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A BRIEF SUMMARY ON "GASTRO RETENTIVE DRUG DELIVERY SYSTEM"

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ABSTRACT

Gastro-retentive drug delivery systems have recently gained popularity in the pharmaceutical industry as a means of achieving better therapeutic benefits such as ease of dosage administration, patient compliance, and formulation in flexibility. Drugs that are rapidly absorbed from the GI tract and have a short half-life are eliminated quickly from systemic circulation.

KEYWORDS: GRDDS, Approaches, Factors affecting efficacy, Applications, Marketed drugs.

INTRODUCTION

Gastro Retentive Drug Delivery Systems: Gastro-retentive drug delivery system contains one of the most effective delivery sites for the delivery of drugs for controlled manner at the stomach or intestine. It is obtained by the remaining drug dose in the active site of the stomach and drugs can be released at the controlled manner to the target the site of the stomach, duodenum, and intestine.[1]

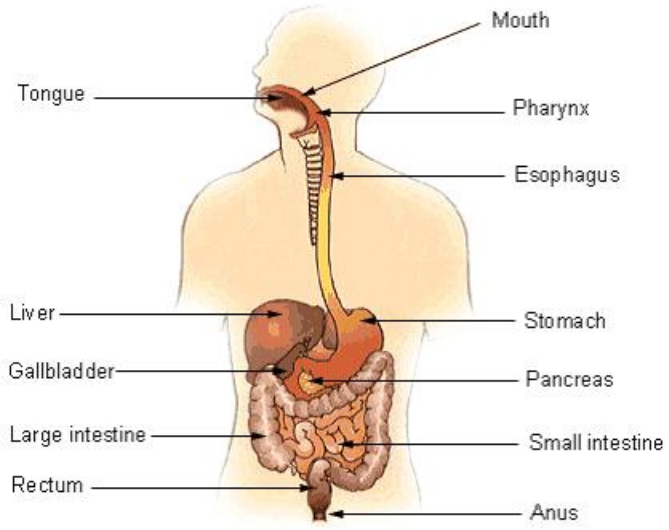

Fig 1: General Gastrointestinal tract.[2]

Basic anatomy & Physiology of stomach: The Gastrointestinal tract (GIT) is made up of muscles. The size of the muscular tube is 9meter. The GIT is started from mouth to anus. The main importance of GIT is to utilized nutrients and discarded body waste materials during this process there are some factors involve like absorption, digestion, metabolism, secretion, and excretion. The basic anatomy of the stomach is having three layers of muscle. The first layer of the stomach is present in the proximal part of the stomach called oblique muscles and the second layer of stomach present near fundus that is branching the last one is called higher regions in the stomach. The stomach having three parts fundus, body, and pylorus. GIT contains main three regions in the body.

a) Stomach, b) Small intestine (duodenum, jejunum, and ileum) and c) Large intestine.[3]

The stomach has expandable property from the esophagus to the small intestine. When the stomach is during a free stage or empty stage present mucosa is throughout into the rugae just because of stomach contraction. The stomach contains four types of skin cells.

- Stomach cells that is accountable for HCL release.
- Mucous cells that is accountable for acrid mucus release.
- G cells that is responsible for hormone gastrin secretion.
- Chief cells are responsible for pepsin secretion.[4]

The structure of the Stomach is J-shaped and contains fundus, body, and pylorus. The proximal tube is the fundus, body store undigested material and pylorus work for elimination. The stomach contains some liquid (50 ml), gastric fluid (1-3 pH) and air during fasting conditions. The mucus present over the epithelium is release by the mucous cells that are responsible for controlling stomach acid. The epithelium gastric cells release chlorohydric acid (HCl). The zymogenic cells emit pepsinase (enzyme). Gastrointestinal tract (GIT) has two modes first modes is inner digestive motility mode and second is stomach related motility. Interdigestive motility mode has another name that is Migrating Motor Complex (MMC). The system contains a cycle and having four stages duration up to 90– 120 minutes. Some hormones are involved in this stage. Each cycle has started in the lower oesophageal sphincter, whole stomach, duodenum, jejunum, and end up to ileum.[5]

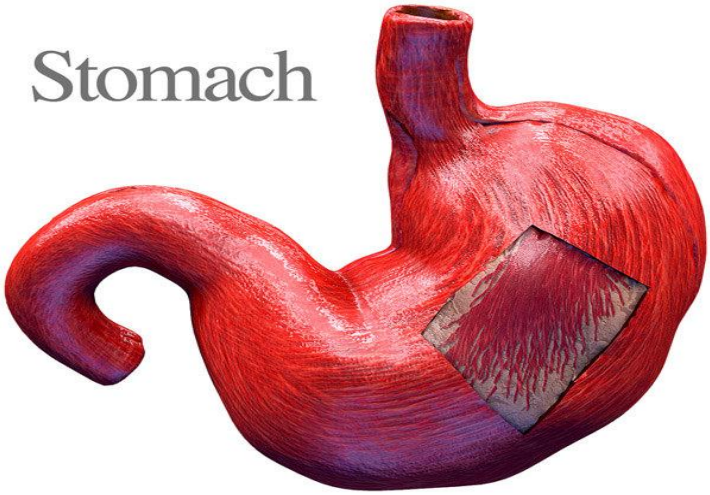

Fig 2: Stomach.

Phase of Gastric motility: Gastric motility divided into four phases-

- Phase I (basal phase) - It shows rare contractions.
- Phase II (pre-burst phase) – It shows constrictions.
- Phase III (burst phase) – It shows reliable constrictions for a minimum period.
- Phase IV – It happens during a phase of III and 1.[6]

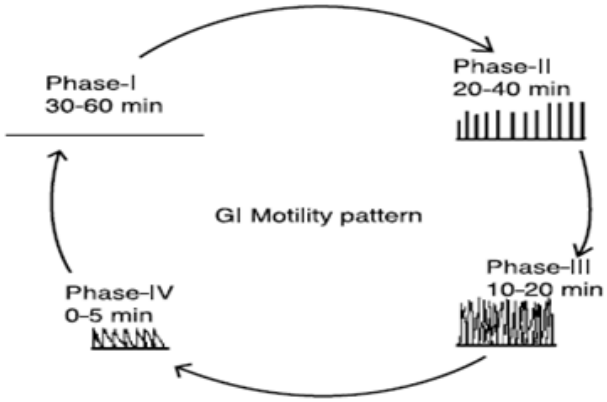

Fig 3: GI Motility pattern.

Advantages of GRDDS

- The GRDDS lower dosing prevalence and boost patient compliance.
- This elasticity increases gastric residence time.
- Improved therapeutic effect.
- The GRDDS system achieved targeted drug delivery.
- Sustained dosage forms can reduce gastric irritation.
- Floating microspheres are making drug uniformity and no dose dumping liability.[7]
- The GRDDS increases bioavailability.
- Achieved targeted therapy in the upper GI tract.[8]

Disadvantages of GRDDS

- In GRDDS the liquid available in the stomach is the capacity for the flow appropriately over the liquid.
- It offers lag gastric emptying time (GET).
- GRDDS formulations are affected by the presence of gastric fluids in the stomach. These dosage forms have stability or solubility problems.[9]
- The Mucoadhesives dosage contains several limitations regarding the increase rate of the mucus layer, solubility factor, and thickness of the mucus layer.
- Before achieving the stomach site the swellable formulations can swell in the system.
- There are several factors like pH, food and gastric motility. Responsible for influenced gastric retention. It cannot be constant and its buoyancy never determined.

The bioadhesive dosage forms are capable of a bind with an esophageal system.[10]

APPROACHES FOR GASTRIC RETENTIVE DRUG DELIVERY SYSTEM

1. **Bio-mucoadhesive systems:** This system contains an interfacial phenomenon. This system contains two materials first is a biological material which is held by interfacial forces. The connection is done between two materials which are an artificial material and a biological substrate like adhesion in the biological membrane and the polymer. The term mucoadhesion is referred to as the polymer directly fixed to the mucosal layer of the tissue.[11] The overall concept of mucoadhesion is responsible for the improvement of high residence times at the several targeted sites of the GIT and also decreases the variability of the dosage. These are also responsible for the improvement of efficacy.[12] This bio-mucoadhesive system work with mucous membrane, absorption tissue, rate of drug released at the target site to make enhanced bioavailability.[12]

2. **Floating drug delivery systems (FDDS):** Davis in 1968 describes the floating drug conveyance frameworks. This framework is low-thickness frameworks and can drift upper the gastric liquid present in the stomach and continued for a more extended term. This floating system is shown drug released at active site gradually. The final results show in this system is lower fluctuations in plasma drug concentration and also enhanced gastric retention time.[13]

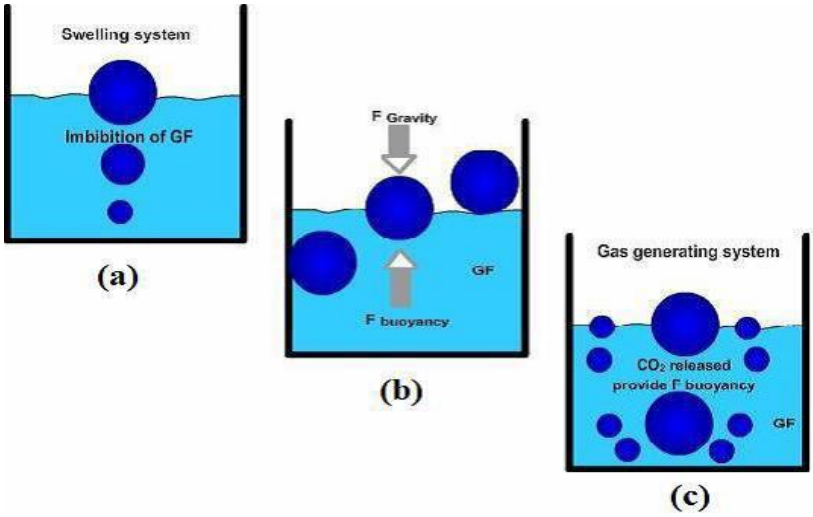

Fig 4: Mechanism.[14]

3. **Magnetic system:** This system can increase gastric residence time (GRT). In this, the essential standard included that the medication plans having a little amount inner magnet and this magnet situated on the mid-region over the situation of the stomach. Despite these magnetic systems look to work with the external magnet. The system may maintain the precision of degree with that of patient compliance.[15]

4. **Swelling systems:** The swelling systems which are growing to a size, which forestalls entry over the pylorus. The outcome shows the medication stays at the stomach for a more drawn out term. This is

otherwise called plug type frameworks. Which is bear to hold stopped at the pyloric sphincter. In the fed stage, the present polymeric grids held in the gastric hole for certain hours. The choice of polymer with sub-atomic weight and some different properties the polymers make the plans compelling, for example, controlled and continued medication discharge. The polymer in contact with gastric fluid polymer retains gastric liquid at that point swells. Accessibility of physical-synthetic crosslink operator in the hydrophilic polymer arranges the outcome shows polymers expanding. The upkeep of definitions physical immaculateness is finished by a cross-connecting specialist. These likewise work in the disintegration boundary of the polymer for anticipation. The degree and length of growing of the polymers are kept up by the level of cross-connecting among polymers. The growing capacity of this framework is hampering by cross-connecting. The subsequent thing is this when the utilization of a low level of cross-connecting can show the huge growing and delivered moderate polymer disintegration. At long last the employments of a perfect measure of cross-connecting materials which is proper to deal with the disintegration and expanding of the dose structure.[16]

5. **Ion exchange resin:** In this system are contains the bicarbonate with a negative charge drug that is attached to the resin. The result shows the final beads are overlapped into the semi-permeable membrane which is used to reduce the loss of carbon dioxide. In the acidic atmospheres of the stomach, these chloride and bicarbonate ion are exchanged to each other. During this ion exchange process, the carbon dioxide gas will be released. The attachments of ions into the gastric mucosa which can bear the polymer beads and is responsible to create a floating layer of resin and while easily sink.[17]

6. **Bonding-mediated adhesion:** The bonding mediated adhesion is used for the coupling of polymers to the gastric mucus layer and cell surface. The Physical-mechanical bond is used for the mixing of adhesive materials with mucosa. Chemical bonds are primary and secondary bonds. The primary bond is covalent and the secondary bond is ionic. The secondary chemical bonds are of two types Vander Waals interactions and second are hydrogen bonds. The hydrogen bonds are hydroxyl and carboxylic functional groups.[18]

7. **High-density system:** High-density system contains the measurements structures with high thickness as that stomach content that is 1.004 g/ml. The high-thickness measurement structure contains the covering materials and a center material scattered inside inactive materials like-barium sulfate, iron powder, zinc oxide, and titanium dioxide, and so on. The outcome shows the pellets secured with the dissemination controlled layer.[8]

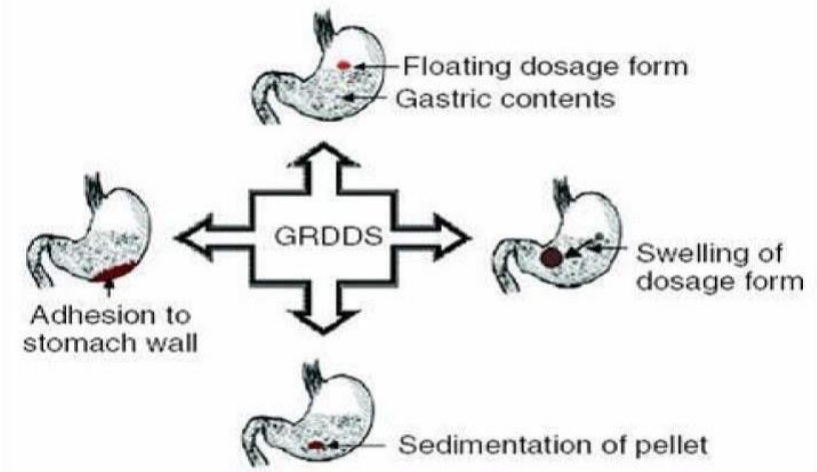

Fig 5: Approaches of GRDDS.[19]

Factors affecting efficacy of GRDF'S

There are several factors:

- **Particle size:** The particle size range up to 1-2 micrometer (mm). Which are going into the intestinal membrane.
- **Density:** The gastric emptying time or rate is affected by the density of the dosage forms. The low-density formulations contain less than 1 which can float over the gastric fluids and available for a long time.
- **Size:** For prolonged GRT the dosage forms particle size must be more than 7.5 mm in diameter.
- **The shape of dosage form:** The shapes of dosage forms are responsible for better GRT that is 90-100%. The shapes involved are the tetrahedron, ring-shaped devices as compared to other shapes of the dosage form.
- **Nature of meal:** Nature of meal affects the stomach motility pattern there are some factors involved that is indigestible polymers and some fatty acids salts.

They can lead the enhanced drug release and low gastric rate.

- **The temperature of the meal:** The gastric emptying rate is affected or decrease by the temperature of the meal.
- **Caloric content of meal:** The caloric meals like proteins or fats are capable of enhancing gastro retention time (4 to 10hr).
- **The frequency of feed:** The high amount of meal is increased the GRT of the stomach (400 minutes).
- **Gender:** GRT in males is about 3.4 ± 0.6 hrs and in females is 4.6 ± 1.2 hrs with their body surface, weight, and height of the patient.
- **Age:** The age affects the GRT in the stomach when the age younger than 70 years leads to increases GRT.
- **Posture:** The posture of the patient can change the GRT.
- **Concomitant drug administration:** There are some drugs involves for stimulation of GRT like some antacids Aluminium hydroxide, atropine, propantheline, narcotic analgesics and Metoclopramide, Imipramine, cisapride, Amitriptyline, and domperidone.
- **Biological factors:** There are some diseases factors which slow the gastric time that is a gastric ulcer, gastroenteritis, diabetes, and hypothyroidism. Some for enhancing the gastric rate that is duodenal ulcer and hypothyroidism.[20]

Suitable drug candidates for GRDDS

A few medications have a phenomenal helpful impact in the stomach and show delayed discharges rate in a controlled way like-:

- The drugs show a narrow absorption window in GIT like Levodopa and Riboflavin.
- The drugs when the absorption is done in the upper part of the gastrointestinal tract and stomach like cinnarizine and chlordiazepoxide.
- Some drugs which locally demonstrated the stomach like Antacids and Misoprostol.
- Some drugs irritate the normal intestinal bacteria like Amoxicillin trihydrate.[21]

Gastro retentive dosage forms characterization

1. The GRDF's buoyancy capabilities: Measured and the floating behaviour is calculated using the weight readings. When compared to deionized water, large molecular weight polymers with a slow rate of hydration have a stronger floating characteristic and are observed more in the simulated meal medium.

2. Floating time and dissolution: The floating time test is usually performed in stimulated gastric fluid or 0.1 N HCl at 37 oC. The procedure is carried out with a USP dissolve device and 900 ml of 0.1 N HCl as the dissolution medium. Floating lag time refers to the time it takes for the dose form to float. The floating time is the amount of time that a dose form floats.

3. Surface characterisation, drug loading, and particle size analysis: In the case of floating beads and microspheres, drug loading is determined by crushing a precisely weighed sample of microspheres/beads in a mortar and adding it to a suitable dissolution medium, which is then centrifuged, filtered, and analysed using spectrophotometry and other analytical techniques. Optical microscopy is used to determine the particle size and size distribution of microspheres or beads in the dry condition. SEM is used to examine cross-sectional and exterior morphology.

4. In-vitro release study: This is done to determine the amount of medicine that is released over a set length of time. Synthetic membranes, Franz diffusion cell systems, and various forms of dissolving equipment are also used.

5. X-Ray/Gamma Scintigraphy: It locates the dose form in the gastrointestinal system, allowing one to forecast and link the GET and dosage form passage. The presence of radio opaque substance in a solid dose form allows X-rays to visualise it. In addition, the use of a emitting radionuclide in the formulation allows for indirect exterior observation via a camera/scintiscanner. The -rays released by the radionuclide are focused on a camera in scintigraphy, which helps to monitor the location of the dosage form in the gastrointestinal system.

6. Swelling analysis: This is used to determine the molecular properties of swollen polymers. Optical microscopy, dissolving equipment, and more advanced methods such as Confocal laser scanning microscopy, 1H NMR imaging, and light scattering are used to determine it.

7. Drug content determination: The percent drug content indicates how much drug is contained in the formulation. It must not go beyond the bounds set by standard monographs. HPTLC, HPLC, Inductively Coupled Plasma Atomic Emission Spectrometer, Micro-titrimetric techniques, near infrared spectroscopy, and other procedures are used to determine it.

8. Entrapment efficiency as a percentage: Quantifying phase distribution of a medication in a manufactured formulation relies on entrapment efficiency. Pressure ultra-filtration, ultra-centrifugation, or micro dialyses are used to determine it.[22,23]

Applications of GRDDS

- **Reduced undesirable activity at the colon:** The drug maintenance in the hydro dynamically balanced system (HBS) is affected by the present drug in the intestine and also their action is restricted. These properties may be shows good GRDF formulations for antibiotics like beta-lactam which are absorbed only in the small intestine and results in the formulation of microorganism's resistances.

- **Enhanced Bioavailability:** The drug riboflavin bioavailability is enhanced by Control Release Gastro retention delivery formulation (CRGRDF) Other than non-GRDF CR dosage forms.
- **Absorption enhancement:** For the development of a floating system some drugs have poor bioavailability at the target site of GIT and regulate absorption.
- **Site-specific drug delivery systems:** The site-specific drug conveyance frameworks imply that the medications are caught up in the small digestive tract and the stomach site. For the controlled way of the medication at the site of the stomach shows better therapeutics impacts. This prompts the base symptoms and furthermore decreases dosing recurrence like Riboflavin and Furosemide.[21]

Table 1: Drug Used in the Formulation of Grdf.

S.NO	DOSAGE FORMS	ACTIVE PHARMACEUTICLAS INGREDIENTS	REFERENCES
1.	Powder forms	Cinnerzine drug	[24]
2.	Microspheres (Floating system)	Ibuprofen, Aspirin, p-nitro aniline, Griseofulvin, Terfenadine etc.	[24]
3.	Tablets (Floating system)	Captopril, Ampicillin, Amoxicillin, Isosorbid mononitrate, Theophylline, Fluorouracil, Verapamil, Diltiazem, Acetaminophen, Prednisolone, Nimodipine etc.	[24]
4.	Granules (Floating system)	Prednisolone, Diclofenac sodium, Indomethacin etc.	[25]
5.	Capsules (Floating system)	Misoprostol, Chlordiazepoxide HCl, Nicardipine, Pepstatin, L-DOPA and Benserazide, and Diazepam etc.	[25]
6.	liquid alginate preparations (Floating system)	Aluminum hydroxide, Magnesium carbonate etc.	[25]
7.	Nanoparticle (Mucoadhesive)	Fluconazole	[26]
8.	Gel- beads (Calcium pectinate)	Famotidine	[27]
9.	Minitablets	Furosemide drug	[28]

Table 2: Marketed Products of Gastroretentive Formulations.[29,30,31]

S.NO	BRAND NAME	DRUGS
1.	Valrelease ®	Diazepam
2.	Liquid Gavison ®	Aluminium hydroxide,
3.	Madopar ®	L-DOPA and Benserazide
4.	Almagate Flot Coat ®	Aluminum -magnesium antacid
5.	Cifran OD ®	Ciprofloxacin
6.	Baclofen GRS	Baclofen
7.	Cytotec®	Misoprostal
8.	Topalkan ®	Aluminum -magnesium antacid
9.	Zanocin OD ®	Ofloxacin
10.	Conviron	Ferrous sulfate
11.	Metformin GR ®	Metformin hydrochloride

CONCLUSION

In current scenario, it is quite challenging to design effective dosage forms for GIT disorders. Developing these kinds of formulations is a huge problem for any scientist. For developing gastro-retentive formulations for various GIT disorders. In this review paper we have concluded that a gastro retentive drug delivery system is a great mode to treat GIT disorders because it provides local action in the stomach for a longer length of time. This will lead to reduced dosing frequency and decreased toxicity. Prolong GI residence time of the dosage form. Ultimately increases drug absorption. So, this drug delivery system overcomes all the problems associated with conventional dosage form.

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REFERENCES

1. Subhramananyam CVS, Setty JT. Laboratory manual of physical pharmaceutics. Vallabh prakashan, 2002; 21.
2. Rathod HJ, Mehta DP, Yadav JS; A review on Gastroretentive Drug Delivery Systems; PharmaTutor, 2016; 4(7): 29-40.
3. Joseph R. Robinson, Lee V. Controlled Drug Delivery, Fundamentals and Applications. 2nd Edition, Revised and Expanded, Marcell. Dekker Inc., New York (2009).
4. Vyas SP, Khar RK. Controlled drug delivery: concept and advances. Vallabh Prakashan Delhi, 2002; 1: 123-231.
5. Chandana S.B., Vishnu P., Babu K.N., Rao, U.K., Sai S. and Sarvani T.A; 2014. brief review of floating drug delivery Systems. South Pacific Journal of Pharma and Biosciences, 2(2): 137-153.
6. Kanekar A.S., Patil A.B., Kanvaje A.M., Khade A.B and Battase A.P.Floating drug delivery systems- A Comprehensive Review and its possible scope. International Journal of Pharmacy Review and research, 2014; 4(3): 183-189.
7. Khan R. Gastro retentive Drug Delivery System – A Review. Int J Pharm Bio Sci, 2013; 4(2): 630-646.
8. Sandhan S., Singh R and Kalra S. Gastro retentive drug delivery system- A review. African Journal of Pharmacy and Pharmacology, 2015; 9(12): 405-417.
9. Sharma S and Pawar A. Low density multiparticulate system for pulsatile release of meloxicam. Int J Pharm., 2006; 313: 150-158.
10. Gandhi S., Pandya P., Umbarkar R., Tambawala T., Shah M. (2011), Mucoadhesive Drug delivery System- An Unusual Maneuver for Site Specific Drug Delivery System, Int J of Pharm Sci., 2: 132-152.
11. Felipe, J.O.Varum; Emma, L. Mc.Connell; Joao, J.S.Sousa; Francisco, Veiga; Basit, Abdul W, (2008), Mucoadhesion and the Gastrointestinal Tract, Critical Reviews in Therapeutic Drug Carrier Systems, 25: 207-258.
12. Patel A.K and Patel V.M. A review- Gastro-retentive drug delivery systems and its rationale in peptic ulcer treatment. Journal of Pharmaceutical Science and Bio scientific Research, 2012; 2(4): 179-188.
13. Gupta G, Singh A; A Short Review on Stomach Specific Drug Delivery System; International Journal of PharmTech Research; 2012; 4(4): 1527-1545.
14. HUANG, Y.; LEOBANDUNG, W.; FOSS, A.; PEPPAS, N. A. Molecular aspects of muco- and bioadhesion: Tetheres structures and site-specific surfaces. *J. Control. Release*, 2000; 65(1): 63-71.
15. Nayal AS, Pandey S, Gnanarajan G, *et al.* Review: An Overview on Gestroretentive Floating Tablet. International Journal of Pharmaceutical and Chemical Sciences, 2013; 2(3): 1357-1365.
16. Sandhan S., Singh R and Kalra S. Gastro retentive drug delivery system- A review. African Journal of Pharmacy and Pharmacology, 2015; 9(12): 405-417.
17. Gajanan R.K., Kadam V.S., Jadhav S.B., Bharkad V.B., Shinde S.G and Zamerruddin M. A review of Gastro-retention Drug Delivery System. World Journal of Pharmacy and Pharmaceutical Sciences, 2014; 3(3): 490-507.
18. Marinaganti RK, Bonthu S, Nagakanyaka DP, Sheik M; A comprehensive review on gastro retentive drug delivery system, 2013; 3(2): 149-164.
19. Binoy B and Jayachandran N.C.V. Floating Drug Delivery Systems- A new approach in the gastric retention- a review, Journal of Drug Delivery Research, 2012; 1(3): 18-31.
20. Chowdary K.P.R. and Chowdary K.L.C. Recent Research Floating Drug Delivery Systems- A review, Journal of Global Trends in Pharmaceutical Sciences, 2014; 5(1): 1361-1373.
21. Agnihotri SA, Jawalkar SS, Aminabhavi TM; Controlled release of cephalexin through gellan gum beads: Effect of formulation parameters on entrapment efficiency, size, and drug release, European Journal of Pharmaceutics and Biopharmaceutics, 2006; 63(3): 249-261.
22. Harries D, Sharma HL; GI transit of potential bioadhesive formulations in man: A scintigraphic study; Journal of Controlled Release, 1990; 12(1): 45-53.
23. Arrora S, Ali J, Khar RK, Baboota S. Floatng drug delivery systems: A review. AAPS Pharm Sci Tech, 2005; 6(3): 372-90.
24. Vyas SP, Khar RK. Gastroretentive systems. In: Controlled drug Delivery. Vallabh Prakashan, Delhi, India, 2006; 197-217.
25. Bhardwaj, L., P.K. Sharma, and R. Malviya, A short review on gastro retentive formulations for stomach specific drug delivery: special emphasis on floating in situ gel systems. African journal of basic & applied sciences, 2011; 3(6): 300-312.
26. Renber, S., et al., Development, characterization, and in vivo assessment of mucoadhesive nanoparticles containing fluconazole for the local treatment of oral candidiasis. International journal of nanomedicine, 2016; 11: 2641.
27. Satheeshababu, B. and G. Sarvaiya, Gastroretentive drug delivery system of famotidine: Formulation and in vitro evaluation of oil entrapped calcium pectinate gel beads. Indian Journal of Pharmaceutical Sciences, 2016; 78(2): 203-209.
28. Meka, L., et al., Design and evaluation of polymeric coated minitablets as multiple unit gastroretentive floating drug delivery systems for furosemide. Journal of pharmaceutical sciences, 2009; 98(6): 2122-2132.
29. Vyas SP, Khar RK. Gastroretentive systems. In: Controlled drug Delivery. Vallabh Prakashan, Delhi, India, 2006; 197-217.
30. Chawla G, Gupta P, Bansal AK. Gastroretentive drug delivery systems. In: Jain NK. editor. Progress

in controlled and novel drug delivery systems. CBS Publishers and Distributors. New Delhi, 2004; 76-97.

31. Carvalho, Flavia Chiva; Bruschi, Marcos Luciano; Evangelista, Raul Cesar; Palmira, Maria; Gremiao, Daflon, (2010), Mucoadhesive drug delivery systems, Brazilian Journal of Pharmaceutical Sciences, 46.