced system
 - ii. Sintering and Sublimation systems
 - iii. Microballoons or hollow microspheres
 - iv. Alginate beads
 - v. Microporous compartment

Floating Drug Delivery System

i. Effervescent System

This system consists of the swellable polymers (e.g. chitosan) and effervescent substances such as sodium bicarbonate, cytoglycine, citric acid and tartaric acid. When the system comes in contact with gastric fluid, it releases carbon (IV) oxide causing the formulation to float in the stomach^[27]. The optimal ratio of tartaric acid and sodium bicarbonate for gas generation is reported to be 0.76:1.²⁸ This system is further divided into single unit matrix tablets or multiple unit pills. Single unit matrix tablet may be single or multilayer type. Floating system with ion exchange resins has also been reported.

ii. Non-effervescent system

In this system, gel forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene are used. After oral administration, this dosage form increases in size when it comes in contact with gastric fluids and attains a lower bulk density than that of the gastric fluid. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The swollen gel-like structure formed acts as a reservoir and allows controlled release of the drug through the gelatinous mass. Superporous hydrogels are good examples of this system. The dosage form swells significantly to several times its original volume upon contact with gastric fluid. The gastric contraction pushes the dosage form to the pylorus, but due to large size of the dosage form, the contractions slip over the surface of the system, as a result of which the dosage form pushes back into the stomach.²⁹

a. *Hydrodynamically balanced system (HBS)*: This system was first designed by Sheth and Tossounian.³⁰ HBS contains the medication with gel-forming hydrocolloids meant to remain afloat on the stomach content. This system contains one or more gel forming cellulose type hydrocolloid e.g., hydroxypropyl methyl cellulose, ethylcellulose, hydroxypropylcellulose, agar, carrageenan or alginate acid. It also contains matrix forming polymers such as polycarbophil, polyacrylate and polystyrene. When these systems come in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface.

b. *Sintering and Sublimation systems*: This system involves formulating the dosage form by incorporation of a sublimating agent such as camphor, ammonium carbonate, etc. and sintering it at a controlled temperature below the melting point of the active ingredient for a given period of time. In the process, the sublimating agent sublimates from the dosage form

creating pores or cavities thereby reducing the bulk density of the dosage form and creating the required buoyancy for the tablets to float and remain afloat.⁵

c. *Microballoons or hollow microspheres*: Microballoons, loaded with medications in their outer polymer shells are formulated by emulsion-solvent diffusion method. Ethanol: dichloromethane solution (1:1) and an acrylic polymer are transferred into an agitated aqueous solution of polyvinyl alcohol at 40°C. The gas phase generated in the dispersed polymer droplet by the evaporation of dichloromethane form an internal cavity in the microsphere of the polymer with the drug. The microballoons remain afloat continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours.³¹

d. *Alginate beads*: Freeze dried calcium alginates have been used to formulate multi-unit floating dosage forms.³² By gently adding sodium alginate solution into aqueous solution of calcium chloride, spherical beads of about 2.5 mm diameter can be produced. These beads are separated and air dried. This results in the formation of a porous system which remains buoyant in the stomach.

e. *Microporous compartment*: In this system, drug reservoir is encapsulated inside a microporous compartment having pores along its top and bottom walls. The floatation chamber containing entrapped air causes the dosage form to float over the gastric content. Gastric fluid passes through the pore, dissolves the medication and carries the dissolved medication in the stomach, duodenum and jejunum for absorption.⁴

Drug candidates suitable for GFDDS

The following are the probable drug candidates for gastro-floating drug delivery system:

- Medications that are required to exert their therapeutic action locally in the stomach: antacids, drugs used in the treatment of *H.pylori*, misoprostol etc.¹⁶
- Drugs with narrow absorption window in the stomach, duodenum and jejunum, e.g., furosemide, riboflavine-5-phosphate, ciprofloxacin, alfosin hydrochloride, ofloxacin, norfloxacin, domperidone, metformin hydrochloride, etc.³⁴
- Medications that alter normal colonic bacteria, e.g., amoxicillin trihydrate.³⁵
- Drugs that are not stable in the lower part of GIT, e.g., captopril.³⁶
- Medications that are not soluble in intestinal fluids, e.g., quinidine, diazepam
- Drugs that degrade in the colon, e.g. metronidazole, ranitidine hydrochloride.³⁷

Some GFDDS which are available in the market are presented in Table 1.

Evaluation parameters of GFDDS

Evaluation parameters of GFDDS generally include:

1. Friability

This evaluates the ability of tablets to withstand pressure due to abrasion, packaging, handling and transportation. It can also be defined as a process whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. Friability is the loss of weight of tablet in the container packaging due to breaking off of fine particles from the surface. Roche Friabilator is the apparatus used in most laboratories for the measurement of this parameter. Friability is related to the hardness of the tablet. Ten (10) tablets from each

Table 1: Commercially available products of GFDDS.

Brand Name	Active ingredients
Glumetza®	Metformin Hydrochloride
Cifran OD®	Ciprofloxacin
Madopar®	L-Dopa and Benserazide
Valrelease®	Diazepam
Topalkan®	Aluminium-magnesium antacid
Almagate FlatCoat®	Aluminium-magnesium antacid
Liquid Gaviskon®	Aluminium hydroxide
Conviro®	Ferrous sulphate
Cytotec®	Misoprostol

formulation are weighed and placed in a Roche friabilator that rotates at 25 rpm for 4 minutes. The tablets are weighed again. The difference in weight should be less than 1%.³⁸ The percentage of weight loss is calculated using the formula:

$$\% \text{ friability, } f = \left[1 - \frac{W}{W_0} \right] \times 100 \text{ -----(1)}$$

Where; W_0 = Weight of tablet before test

W = weight of tablets after test

2. Crushing Strength

This is often called hardness test. It is usually expressed as the force required to break a tablet placed between the anvil and the plunger of a hardness tester, one of which moves towards the other. The simplest instruments for measuring crushing strength are hand operated in which the tablet is held between a fixed anvil and a plunger. Examples of devices employed in this test include Monsanto tester, the Strong Cobb tester, the Pfizer tester, the Erweka tester and the Schleuniger tester. Tablet hardness usually affects drug dissolution and release as well as bioavailability. The principle of measurement involves subjecting the tablet to an increasing load until the tablet breaks or fractures. The load is applied along the radial axis of the tablet. Factors that may alter tablet hardness are changes in particle size distribution of the granulation mix and machine speed. Lubricants can also have a significant effect on the hardness when used in too high a concentration. Hardness is dependent on the tablet dimensions; thus, it will be difficult to compare the strengths of tablets of different sizes.³⁸

3. Floating Lag time

The floating properties of the dosage form should be evaluated because they influence dosage form behaviour. Floating lag time is determined in order to assess the time taken by the dosage form to rise on top of the dissolution medium after it is placed in the medium. Baumgartner *et al.*³⁹ reported a method for determining the floating lag time of a single unit system in which the dosage form is placed in a dissolution vessel previously filled with 500 ml of simulated gastric fluid without pepsin and stirred at 100 rpm.

The commonest method is the one described by Rosa *et al.*⁴⁰ This is performed by placing the tablets in a 250 mL beaker containing a known amount of simulated gastric fluid without pepsin (0.1 N HCl) maintained at $37 \pm 0.5^\circ\text{C}$. The time between introduction of the dosage form and its rising to the top of the medium is the floating lag time.

4. In vitro Buoyancy test

This measures the floating ability of the system, i.e., the time taken for the dosage form to stay afloat on the dissolution medium. It is also referred to as the floating duration. This test can be performed as part of the dissolution test. A tablet is placed in a 1 L beaker containing about 900 ml of simulated gastric fluid with no pepsin and maintained at $37 \pm 0.5^\circ\text{C}$. The time during which the dosage form remains buoyant (total buoyancy time) in the medium is then determined visually.⁴⁰

5. In vitro drug release study

The *in vitro* drug release studies of floating dosage systems are usually performed using dissolution testing apparatus. The general method of testing involves incorporating the dosage form into the simulated gastric fluid (in order to mimic the *in vivo* conditions) contained in the dissolution vessel under uniform agitation and performing the dissolution as per the standard of the pharmacopoeias. This dissolution test is the most important way to study the release of drug from a solid dosage form. Usually, an orally administered solid dosage form must undergo dissolution before it can be absorbed and transported into the systemic circulation. The cumulative amount of drug that passes into solution is measured as a function of time. The apparatus adopted is the paddle and basket assembly.⁴¹

6. Drug-excipient interaction

It is done by using Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC) and High-Performance Liquid Chromatography (HPLC). Appearance of a new peak and/or disappearance of original drug or excipient peaks indicate drug excipient interaction.

7. *In vivo* evaluation of gastric retention

Analysis of the position of the dosage form in the GIT involves an imaging technique such as γ -scintigraphy and X-ray.

- In γ -scintigraphy, a small amount of stable isotope is compounded in the dosage form during its preparation. The inclusion of a γ -emitting radio-nuclide in a formulation allows indirect external observation using a γ -camera or scinti scanner.⁴
- For X-ray, barium sulphate is used as a contrast medium. It helps to locate dosage form in the GIT by which one can predict and correlate the gastric emptying time and the passage of dosage form. In addition, gastroscopy and ultrasonography studies can be included in the *in vivo* evaluation of GFDDS. Gastroscopy comprises of per-oral endoscopy, used with a fibre optic and video systems. Ultrasonography is not routinely used in the evaluation of GFDDS. *In vivo* plasma profile can also be obtained by performing the study in suitable animal model.⁴

8. Water uptake study

It is done by immersing the dosage form in simulated gastric fluid at 37°C and determining the dimensional changes, such as diameter and thickness, at regular intervals of time. After the stipulated time, the swollen tablets are weighed and water uptake is measured in the terms of percentage weight gain, as given:

$$\text{Water Uptake} = \frac{(W_t - W_o)}{W_o} \times 100 \text{-----(2)}$$

Where; W_t and W_o are the weight of the tablet after time t and initially, respectively.

The tablets are also evaluated for content uniformity, specific gravity and pharmacokinetic properties.²⁹ For the multiple unit dosage forms like microsphere, the following tests are also essential apart from tests listed above:

- Morphological and dimensional analysis: It is done with the aid of scanning electron microscopy and optical microscopy.
- Entrapment efficiency: The drug is extracted by a suitable method and analyzed to determine the amount of drug present.
- Percentage yield of microsphere.²⁹

Conclusion

GFDDS have been explored extensively in recent years. FDDES has the potential for controlled and sustained drug delivery thereby reducing the frequency of dosing and remains useful for drugs having NAW in the stomach and/or upper part of the intestine. However, there are numerous challenges that need to be overcome such as the long floating lag time. The non-effervescent GFDDS using the sintering and sublimation technique has been able to overcome this challenge with no floating lag time.⁸

Despite this, many researches are still geared towards optimising this technique, some with success and others with failure due to unpredictability of the human GIT. Thus, to formulate a successful GFDDS, it is necessary to take into cognisance the physiological event in the GIT, selection of appropriate combinations of active ingredients and excipients and design of right formulation strategies.

Conflict of interest

The authors declare no conflict of interest.

Authors declaration

The authors hereby declare that the works presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

References

1. Yie WC. "Novel Drug Delivery System", Marcel Dekker Inc., New York. 1992; 2:1-3p.
2. Orakwe C, Airemwen CO, Uhumwangho MU. Formulation And Evaluation of Gastroretentive Floating Matrix Tablets of Metronidazole Using Khaya Ivorensis Gum. Asian J of Pharm Tech and Inn. 2015; 03(12):01-09.
3. Airemwen CO, Uhumwangho MU. Formulation and Evaluation of floating matrix tablets of metformin using acrylate methacrylate copolymer and Irvingia gabonensis gum. J Pharm and Allied Sci. 2016;13(1):2331-2343.
4. Chhetri HP, Panna T. An overview on Gastroretentive Drug Delivery System. Kathmandu Univ J Sci and Tech. 2014; 10(1):90-103.
5. Huanbutta K, Limmatvapirat S, Sungthongjeen S. Novel Strategy to Fabricate Floating Drug Delivery System Based on Sublimation Technique. AAPS Pharm Sci Tech. 2016; 17:693.
6. Pawar VK, Kansal S, Garg G, Awasthi R, Singodia D, Kulkarni GT. Gastroretentive dosage forms: a review with special emphasis on floating drug delivery systems. Drug Deliv. 2011; 18(2):97-110.
7. Hardenia SS, Jain A, Patel R, Kaushal A. Floating drug delivery systems: a review. Asian J Pharm Life Sci. 2011; 1(3):284-93.
8. Oh TO, Kim JY, Ha JM, Chi SC, Rhee YS, Park CW. Preparation of highly porous gastroretentive metformin tablets using a sublimation method. Eur J Pharm Biopharm. 2013; 83(3):460-467.
9. Raakesh P, Ashok B. Formulation development and process optimization of theophylline sustained release matrix tablet. Int J Pharm Sci. 2009; 2:30-42.
10. Tejaswini SP, Ramdas BR. A Review on sintering method in pharmaceutical sciences. Asian J Pharm Tech. 2014; 4(2):106-109.
11. Soppimath KS, Kulkarni AR, Aminabhavi TM. Development of hollow microspheres as floating controlled release systems for cardiovascular drugs: preparation and release characteristics. Drug Dev Ind Pharm. 2001; 27:507-514.
12. Whitehead L, Collett JH, Fell JT. Amoxicillin release from a floating dosage form based on alginates. Int J Pharm. 2000; 210:45-52.
13. Basit A. Colonic metabolism of ranitidine: implications for its delivery and absorption. Int J Pharm. 2001; 227:157-164.
14. Hoffman A, Stepensky D, Lavy E, Eyal S, Klausner E, Friedman M. Pharmacokinetic and pharmacodynamic aspects of gastroretentive dosage forms. Int J Pharm. 2004; 277:141-154.
15. Whitehead L, Fell JT, Collett JH, Sharma HL, Smith AM. Floating dosage forms: an *in vivo* study demonstrating prolonged gastric retention. J Contr Rel. 1998; 3:55-64.
16. Oth M, Franze M, Timmermans J, Moes A. The bilayer-floated capsule: a stomach directed drug delivery system for misoprostol. Pharma Res. 1992; 9:298-302.
17. Cargill R, Cadwell LJ, Engle K, Fix JA, Porter PA, Gardner CR. Controlled gastric emptying: Effects of physical properties on gastric residence times of non-disintegrating geometric shapes in beagle dogs. J Pharm Res. 1998; 5:533-536.
18. Li S, Lin S, Daggy BP, Mirchandani HL, Chien YW. Effect of HPMC and Carbopol on the release and floating properties of gastric floating drug delivery system using factorial design. Int J Pharm. 2003; 253:13-22.
19. Patel GM. Floating drug delivery system: An innovative approach to prolong gastric retention. J Pharm Sci Tech. 2005; 6:372-383.
20. Kellner PE, Mojaverian P, Vlases PH, Rocci ML. Effects of gender, posture and age on gastric residence time of indigestible solid: Pharmaceutical considerations. J Pharm Res. 1988; 10:639-656.
21. Timmermans J, Andre JM. Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: New data for reconsidering the controversy. J Pharm Sci. 1994; 83:18-24.
22. Chawla G, Gupta P, Koradia V, Bansal AK. Gastroretention: A Means to address regional variability in intestinal drug absorption. J Pharm Tech. 2003; 27:250-268.

23. Mojaverian P, Vlasses PH, Kellner PE, Rocci ML. Effects of gender, posture, and age on gastric residence time of indigestible solid: pharmaceutical considerations. *J Pharm Res.* 1998; 10:639-656.
24. Deshpande AA, Rhodes CT, Shah NH, Malick AW. Controlled-Release Drug Delivery Systems for Prolonged Gastric Residence: An Overview. *Drug Dev Ind Pharm.* 1996; 22:531-543.
25. Abrahamsson B, Alpsten M, Hugosson M, Jonsson UE, Sundgren M, Svenheden A, Tölli J. Absorption, Gastrointestinal Transit, and Tablet Erosion of Felodipine Extended Release (ER) Tablets. *J Pharm Res.* 1993; 10:709-718.
26. Hocking MP, Brunson ME, Vogel SB. Effect of various prokinetic agents on gastrointestinal motility. *J Pharm Sci.* 1996; 4:182-191.
27. Bennett CE, Hardy JG, Wilson CG. The influence of posture on the gastric emptying of antacids. *Int J Pharm.* 1984; 21:341-354.
28. Rao BP, Kottan NA, Snehith VH, Ramesh C. Development of gastroretentive drug delivery system of cephalexin by using factorial design. *ARS Pharm.* 2009; 50:8-16.
29. Garg S, Sharma S. Gastroretentive Drug Delivery System, Business Briefing: Pharmatech. 2003; 1:160-162.
30. Neha N. An Updated Review on Floating Drug Delivery System. *Int J Appl Pharm.* 2011; 3(1):1-7.
31. Sheth PR, Tossounian J. The Hydrodynamically Balanced System. A Novel Drug Delivery System for Oral Use. *Drug Dev Ind Pharm.* 1984; 10:313-321.
32. Kawashima Y, Niwa T, Takeuchi H, Hino T, Itoh Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. *J Pharm Sci.* 1992; 81:135-148.
33. Whitehead L, Fell JT, Collett JH. Development of a gastroretentive dosage form. *Eur J Pharm Sci.* 1996; 4S:182-193.
34. Ali J, Arora S, Ahuja A, Babbar AK, Sharma RK, Khar RK, Baboota S. Formulation and development of hydrodynamically balanced system for metformin: *In vitro* and *in vivo* evaluation. *Eur J Pharm Biopharm.* 2007; 67:196-205.
35. Yellanki SK, Singh J, Syed JA, Bigala R, Goranti S, Nerella KN. Design and Characterization of Amoxicillin Trihydrate Mucoadhesive Microspheres for Prolonged Gastric Retention. *Int J Pharm Sci Drug Res.* 2010; 2:112-118.
36. Meka L, Kesavan B, Chinnala KM, Vobalaboina V, Yamsani MR. Preparation of a Matrix Type Multiple-Unit Gastro Retentive Floating Drug Delivery System for Captopril Based on Gas Formation Technique: *In Vitro* Evaluation. *AAPS Pharm Sci Tech.* 2008; 9:612-623.
37. Dave BS, Amin AF, Patel MM. Gastroretentive drug delivery system of Ranitidine Hydrochloride: Formulation and *In Vitro* Evaluation. *AAPS Pharm Sci Tech.* 2004; 5:1-14.
38. Aulton, M. *Aulton's Pharmaceutics: The design and manufacture of medicines*, Churchill Livingstone, London. 2007. 397p.
39. Baumgartner S, Kristl J, Vrečer F, Vodopivec P, Zorko B. Optimization of floating matrix tablets and evaluation of their gastric residence time. *Int J Pharm.* 2000; 195:125-135.
40. Rosa M, Zia H, Rhodes T. Dosing and testing in vitro of a bioadhesive and floating drug delivery system for oral application. *Int J Pharm.* 1994; 105:65-70.
41. United States Pharmacopoeia/ National Formulary. *US Pharmacopoeial Convention Inc.*, Rockville, 2004. 2125-2126p.