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NEW APPROACHES TO ACHIEVE CONTROLLED DRUG DELIVRY THROUGH GASTRIC RETENTION

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ABSTRACT

The present review addresses briefly about the floating drug delivery systems. Oral sustained release gastro-retentive dosage forms (GRDFs) offer many advantages for drugs with absorption from upper parts of gastrointestinal tract and for those acting locally in the stomach, improving the bioavailability of the medication. Floating Drug Delivery Systems (FDDS) is one amongst the GRDFs used to achieve prolonged gastric residence time. GRDDS has become leading methodology in site specific orally administered controlled release drug delivery system. Various drugs, which are unstable in alkaline pH, soluble in acidic pH, having narrow absorption window, site of action specific to stomach can be developed by using this technique. Those gastro retentive systems which depend on liberation of carbon dioxide show poor patient compliance because of flatulence and belching.

KEY WORDS

Gastric retention, Floating Drug delivery system, Factors and Application.

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INTRODUCTION

Gastro retentive drug delivery system is an approach to prolong gastric residence time, thereby targeting site-specific drug release in upper gastro intestinal tract. The gastro retentive drug delivery system can be retained in the stomach and assist in an improving the oral sustained delivery of drug that have an absorption window in a particular region of the gastrointestinal tract. The systems help is occasionally releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailabilty[1].

The goal of any drug delivery system is to provide a therapeutic amount of drug at the proper site in the body and then maintain the desired drug concentration. Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biological parameters pertinent to their Performance. Oral delivery of drugs is by far the most preferable route of drug delivery due to ease of administration, patient compliance and flexibility in formulation and handling of these forms.

A major constraint in oral controlled drug delivery is that, not all drug candidates are absorbed uniformly throughout the Gastrointestinal Tract (GIT). Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. The extent of GIT drug absorption is related to contact time with the small intestinal mucosa. Conventional drug delivery system maintains the drug concentration within the therapeutically effective range needed for treatment, only when taken several times a day. Success of oral drug delivery system depends on its degree of absorption through GIT. Thus, the idea of enhancing drug absorption pioneered the idea of development of Gastro retentive drug delivery system (GRDDS). On the basis of the mechanism of muco adhesion, floatation, sedimentation or by the simultaneous administration of pharmacological agents, the controlled gastric retention of solid dosage forms may be achieved[2].

FLOATING DRUG DELIVERY SYSTEM

Floating systems or Hydro dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres[3].

Recently Multi-particulate drug delivery systems are emerged as oral dosage forms which consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00mm. Thus multi-particulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet. Floating multi-particulate systems include: hollow microspheres (micro-balloons), low density floating micro-pellets and floating micro-beads. Hollow microspheres are in strict sense, spherical empty particles without core[4,5]. The rationale behind the use of GRDDS is

- Improved solubility
- Taste masking
- Sustained release
- Patient compliance
- Improved bioavailability
- Increase therapeutic efficiency[6]

Advantages of Gastro retentive Delivery Systems[7]

1. The HBS can be used to deliver any medicament or class of medicament.
2. The HBS formulations are not only restricted to medicaments that are principally absorbed from the stomach but also for medicaments that are

absorbed from the intestine e.g. Chlorpheniramine maleate.

3. The HBS are advantageous for drugs that are absorbed through the stomach and for drugs meant for local action in the stomach.
4. The efficacy of the medicaments that are utilizing the sustained mechanism has been found to be independent of the site of absorption.
5. Prolonged release floating dosage forms of tablet may results in dissolution of the drug in gastric fluid, so that the dissolved drug gets fully absorbed after food is emptied from the stomach.
6. It may be advantageous to keep the drug in floating condition in stomach to get a relatively better response during vigorous peristalsis and diarrheal condition.
7. Gastric retention helps in the delivery of drugs which having narrow absorption windows in the small intestinal region.
8. Once-a-day dosage forms will have a suboptimal absorption due to dependence on the transit time of the dosage form, so a system designed for longer gastric retention will prolong the time of dosage form to increase the absorption.
9. Classified drugs are having benefit from using gastro retentive devices.

Disadvantages of floating drug delivery system[8]

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-coat, water.
3. The drugs that are significantly absorbed throughout 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.

Basic Gastrointestinal Tract Physiology[9]

Anatomically the stomach is divided into 3 regions: fundus, body, and atrium pylorus. The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the atrium is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an inter digestive series of electrical events takes place, which cycle through both stomach and intestine every 2 to 3 hours. This is called the inter digestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 phases.

1. Phase I (basal phase)
2. Phase II (pre burst phase)
3. Phase III (burst phase)
4. Phase IV

Four phases in migrating myoelectric complex (MMC)[10]

Phase I - It is a quiescent period lasting from 30 to 60 minutes with no contractions

Phase II - It consists of intermittent contractions that gradually increase in intensity as the Progresses and it lasts about 20 to 40 minutes. Gastric discharge of fluid and very small particles begin later in this phase.

Phase III - This is a short period of intense distal and proximal gastric contractions (4–5 contractions per minute) lasting about 10 to 20 minutes; these contractions, also ‘‘house-keeper wave,’’ sweep gastric contents down the small Intestine.

Phase IV- This is a short transitory period of about 0 to 5 minutes, and the contractions dissipate between the last part of phase III and quiescence of phase I.

Factors Affecting Gastric Retention[11]

Gastric residence time of an oral dosage form is affected by several factors. To pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm. The pH of the stomach in fasting state is ~1.5 to 2.0 and in fed state is 2.0 to 6.0. A large volume of water administered with an oral dosage form raises the pH of stomach contents to 6.0 to 9.0. Stomach doesn’t get time to produce sufficient acid when the liquid empties the stomach; hence generally basic drugs

have a better chance of dissolving in fed state than in a fasting state. The rate of gastric emptying depends mainly on viscosity, volume, and caloric content of meals. Nutritive density of meals helps determine gastric emptying time. It does not make any difference whether the meal has high protein, fat, or carbohydrate content as long as the caloric content is the same. However, increase in acidity and caloric value slows down gastric emptying time. In the case of elderly persons, gastric emptying is slowed down. Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down. The gastric retention time (GRT) of dosage form is controlled by several factors that affect their efficacy as a gastro retentive system.

Density

Density of the dosage form should be less than the gastric contents (1.004gm/ml).

Size

Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm.

Shape of dosage form

Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT. 90% to 100% retention at 24 hours compared with other shapes.

Single or multiple unit formulation

Multiple unit formulations show a more predictable due to failure of units, allow co- administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

Fed or unfed state

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

Nature of meal

Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release[12].

Caloric content

GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.

Frequency of feed

The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

Gender

Mean ambulatory GRT in males (3.4 0.6 hours) is less compared with their age and race-matched female counterparts (4.6 1.2 hours), regardless of the weight, height and body surface.

Age

Elderly people, especially those over 70, have a significantly longer GRT.

Posture – GRT can vary between supine and upright ambulatory states of the patient. [13]

Concomitant drug administration

Anticholinergics like Atropine and Propantheline, Opiates like Codeine and Prokinetic agents like Metoclopramide and Cisapride.

Biological factors

Diabetes and Crohn's disease.

Ideal properties for GRDDS[14]

- Effective retention in the stomach
- Sufficient drug loading capacity
- Controlled drug release profile
- Full degradation and evacuation after the drug release
- No effect on gastric motility including emptying pattern
- No other local side effects

Approaches to Design Floating Dosage Forms[3]

The following approaches have been used for the design of floating dosage forms of single and multiple unit systems.

Single-Unit Dosage Forms

In low density approaches, the globular shells

apparently having lower density than that of gastric fluid can be used as a carrier for drug for its controlled release. A buoyant dosage form can also be obtained by using a fluid-filled system that floats in the stomach. In coated shells popcorn, pop rice, and polystyrol have been exploited as drug carriers. Sugar polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been used to undercoat these shells. These are further coated with a drug-polymer mixture. The polymer of choice can be either ethyl cellulose or hydroxyl propyl cellulose depending on the type of released desired. Finally the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration. Fluid-filled floating chamber type of dosage forms includes incorporation of a gas-filled floatation chamber into a micro porous component that houses a drug reservoir. Aperture or opening are present along the top and bottom walls through which the gastrointestinal fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein. The fluid present could be air, under partial vacuum or any other suitable gas, liquid, or solid having an appropriate specific gravity and an inert behaviour. The device is of swallowable size, remains afloat within the stomach for a prolong time, and after the complete release the shell disintegrates, passes off to the intestine, and is eliminated. Hydrodynamically balanced systems (HBS) are designed to prolong the stay of the dosage form in the gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolong period of time the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form. Single unit formulations are associated with problems such as sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation.

Multiple-Unit Dosage Forms

The purpose of designing multiple-unit dosage form is to develop a reliable formulation that has all the advantages of a single-unit form and also is devoid of any of the above mentioned disadvantages of single-unit formulations. In pursuit of this endeavour many multiple unit floatable dosage forms have been designed. Microspheres have high loading capacity and many polymers have been used such as albumin, gelatin, starch, poly methacrylate, polyacrylamide, and poly alkyl cyanoacrylate. Spherical polymeric micro sponges also referred to as “micro balloons” have been prepared. Microspheres have a characteristic internal hollow structure and show an excellent in vitro floatability. In Carbon dioxide- generating multiple-unit oral formulations several devices with features that extend, unfold, or are inflated by carbon dioxide generated in the devices after administration have been described. These dosage forms are excluded from the passage of the pyloric sphincter if a diameter of ~12 to18 mm in their expanded state is exceeded.

SUITABLE DRUG CANDIDATES FOR GASTRORETENTION[15]

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

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

Drugs those are unsuitable for gastro retentive drug delivery systems[16]

- Drugs that have very limited acid solubility

e.g., phenytoin etc.

- Drugs that suffer instability in the gastric environment
  e.g., erythromycin etc.
- Drugs intended for selective release in the colon
  e.g., 5-amino salicylic acid and corticosteroids etc.

Polymers and other ingredients used in the formulation of grdds[17]

Category materials

Polymers: HPMC K4 M, Calcium alginate, Eudragit S100 Eudragit RL, Propylene foam, Eudragit RS, ethyl cellulose, poly methyl meth acrylate, Methocel K4M, Polyethylene oxide, β Cyclodextrin, HPMC 4000, HPMC 100, CMC, Polyethylene glycol, polycarbonate, PVA, Polycarbonate, Sodium alginate, HPC-L, CP 934P, HPC, Eudragit S, HPMC, Metolose S.M. 100, PVP, HPC-H, HPC-M, HPMC K15, Polyox, HPMC K4, Acrylic polymer, E4 M and Carbopol.

Inert fatty materials (5%-75%)

Edible, inert fatty materials having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. E.g. Beeswax, Fatty acids, long chain fatty alcohols, Gelucires.

Other materials

1. Effervescent agents - Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di- Sodium.]
2. Glycine Carbonate, CG (Citro glycine).
3. Release rate accelerants (5%-60%) - Lactose, mannitol.
4. Release rate retardants (5%-60%) – Di calcium phosphate, talc, magnesium stearate.
5. Buoyancy increasing agents (upto80%) - Ethyl cellulose.
6. Low density material - Polypropylene foam powder.

Table No.1: Marketed products of GRDFs[18]

S.No	Brand name	Drug	Company	Country	Remarks
1	Madopar	Levodopa(100 mg), Benserazide(25 mg)	Roche products	USA	Floating CR capsule
2	Val release	iazepam(15 mg)	Hoffman-Laroche	USA	Floating capsule
3	Liquid gaviscon	Aluminium hydroxide (95 mg), Magnesium carbonate (358 mg)	Glaxo smith kline	India	Effervescent floating liquid alginate preparation
4	Topalkan	Al-Mg antacid	Pierre Fabre drug	France	Floating alginate preparation
5	Conviron	Ferrous sulphate	Ranbaxy	India	Colloidal gel forming FDDS
6	Cifran O D	Ciprofloxacin(1 gm)	Ranbaxy	India	Gas generating or floating tablet
7	Cytotec	Misoprostol (100mcg/200mcg)	Pharmacia	USA	Bilayer floating capsule
8	Olfin O D	Ofloxacin (400 mg)	Ranbaxy	India	Gas generating floating tablet

Application of Floating Drug Delivery Systems

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

1. Sustained Drug Delivery

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short

gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. 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. Eg. Sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated *invivo*. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours)[19].

2. Enhanced bioavailability

The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption[20].

3. Enhanced first-pass biotransformation

In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input[21].

4. Reduced fluctuations of drug concentration

Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index[22].

5. Sustained drug delivery/reduced frequency of dosing

For drugs with relatively short biological half-life, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.

6. Targeted therapy for local ailments in the upper GIT

The prolonged and sustained administration of the drug from GRDF to the stomach may be advantageous for local therapy in the stomach and small intestine. By this mode of administration, therapeutic drug concentrations may be attained locally while systemic concentrations, following drug absorption and distribution, are minimal.

7. Improved selectivity in receptor activation

Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

8. Reduced counter-activity of the body

In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

9. Extended time over critical (effective) concentration

For certain drugs that have non-concentration dependent pharmacodynamics, such as beta lactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration. The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.

10. Minimized adverse activity at the colon

Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamics aspect provides the rationale for GRDF formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon

leads to the development of microorganism's resistance.

11. Site specific drug delivery

A floating dosage form is a feasible approach especially for drugs which have limited absorption sites in upper small intestine30. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency[23].

Limitations[24]

1. A high level of field in the stomach is required for drug delivery to float and work efficiently.
2. Drugs which have stability and solubility problems in GIT are not suitable candidates for this system.
3. Drugs which are irritant to Gastric mucosa are also not desirable.
4. Drugs which under goes first pass metabolism may not be desirable for the preparation of these type of systems[25].
5. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems[26].
6. Less gastric retention time.
7. Narrow absorption window in GI tract ex: riboflavin and Levodopa.
8. Basically absorbed from stomach and upper part of GIT. Ex: chlordiazoperoxide, cinnarazine.
9. Drugs that disturb normal colonic bacteria. Ex: Amoxicillin trihydrate.
10. Locally active in stomach ex: antacids and misoprostol.
11. Drugs that degrade in the colon ex: ranitidine and metronodazole.

CONCLUSION

Based on the literature surveyed, this study concludes that GRDDS is one of the efficient techniques to maintain the sustained release of drug in gastric environment and there by increases its absorption and bioavailability. All these GRDDS are interesting and more feasible when compared to other drug delivery systems and have their own advantages and disadvantages. FDDS promises to be a potential approach for gastric retention. The drug absorption in the gastrointestinal tract is a highly variable process and prolonging gastric retention of the dosage form extends the time for drug absorption. GRDDS is much safer dosage form and have systemic, localized actions as well GRDDS do help in the treatment of chronic diseases like ulcers and carcinoma of GIT, and also reduces dose frequency there by minimize contra indication, systemic toxicity, drug dependence. Ultimately GRDDS is an simple yet effective drug delivery system and these systems have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs with improved patient compliance.

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BIBLIOGRAPHY

1. Mishra Jhansee, Dash Alok Kumar. Recent advances in gastro retentive drug delivery system, *Mintage J pharm med sci*, 2(2), 2013, 25-27.
2. Monica Kawatra, Upendra jain, Jaspreet Ramana. Recent advances in floating microspheres as gastro retentive drug delivery system, *Int J Res*, 2(3), 2012, 5-23.
3. Mayavanshi A V and Gajjar S S. Floating drug delivery systems to increase gastric retention of drugs, *Res J Pharm tech*, 1(4), 2008, 345-348.
4. Dhole A R, Gaikwad P D, Bankar V H, Pawar S P. A Review on Floating Multi-particulate Drug Delivery System - A Novel Approach to Gastric Retention, *IJPSRR*, 6(2), 2011, 205-211.
5. Somwanshi S B, Dolas R T, Nikam V K, Gaware V M *et al.*, A Floating Multiparticulate Oral Sustained Release Drug Delivery System, *J Chem Pharm Res*, 3(1), 2011, 536-547.

6. Kavitha K, Yadav S K and Tamizh M T. The Need of Floating Drug Delivery System: A Review, *RJBPS*, 1(2), 2010, 396-405.
7. Binoy B, Jayachandran Nair C V. Floating drug delivery system - A new approach in gastric retention-A review, *J drug delivery res*, 1(3), 2012, 18-31.
8. Vyas S P, Khar R K. Controlled Drug Delivery, concepts and advances, *Vallabh Prakashan*, 2(1), 2002, 196-217.
9. Singh B N and Kim K H. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention, *J Control Release*, 63, 2000, 235-259.
10. Talukder R and Fassihi R. Gastro retentive delivery systems: A mini review, *Drug Dev Ind Pharm*, 30(10), 2004, 1019-1028.
11. Nikita Dixith. Floating drug delivery system, *J Current Pharm Res*, 7(1), 2011, 6-20.
12. A J. Gastro retentive dosage forms, *Crit Rev Ther Drug Carrier Syst*, 10(2), 1993, 193-95.
13. Well L J, Gardner R C, Cargill R C. Drug delivery device which can be retained in the stomach for a controlled period of time, *US Patent*, 4, 1998, 767-627.
14. Vinod K R, Santhosh Vasa, Anbuazaghan S, David Banji *et al.*, Approaches for gastro retentive drug delivery system, *Int J applied Bio Pharm Tech*, 1(2), 2010, 589.
15. Garg R, Gupta G D. Progress in controlled gastro retentive delivery system, *Trop pharm Res*, 7(3), 2008, 1055-1066.
16. Aterman K C. A Critical Review of Gastro Retentive Controlled Drug Delivery, *Pharm Development tech*, 12, 2007, 1-10.
17. Yale P G, Khan S and Patel V F. Floating Drug Delivery Systems: Need and Development, *Ind J Pharm Sci*, 67, 2005, 265-272.
18. Marinaganti Rajeev Kumar, Bonthu Satyanarayana, Nagakanyaka devi paladugu, Neeru Kondavamsi *et al*., A comprehensive review on gastro retentive drug delivery system, *Acta Chem Pharm Indica*, 3(2), 2013, 159.
19. Fell J T, Whitehead L and Collet H. Prolonged gastric retention using floating dosage forms, *Pharm Tech*, 24(3), 2000, 82-90.
20. Klausner E A, Eyal S, Lavy E, Friedman M *et al.*, Novel Levodopa gastro retentive dosage form *invivo* evaluation in dogs, *J Controlled release*, 88, 2003, 117-126.
21. Hoffman A. Pharmacodynamic aspects of sustained release preparation, *Adv Drug Deliv Rev*, 33, 1998, 185-199.
22. Hoffman A and Stepensky D. Pharmacodynamic aspects of modes of drug administration for optimization of drug therapy, *Crit Rev Ther Drug carrier Syst*, 16, 1999, 571-639.
23. Sunil Kumar, Faraz Jamil, Meenu Rajput and Saurabh Sharma. Gastro retentive drug delivery system: Features and Facts, *Int J Res Pharm Biomed sci*, 3(1), 2012, 118-124.
24. Suresh Karudumpala, Madhusudhana Chetty C, Gnanaprakash K, Venkatesh B *et al.*, A review on bilayer floating tablets, *Int J Res pharm Sci*, 4(2), 2013, 354-360.
25. Maniya shrikant, Shreeraj shah, Pratik Upadhay. Floating bilayer drug delivery system - An unconventional approach in conventional form, *Ame J Pharm Tech Res*, 2(2), 2012, 609-628.
26. Naisarg D Pujara, Ronak K Gokani, Jalpa S Paun. Bilayer tablet - An emerging trend, *IJPRD*, 4(4), 2012, 102-111.