International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 4(2): March-April 2014

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences **Review Article……!!!**

Received: 19-12-2012; Revised; Accepted: 21-04-2014

FLOATING DRUG DELIVERY SYSTEM: A CHRONOTHERAPEUTIC APPROACH

Trupti Ail*, Itishree Vaidya

Department of Quality Assurance Dr. L.H.Hiranandani College of Pharmacy, CHM College Campus, opp railway station, Ulhasnagar, Mumbai 03.

Keywords:

Floating drug delivery system, In-vitro, In-vivo evaluation parameters, Hydrodyanamically balanced system, Floating mechanism

For Correspondence:

Trupti Ail

Department of Quality Assurance Dr. L.H.Hiranandani College of Pharmacy, CHM College Campus, opp railway station, Ulhasnagar, Mumbai 03

E-mail:

ailtrupti@gmail.com

ABSTRACT

The purpose of this review on floating drug delivery system was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. The recent developments of FDDS including the physiological and formulation variables which affect the gastric retention and approach to design single unit and multiple unit floating system, their classification is covered in detail. This review also summarizes various in-vivo and in-vitro techniques to evaluate performance, advantages and application of floating systems. These systems are useful to avoid all problems encountered during the developments for the pharmaceutical dosage form. Thus floating drug delivery system seems to be promising delivery for the control release of drug.

INTRODUCTION[1]

The aim of controlled drug delivery is to achieve more predictable and increased bioavailability of the drugs. There are some physiological difficulties which has to be overcome to achieve the same, like inability to retain in the regions of gastrointestinal tract (GIT) and highly variable nature of gastric emptying process. Drug absorption from GIT is quite a complex phenomenon,

the extent of GIT drug absorption being related to the contact time with small intestinal mucosa.1Therefore, small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Prolonged gastric retention improves bioavailability, solubility, and reduces drug wastage. This also helps to provide better acceptability of new and existing products with potential therapeutic benefits for patients. The controlled gastric retention of solid dosage form may be achieved by mucoadhesion, floatation, sedimentation, expansion, modified shaped systems, or by the administration of pharmacologic.

BASIC GASTROINTESTINAL TRACT PHYSIOLOGY[2]

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material,

Whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions13. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the two states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is divided in 4 phases.

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.

2. Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

3. Phase III (burst phase) lasts for 4 to 6 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.

4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

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. Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage short gastric residence time and unpredictable gastric emptying rate.

FACTORS CONTROLLING GASTRIC RETENTION OF DOSAGE FORMS [3]

The stomach anatomy and physiology contain parameters to be considered in the development of gastro retentive dosage forms. To pass through the pyloric valve in to the small intestine the particle size should be in the range of 1 to 2 mm . The most important parameters controlling the gastric retention time (GRT) of oral dosage forms include : density, size and shape of the dosage form, food intake and its nature, caloric content and frequency of intake, posture, gender, age, sex, sleep, body mass index, physical activity and diseased states of the individual (e.g. chronic disease, diabetes etc.) and administration of drugs with impact on gastrointestinal transit time for example drugs acting as anticholinergic agents (e.g. atropine,propantheline), Opiates (e.g. codeine) and prokinetic agents (e.g. metclopramide, cisapride.). The molecular weight and lipophilicity of the drug depending on its ionization state are also important parameters .

Density of dosage forms

The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach . Both positions may isolate the dosage system from the pylorus. A density of < 1.0 gm/ cm3 is required to exhibit floating property.

Shape and size of the dosage form

Shape and size of the dosage forms are important in designing indigestible single unit solid dosage forms. The mean gastric residence times of nonfloating dosage forms are highly variable and greatly dependent on their size, which may be large,medium and small units. In most cases, the larger the dosage form the greater will be the gastric retention time (GRT) due to the larger size of the dosage form would not allow this to quickly pass through the pyloric antrum into the intestine .Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm. Ring-shaped and tetrahedron-shaped devices have a better gastric residence time as compared with other shapes .

Food intake and its nature

Food intake, viscosity and volume of food, caloric value and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the gastrointestinal tract (GIT) influences the gastric retention time (GRT) of the dosage form. Usually the presence of food in the gastrointestinal tract (GIT) improves the gastric retention time (GRT) of the dosage form and thus, the drugs absorption increases by allowing its stay at the absorption site for a longer period. Again, increase in acidity and caloric value shows down gastric emptying time (GET), which can improve the gastric retention of dosage forms.

Effect of gender, posture and age.

Generally females have slower gastric emptying rates than male. The effect of posture does not have any significant difference in the mean gastric retention time (GRT) for individuals in upright, ambulatory and supine state. In case of elderly persons, gastric emptying is slowed down.

POTENTIAL DRUG CANDIDATES FOR GASTRORETENTIVE DRUG DELIVERY SYSTEMS

1) Drugs those are locally active in the stomach e.g.misroprostol, antacids etc.

2) Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g. L-DOPA, paraaminobenzoic acid, furosemide, riboflavin etc.

3) Drugs those are unstable in the intestinal or colonic environment e.g. captopril4) Drugs that disturb normal colonic microbes e.g. antibiotics against helicobactor pyroli.

5) Drugs that exhibit low solubility at high pH values e.g. diazepam, verapamil HCl

DRUGS THOSE ARE UNSUITABLE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEMS

1) Drugs that have very limited acid solubility e.g. phenytoin etc.

2) Drugs that suffer instability in the gastric environment e.g. erythromycin etc.

3) Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc.

SELECTION OF POLYMERS FOR SUSTAINED RELEASE. [4]

Gas generating process.

Sodium bicarbonate, calcium carbonate, citric acid, tartaric acid, adipic acid.

Rational behind selection.

Effervescence compound is generally used because when these compounds come in contact with the gastric content carbandioxide is liberated and get entrapped in hydrocollides which

provide buoyancy to the dosage forms. The gas generated trapped and protected with the gel formed by the hydration of polymer. Thus decreasing the density of tablets i.e it fall below 1.

Acidulent is used since the PH of the stomach is elevated under fed condition (~3.5) acidulent (citric acid, tartaric acid, adipic acid) was incorporated in the formulation to prevent an acidic medium for sodium bicarbonate.

Viscoliyzing agent

sodium alginate, carbopol 934.

Rational behind selection.

To increase the viscosity in the system. Carbopol is being used in the controlled release. The polymers are effective under lower concentration (less than 10%).

They show extremely rapid and efficient swelling characteristics in both simulated gastric fluids(SGF) and simulated intestinal fluid (SIF).

Produce the tablets of excellent hardness and low friability.

Mechanism of carbopol.

In dry state the drug is trapped in glassy core. As external surface tablet is hydrated and it form gelatanious layer upon hydration. The hydrogels are not entangled chain of polymers, but descrete microgels made up of many polymers particles in which drug is dispersed.

The rate of swelling and hydration depend upon following factors.

Molecular structure of polymers.

Crosslink density.

Chain entanglement.

Crystallinity of polymer matrix.

PH of dissolution medium.

Swelling agent/ gel forming polymer.

Hydroxy propyl methyl cellulose.(HPMC**)**

Rational behind the selection.

Hypermellose powder is stable material although it is hygroscopic after drying.

Solution is stable at PH 3-11

Increasing tempertature reduces viscosity of the solution.

Hypermellose undergoes a reversible sol-gel transformation upon heating and cooling respectively.

Gel point is 50-90^{o}c, depending upon grades used and that are highly viscous in nature.grades that are available HPMC K100, HPMC K 4, HPMC K15.

Disintegrating agent

Povidone ,polyplasdone XL and XL -10.

Rational behind selection.

Povidone solution is used as binder in wet granulating process.

APPROACHES FOR FLOATING DRUG DELIVERY SYSTEM [5]

Depending upon the mechanism of buyoncy two different technologies have been used in the development of floating drug delivery system. These include,

Effervescent system

Non-effervescent system.

EFFERVESCENT SYSTEM

Effervescent system include the use of gas generating agents. Carbonates (eg sodium and organic acid. Eg citric acid and tartaric acid) present in the formulation to produce carbandioxide(co_2) gas , thus reducing density of the system and making it to float on the gastric fluid. An alternative is the inco-operation of matrix containing portion of the liquid which produces gas and they evaporate at body temperature.

The effervescent system further classified in to two types.[5]

1. Gas generating system.
2. Volatile liquid or vacuum containing system.

✓ Gas generating system

Tablets

Intragastric single layer floating tablets or hydrodynamically balanced systems (HBS)

These formulation have bulk density lower than gastric fluid and float in the stomach that increases the gastric emptying rate for prolonged period. These are the formulation by intimately mixing the gas CO_2 generating agents and the drug within the matrix tablet. The drug release slowly at desired rate from floating system and the residual system is emptied from the stomach after the complete release of the drug. These leads to an increase in gastric residence time(GRT) and better fluctuations in the plasma drug concentration.

Intragastric bilayer floating tablets

These are the compressed tablets containing two layer.

Immediate release tablets.

Sustained release tablets.

Floating capsules These floating capsules are formulated by filling with mixture of sodium alginate and sodium bicarbonate. The system float as a result of generation of CO_2 that was trapped in the hydrating gel network on exposure to an acidic environment.

Multiple unit type floating pills

These multiple unit type floating pills are sustained pills known as seeds, which is surrounded by the two layers. The outer layer is swellable membrane layer consist of effervescent agents. These system sinks at once and then it forms swollen pills like ballons which floats as they have lower density when it is immersed in the dissolution medium at the body temperature. The lowest density is due to generation and entrapment of CO_2 within the system.

Floating system with ion exchange resins.

Floating system using bicarbonate loaded ion-exchange resin was made by mixing the beads with sodium bicarbonate solution, and then the semi-permeable membrane is used to surround the loaded beads to avoid sudden loss of CO_2. On contact with gastric contents an exchange of bicarbonate and chloride ions take place that result the top of gastric contents and produe floatiog layer in resin bed.

2) volatile liquid or vaccum containing system.

a) Intragastric floating gastrointestinal drug delivery system.

The system floats in the stomach because of flotation chamber, which is vaccum or filled with harmless gas or air, while the drug reservoir is encapsulated by microporus compartment.

b) Inflatable gastrointestinal delivery system.

Inflatable chamber are incorporated, which contains liquid ether that gasfies at the body temperature to inflate the chamber in the stomach. These systems are fabricated by loading inflatable chamber with drug reservoir together wuth the inflatable chamber. The inflatable chamber automatically inflates and retain the drug reservoir compartment in the stomach the drug is continuously released in gastric fluid.

c) Intragastric osmotically controlled drug delivery system.

It is comprised of an osmatic pressure controlled drug delivery device and inflatable floating support in biodegradable capsule. In the stomach, the capsule quickly disintegrate to release the intragastric somatically controlled drug delivery device. The inflatable support inside forms a deformable hallow polymer bag that contain liquid that gasifies at body temperature to inflate the bag. The osmatic pressure controlled drug delivery consists of two components, drug reservoir compartment and somatically active compartment. The floating support is also made to contain bioerodible plug that erodes after a predetermined time to deflate the support. The deflatable drug delivery system is them emptied from the stomach.

NON- EFFERVESCENT SYSTEM

Non-effervescent system are usually prepared from gel forming or highly swellable cellulose type hydrocolloid polysaccharides or matrix forming polymers like polyacralate , polycarbonates polystyrene and polymethacrylate. tn one approach, intimate mixing of drug with gel forming hydrocolloid which result in contact with gastric fluid after oral administration and maintain relative integrity of the shape and bulk density less than unity within the gastric envirornmemt. The air entrapped by swollen polymers confers buoyancy to these dosage form. Excipients used commonly in these systems HPMC, polyacrylate, polyvinyl acetate, carbopol agar, sodium alginates, calcium chloride, polyethylene oxides and polycarbonates. This systems can be further divided in to subtypes

Single layer floating tablets.

These are formulated by intimate mixing the drug with gel forming hydrocolloid that swells on contact with gastric fluids and maintain bulk density of less than unity. The air entrapped by the swollen polymer conforma buoyancy of the dosage forms.

Bilayer floating tablet

The bilayer tablet contain two layer one immediate release layer which release initial dose from the system while another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier.

Alginate beads

Multiple unit floating system based on cross-linked beads. They were made by using calcium and low methoxlyated pectin and sodium alginate. In the approach generally sodium alginate solution is dropped into aqueous solution of calcium chloride and causes the precipitation of calcium alginate. These beads are then separated and dried by air convection and freeze drying leading to the formation of porus system which can maintain a floating force for over 12 hrs. These improve gastric retension time (GRT) more than 55 hrs.

Hollow microspheres.

Hollow microspheres (microballons) with the drug in their outer polymer shell were prepared by novel emulsion solvent diffusion method. The ethanol:dichloromethane solution of the drug and enteric acrylic polymers was poured into an agitated aqueous solution of PVA that thermally controlled at 40^{o}c. The gas phase generated into dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug. The microballons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hrs *invitro*.

MECHANISM OF FLOATING TABLETS

Floating drug delivery system have bulk density less than gastric fluid and so remain buoyant in the stomach without affecting the gastric emptying rate for prolong period of time while the system is floating on the gastric content given in the (fig). The drug release slowly at the desired rate from the system. After the release of drug, the residual system is eliminated from the stomach. This result in an increase in GRT and better control in fluctuation in plasma drug concentration , however besides a minimal gastric content needed to allow proper achievement of buoyancy of the dosage forms, retention effect , minimal level floating force (F) is also required to maintain the buoyancy of dosage form on the surface of the meal, to measure the floating force kinetics, a novel apparatus for determination of resultant weight. The apparatus operates by measuring continuously force equivalent to F (as a function of time) that is required to maintain a submerged object. The object float better if F is on higher positive side (fig B). This apparatus help in optimizing floating drug delivery system with respect to stability and sustainability of floating forces produce in order to prevent any unforeseansic variation intragastric buoyancy.

F= F buoyancy-F gravity= (Df-Ds)gv

Where F= total vertical force
Df = fluid density
Ds= object density
V=Volume
g=acceleration due to gravity.

EVALUATION PARAMETERS OF STOMACH SPECIFIC FLOATING DRUG DELIVERY SYSTEM.

Pharmaceutical dosage form exhibiting gastric residence in vitro floating behavior showed prolong gastric residence invivo. However it is pointed that good in-vitro floating behavior alone is not sufficient proof for efficiency gastric retension invivo. The effects of the simultaneous presence of food and of complex motility of the stomach are difficult to estimate obviously, only invivo studies can provide sufficient proof that prolong residence is obtained.

INVITRO EVALUATION PARAMETERS [6,7,48]

- ✓ **Measurement of buoyancy capabilities of floating drug delivery system.**

The floating behavior was evaluated with resultant weight measurment. The experiment was carried out in two different media like deionised water and simulated meal, in order to monitor possible difficulties. The result showed that higher molecular weight polymers with slower rate of hydration had enhanced floating behavior and which was more in simulated meal medium compare to deionised water.

- ✓ **Floating time**

The test for floating time is usually performed in simulated gastric fluid or 0.1 mole-litre Hcl maintained at 37^0C by using USP dissolution apparatus containing 900ml of 0.1 molar HCl as the dissolution medium. The time taken by dosage form to float is termed as floating lag time and the time for which dosage form floats is termed as floating or floatation time.

- ✓ **Swelling studies**

Swelling studies are performed to calculate molecular parameters of swollen polymers. Swelling studies was determined by using dissolution apparatus, optical microscopy and other sophisticated techniques which include confocal laser microscopy, Crysogenic scanning scanning electron microscopy (cryo-SEM) light scattering images. Swelling studies was calculated as per following.

Swelling studies = weight of wet formulation/weight of formulation.

- ✓ **Determination of moisture content.**

Moisture content of the prepared formulation was determined by karl fischer titration, vacuum drying, thermo gravimetric methods, air oven methods, moisture meters, freeze drying as well as physical methods.

- ✓ **Drug release.**

Dissolution are performed using the dissolution apparatus. Samples are withdrawn periodically from dissolution medium with replacement and then analysed for their drug concentration after an appropriate dilution.

- ✓ **Hardness, friability (tablets).**

Hardness is defined as the "force required to break a tablet in diametric compression test." Hardness is hence, also termed as the tablet crushing strength. Some devices which are used to test hardness are Monsanto tester, strong Cobb tester, Pfizer tester, etc. The laboratory friability tester is known as the **Roche Friabilator**. This consists of a device which subjects a number of tablets to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm & drop the tablet to a distance of six inches with each revolution. Normally, a pre-weighed tablet sample is placed in the friabilator which is then operated for 100 revolutions. Conventional compressed tablets that lose less than 0.5 to 1.0 % of their weight are generally considered acceptable. Most of the effervescent tablets undergo high friability weight losses, which accounts for the special stack packaging, that may be required for these types of tablets.

- ✓ **Drug loading, drug entrapment efficiency, particle size analysis and surface characterization.(for floating microspheres and beads).**

Drug loading is assessed by crushing accurately weighed sample of beads and microspheres in a mortar and added to appropriate dissolution medium which is then centrifuged, filtered and analyzed by various analytical method like spectrometry. The percentage of drug loading is calculated by dividing the amount of drug in the sample by weight of total beads or microspheres. The particle and size distribution of beads or microspheres is determined in the dry state using the optical microscopy method. The external and cross-sectional morphology (surface characterization is done by scanning microscope.(SEM)

- ✓ **Weight variation**

Samples of tablets (usually 10)are taken and weighed throughout the compression process. The composite weight divided by 10 however provides an average weight but contain problem of averaged value. To help to alleviate (USP) provides limit for permisible Variation in the weight of the individual tablets expressed in percentage of the average weight of the sample. The USP provides the weight variation test by weighing 20 tablets individually, calculating average weight and comparing the individual tablet weight to the average. The tablet meet the specificication of (USP) if not more than two tablets outside yhe percentage limit and if no tablets differs by more than 2 times the percentage limit.

***INVIVO* PARAMETERS**

- ✓ **Magnetic marker monitoring.**

In this technique dosage form is magnetically marked with inco-operating iron powder inside and images can be taken by very sensitive biomagnetic measurement equipment. Advantages of method is that it is radiation less and so not hazards.

- ✓ **^{13C} octonoic acid breath test**

^{13C} octonoic acid is incop-operated into GRDDS. In the stomach due to chemical reaction octonoic acid liberates co_2 gas which comes out in breath. The important carbon atom which will come in CO_2 is replaced with ^{13C} isotope. So time up to which $^{13}CO_2$ gas is observed can be considered as gastric retension time of dosage form. As dosage form moves to intestine, there is no reaction and no CO_2 release. So this method is cheaper than other.

- ✓ **X-ray/gamma scintigraphy.**

X-ray/Gamma scintigraphy is very popular evaluation parameters for floating dosage forms.it helps to locate dosage form in GIT by which one can predict and correlate gastric emptying time and passage of dosage form in the GIT. Here the inclusion of the radio opaque material

in to a solid dosage form enables it to be visualized by X-rays, similarly the inclusion of a gamma radionuclide in a formulation allow indirect external observation using gamma camera or scintiscanner. In case of gamma scintigraphy, the gamma rays emitted by radionuclide are focused on cameras, which help to moniter the location of the dosage form.

APPLICATIONS

- ✓ Enhanced bioavaibility.
- ✓ Sustained drug delivery.
- ✓ Site specific drug delivery system.
- ✓ Absorption enhancement.
- ✓ Minimize adverse action at the colon.
- ✓ Reduce fluctuation of drug concentration, specially featured for narrow therapeutic index drug.

CONCLUSION

Gastroretentive floating drug delivery system have emerged as an efficient means of enhancing bioavailability and controlled drug delivery of many drugs. This system is for formulation of drugs with narrow therapeutic index, less soluble drugs, drug with extensive first pass metabolism, best suitable for targeting organ. Floating drug delivery system is emerging tool in pharmaceutical industry to obtain sustain drug delivery and increase bioavailability.

Marketed products of floating drug delivery system

BRAND NAME	DELIVERY SYSTEM	DRUG (DOSE)	COMPANY NAME
Valrelease	Floating capsules	Diazepam (15 mg)	Hoffmann La Roche
Madopar HBS	Floating capsules	Benserazide (25mg) and L-dopa (100 mg)	Roche pdts USA
Liquid Gaviscon	Effervescent floating liquid alginate preperations	Aluminium hydroxide (95mg), magnesium carbonate (358mg)	GlaxoSmithkline India
Topalkan	Floating liquid alginate preperation	Aluminium and magnesium antacid	Pierre Fabre Drug
Almagate flot coat	Floating dosage form	Aluminium – magnesium antacid	
Conviron	Colloidal gel forming FDDS	Ferrous sulphate	Ranbaxy, India
Cytotech	Bilayer floating capsules	Misoprotol (100mcg/200mcg)	Pharmacia USA
Cifran OD	Gas generating floating form	ciprofloxacin	Ranbaxy, India

List of drugs explored for floating dosage forms

Tablets[8,30,2.10,11,12,13,14--31]

Captropril,ˈAtenolol ,Carbamazepine ,Clarithromycin ,Norfloxacin ,Famotidine ,Diltiazem ,Indomethacin Montelukast sodium ,Ofloxacin ,Cefixime ,Cinnarizine ,Glipizide ,Silymarin ,Mebendazole ,Cefuroxime ,Furosemide ,Metoprolol ,Ranitidine Hcl

Capsules[31,32,33,34,35,36,37]

Nicardipine, Misoprotal,Acyclovir ,Thiophylline,Captropril, Celecoxib, Ofloxacin

Films [38,39,40,41,42,43]

p-aminobenzoic acid,cinnarizine ,peritamide, quinidine gluconate.

Powders[44,45,46]

Riboflavin- 59-phosphate, Sotalol, Theophylline.

REFERENCES

1. Patil J.M, Gide P.S etal " Trends in floating drug delivery system", Journal of scientific and industrial research; jan 2006 Vol 65 : 11-21
2. Gogal Manoj, Prajapati Rajesh "Floating drug delivery system", Journal of current pharmaceutical research 2011; Vol 5(1): 7-18.
3. Nayak Amitkumar, Das Ruma Maji, "Gastrotetentive drug delivery system : a review; Asian Journal of pharmaceutical and clinical research Jan-Mar 2010 ; Vol 3(1).
4. Sharma Natasha,; "A comprehensive review on floating drug delivery system"; International journal of Research and Biomedical science; Apr-Jun 2011; Vol (2).
5. Dixit Nikita; "Floating drug delivery system"; Journal of current pharmaceutical research; Vol 7(1) 6-20.
6. Mathur Pooja, " Floating drug delivery system: an innovative acceptable in gastroretentive drug delivery"; Archivers of applied science research 2010, Vol 2(2) 257-270.
7. Soni Ravi, Patel Ashish, etal "Gastroretentive drug delivery system: a review"; International Journal of Pharma world research; Jan-Apr 2011 Vol 2(1).
8. Reddy Sreenivasa,; "Development of floating matrix tablet: An approach using natural gums"; International journal of pharma world research; jun-sep 2010; Vol 1(3).
9. Manivannan Rangasamy, Chakole Vivek ; "Formulation and development of extended release floating tablet of atenolol"; International Journal of recent advance in pharmaceutical research; july 2011; Vol-3 25-30.

10. S Mohamed Halith, Abhirami e.tal, “Pharmaceutical design and invitro evaluation of sustained release matrix tablet of carbamazepine”;International Journal of PharmaTech Research ; jan-mar 2010; Vol2(1) 788-793.
11. R Charulatha e.tal; “Evaluation of carbamazepine controlled drug delivery system”; International Journal of PharmaTech research; jan-march 2012; Vol 4(1) 25-34.
12. Sheth Nirav; “Formulation and evaluation of floating drug delivery system”; International Journal of pharma and bioscience; jan-march 2011; Vol 2(1).
13. Bomma Ramesh, Naidu Rongala Appala Swamy, “ Development and evaluation of gastroretentive norfloxacin floating tablets” Aceta Pharma 59 2009 211-221.
14. Namma Muralidhar, Reddy Prabhakar ; “formulation and evaluation of gastroretentive dosage form of clarithromycin”; AAPS pharma Sci Tech; mar 2008; Vol 9(1).
15. Mohammad Muqtader, Ali Sadath; “Development and in-vitro evaluation of gastroretentive floating tablets of famotidine”; International Journal of pharmacy and industrial research; oct-dec 2011; Vol 1(4).
16. Bose Subhash Chandra P, Reddy Srikanth P. e.tal “Formulation and evaluation of sustainrd release floating tablet of diltiazem hcl using xanthum gum”; Research Journal of pharmaceutical biological and chemical science; apr-june 2011; Vol2(2). 319-328.
17. Jain Jitendra, Marya Bhavna H, e.tal “Formulation of indomethacin bilayer sustained release tablets”; International Journal of Pharma Tech Research; Apr-June 2011; Vol 3(2).
18. Fernandes Truman, Goli Divakar e.tal; “Formulation and evaluation of floating drug delivery system using an antiasthmatic drug”; Research Journal of pharmaceutical , biological and chemical science; Apr-June 2012; Vol 3(2) 249-262.
19. Tiwari Diwakar, Kheri Rajat; “Preformulation studies for floating tablets of ofloxacin”; International Journal of pharmacy and life sciences; Nov 2010; Vol 1 (7) 419-427.
20. Rao Raghavendra, Pentewar Ram e.tal; “Formulation and invitro evaluation of gastric oral floating tablets of cefixime for controlled release”; Reseach Journal of pharmaceutical , biological and chemical science; July-Sept 2010; Vol 1 (3) 144-154.
21. Karwa Preeti, Kasture P. V; “ Formulation and evaluation of controlled floating matrix tablets of weakly basic drug cinnarizine”; Journal of pharmacy research 2011, Vol 4(8) 2665-2669.
22. Ranga Rajesh Kumar, Siva P; “ Formulation and evaluation of gastroretentive floating bioadhesive tablets of glipizide”; Internationl journal of Research in pharmaceuticals; March 2011, Vol 2(2) 252-260.

23. D Vinay Kumar, K. Srinivas; "Hepatoprotective activity of silymarin floating drug delivery system against antituberculosis drug; International Journal of pharmacy and technology, March 2010; Vol 2(2) 233-244.
24. Patel Krunal, Biswas Biswajit; "Preparation and evaluation of gastroretentive floating tablets of mebendazole"; International Journal of current pharmaceutical research 2011; Vol 3(1) 63-65.
25. Patel Viral, Patel Natavarlal; "Intragastric floating drug delivery system of cefuroxime axetil: In vitro evaluation"; AAPS Pharma SciTech 2006; Vol 7(1).
26. Karkhile Vishal, "Formulation and evaluation of floating tablets of furosemide"; International Journal of Pharma research and development 2010; Vol 1(2).
27. C Narendra, M.S.Srinath e.tal "Optimization of bilayer floating tablets containing metoprolol tartarate as a model of gastric retension";AAPS Pharma SciTech 2006; 7(2).
28. Dave Brijesh, Amin Avani e.tal " Gastroretentive drug delivery system of ranitidine hydrochloride formulation and in-vitro evaluation";AAPS Pharma SciTech 2006; 5(2).
29. M. Jaimini, Tanwar Y.S; "Formulation and evaluation of famotidine floating tablets"; Current drug delivery; Vol (4) 2007 51-55.
30. K. Jagadeesh, V. Edukondalu,Sade Satyanarayan e.tal. "Formulation and evaluation of oral floating tablets of atenolol using okra gum"; Scholars Research library 2011; Vol3(3).
31. Patel Anand, Modasiya Moin; "Development and in-vivo floating behavior of verapamil HCl intragastric floating tablets"; AAPS Pharma Sci Tech, March 2009; Vol 10 (1).
32. Rao Chandrashekhara, Rao Raghavendra; "Formulation and evaluation of ibuprofen floating tablets"; International Journal of pharmaceutical , chemical and biological sciences 2012,; Vol 2(4) 472-481.
33. Drabu Sushma, Khatri Smriti; "Formulation and evaluation of acyclovir capsules"; International journal of drug development and research; oct-dec 2011, Vol 3(1).
34. Matharu Rajinder Singh, Sanghavi Nalini; " Novel drug delivery system of captropril", Drug development and industrial pharmacy, Vol 8 1992.
35. Ali Javed, Arora shweta, Sharma Rakesh, e.tal. "Formulation and development of hydrodynamically balanced system of metmorfin"; European Journal of pharmaceutics and biopharmaceutics 2007, 67 196,201.
36. Nayak Amit Kumar, Das Biswarup, "gastroretentive hydrodynamically balanced system of ofloxacin: invitro evaluation, Suadi pharmaceutical Journal, 2011.

37. Shukla Shruti, Patidar Ashish e.tal; " A review on: Recent advancement of stomach specific floating drug delivery system"; International Journal of pharmaceuticals and biological archivers 2011: Vol 2(6).
38. Ichikawa, T.Kawahara e.tal; "A new in-vivo evaluation of floating and sustained release characteristic with p-aminobenzoic acid and isosorbide dinitrate as model drugs, J pharm sci, 1991, 1153-1156.
39. Ichikawa, Watanabe M, Miyake S; "A new multiple unit oral floating dosage system: preparation and in-vitro evaluation of floating and sustained release characteristics, J pharm sci 1991, 80, 1062-1066.
40. Machida, Inouye Y e.tal "Preperation and evaluation of intragastric buoyant preperations" Drug design del 4, 1989, 155-161.
41. N Rouge, Buoyancy and drug release pattern of floating minitablet containing pirctanide and atenolol model drugs, Pharm Development technol 1998, 3 73-84.
42. K Inouye, T Nagai; "Buoyant sustained release granules based on chitosan, drug design development 1989, 4, 55-67.
43. Gyilirah A, Green G.A, e.tal; "Evaluation of the gastric retension properties of crosslinked properties coated tablets versus those of a non-disintegrating tablet, Int. J. pharma 1991, 75 241-247.
44. Deshpande A, Shah A, "Development of novel controlled release system for gastric retention, Pharma Res 1997, 14, 815-819.
45. Ingani, H.M Timmermans, e.tal, " Conception and In-vivo Investigation of peroral sustained release floating dosage form with enhanced gastrointestinal transit, Int.J. pharma, 1987, 351 157-164.
46. Chuch , H.R Zia, e.tal "Optimization of sotalol floating and bioadhesive extended release tablet formulation, Drug development Int Pharm 21, 1995, 1725-1747.
47. B Samayuktha," The development on gastric floating drug delivery system: An overview" International journal of pharma Tech research 2010, Vol 2(1) 524-534.
48. Nasa Praveen, Mahant Sheefali; " A novel approach towards gastroretentive drug delivery system; International Journal of pharmacy and pharmaceutical science, Vol 2(3) 2010.