WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Gastroretentive Drug Delivery System :A Review

Pote Apeksha Sahadev, Dr.Cholke Pravin

Dharmaraj Shikshanik Pratishtan College of Pharmacy Walki Ahmednagar

ABSTRACT-

This review on gastroretentive drug delivery system to compile the recent literature with special focus on various gastroretentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery. In order to understand various physiological action achieve gastric retention, we have summarize . Oral controlled release and site specific drug delivery system has been of great interest in pharmaceutical field to achieve improved therapeutic advantage. Concept of novel drug delivery system overcome certain aspect related to physicochemical properties of drug molecule and the related Gastro retentive drug delivery system is one of such novel approaches to prolong gastric residence time, thereby targeting site specific drug release in the stomach for local or systemic effects. This approach is useful particularly for the drugs which have narrow absorption window in the upper part of gastro intestinal tract In this review we have been discussed various approaches of gastro retentive drug delivery system, such as floating and non-floating system

Keyword –floating system, non-floating system, gastric residence time

Introduction-

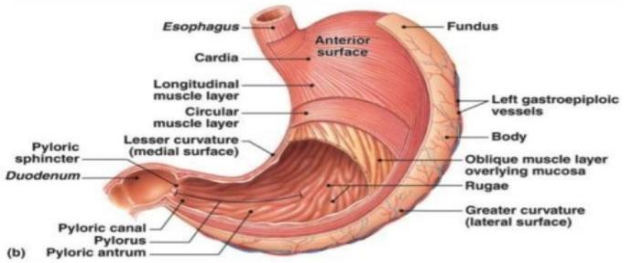
The conventional oral delivery system show limited bioavailbility because of fast gastric emptying time among many other reason involved.However the recent technological development has resulted to novel pharmaceutical products,mainly the controlled release drug delivery system to overcome this problem.Gastro retentive drug delivery system (GRDDS) is one such example where the attribute like gastric retention time coupled with the drug release forextended time has significantly improved. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation.

Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT). Also, the drugs which a narrow absorption window (NAW) in the upper part GIT not suitable for oral sustained release drug delivery system due to the brief gastric emptying time as tablet have

2.7 ± 1.5 hours (h) stomach transit and 3.1 ±0.4 h intestinal transit time (4), thus the bioavailability of such drugs having absorption window in stomach is generally limited . Over the last few decades , several gastroretentive drug delivery approaches being designed and developed ,including :high density(sinking)system that is retained in the bottom of the stomach ,low density (floating) system that causes buoyancy in gastric fluid ,mucoadhesive system that causes bioadhesion to stomach mucosa ,unfoldable,extendible or swellable system which limits emptying of the dosage form through the pyloric sphincter of stomch , superporous hydrogel system ,magnetic system etc. The current review deals with various gastroretentive approaches that have recently become leading methodologies in the field of site specific orally administered controlled release drug delivery system.

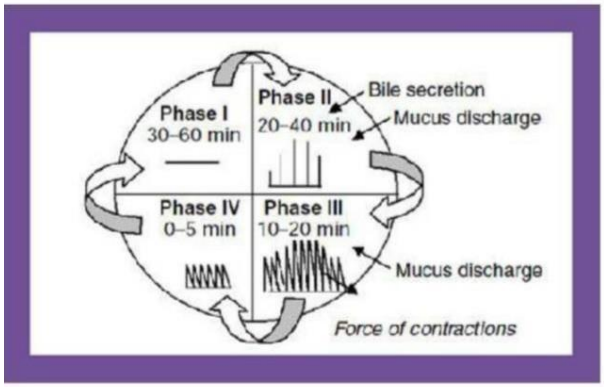
Physiology of stomach-

The Gastrointestinal tract is essentially a tube about 9meters long that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx),esophagus, stomach, small intestine(consisting of the duodenum, jejunum and ileum) and large intestine (consisting ot the



cecum, appendix, colon and rectum)stomach is an organ with a capacity for storage and mixing. The antrum region is responsible for the mixing and grinding of gastric content.

The inter digestive motility pattern is commonly called the‘migrating motor complex’ (‘MMC’)and is organized in cycles of activity and quiescence. Each cycle lasts 90–120 minutes and consists of four phases.



Features Of Stomach

Gastric pH: Fasted healthy subject 1.1 ± 0.15

Volume: Resting volume is about 25-50 mL

Gastric Secretion: Acid, pepsin, gastrin, mucus and some enzymes about 60 mlwith approximately 4 mm of hydrogen ions per hour.

Different Approaches Of Gastrointestinal DrugDelivery System:

Different approaches have been pursued to increase the retention of oral dosage forms in the stomach. Some are formulated as single component whereas others are formulated as multi- component dosage forms

- GRDDS can be broadly categorized into floating and non-floating system.
- Floating system
- Non-floating system:

Floating System-

This delivery systems is desirable for drugs with an absorption window in the stomach or in the upper small intestine . This have a bulk density less then gastric fluids and so remain buoyant inthe stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly.

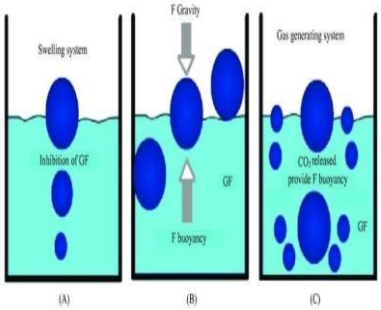
Buoyancy principal-

The object floats better if F is on the higher positive side as shown in fig. This apparatus

helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unfore seeable intragastric buoyancy capability variations

F = F buoyancy – F gravity = (DF – Ds) gvWhere, F= total vertical force,

DF = fluid density, Ds= object density, v = volume and g = acceleration due to gravity.



1.The major requirement for floating drug delivery system-1.It should release contents slowly to serve as a reservior
2.It must maintain specific gravity lower than gastric contents(1.004-1.01 gm/cm³)
3.It must form a cohesive gel barrier

Effervescent-

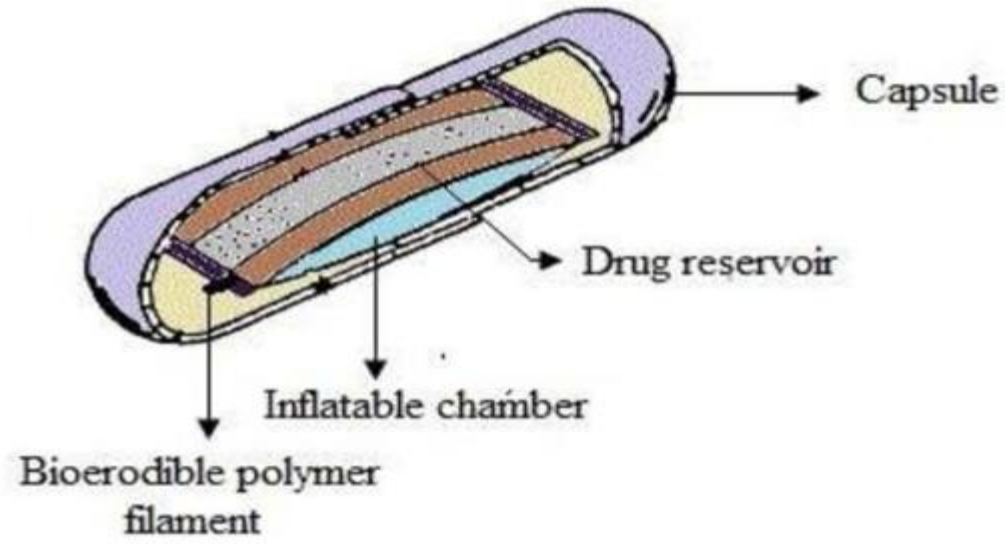
These are matrix type of system. Prepared with the help of swellable polymer such asmethylcellulose and Chitosan and various effervescent compounds.

Ex: sodium bicarbonate, tartaric acid, citric acid. These are formulated in such a way that when they come in contact with gastric content, CO2 is liberated and gets entrapped in swollen hydrocolloid which provides
Buoyancy to dosage form. The design of delivery system was based on swellable asymmetric triple layer tablet approach.These systems are further classified as below:

Gas Generating System: The main mechanism is involved in this system is the production of CO2 gas due to reaction between sodium bicarbonate, citric acid and tartaric acid.The material that have been reported are mixture of sodiun alginate and sodium bicarbonate,multiple unit floating dosage form that generate gas (carbon dioxide)when ingested floating mini capsule with a core of sodiun biacarbonate ,lactose and polyvinyl pyrrolidine coated with hydroxypropyl methylcellulose(HPMC)and floating system based on ionexchange resin technology etc.

Inflatable Gastrointestinal Drug Delivery system:

These systems possess inflatable chamber containing liquid ether which gasifiers at body temperature to inflate the stomach. Inflatable chamber contains bio erodible polymer filament (e.g. Copolymer of poly vinyl alcohol and poly ethylene) that gradually dissolves in gastric fluid and finally cause inflatable chamber to release gas and collapse.



Raft Forming System: Raft forming system has received much attention for the delivery of antacid and drug Delivery for gastro infection and disorders on contact with gastric fluid a gel forming Solution swells and forms a viscous cohesive gel containing entrapped co2 bubbles. Which Forms raft layer on top of gastric fluid which releases drug slowly in stomach.
A scientist Reckitt and colman products Ltd..,describe a raft forming formulation for the treatment of Helicobacter pyroli (H pyroli)infection in the GIT.The composition contained drug,alginic acid,sodium bicarbonate ,calcium carbonate,mannitol and sweetner.These ingredients were granulated and citric acid was added to the granules.The formulation produces effervescene and aerates the raft formed ,making it to float.

Non-effervescent Systems -

Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate.Excipients used most commonly in these systems include hydroxypropyl methylcellulose (HPMC) polyacrylates, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates .

This system can be further divided into the sub-types:

Hydrodynamically Balanced System:

Sheth and Tossounian first designated these 'hydrodynamically balanced systems'. These systems contains drug with gel forming hydrocolloids meant to remain buoyant on the stomach content. These are single-unit dosage form, containing one or more gel-forming hydrophilic polymers. Hydroxypropyl methylcellulose (HPMC), hydroxethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans or alginic acid are commonly used excipients to develop these systems

Microballoons / Hollow Microspheres:-

Microballoons / hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion / evaporation methods to prolong the gastric retention time (GRT) of the dosage form. Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and pectin etc. Buoyancy and drug release from dosage form are dependent on quantityof polymers, the plasticizer polymer ratio and the solvent used for formulation.

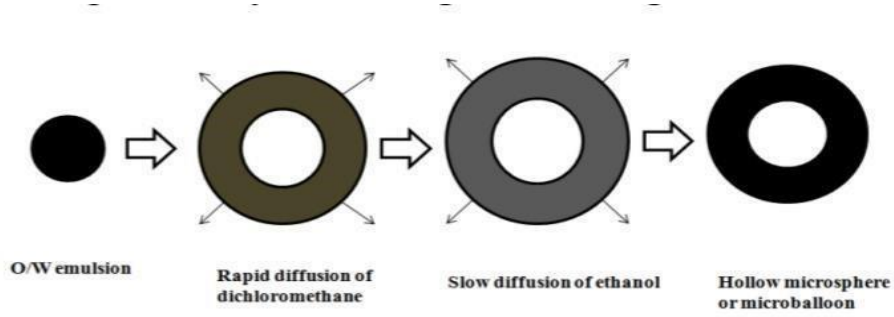
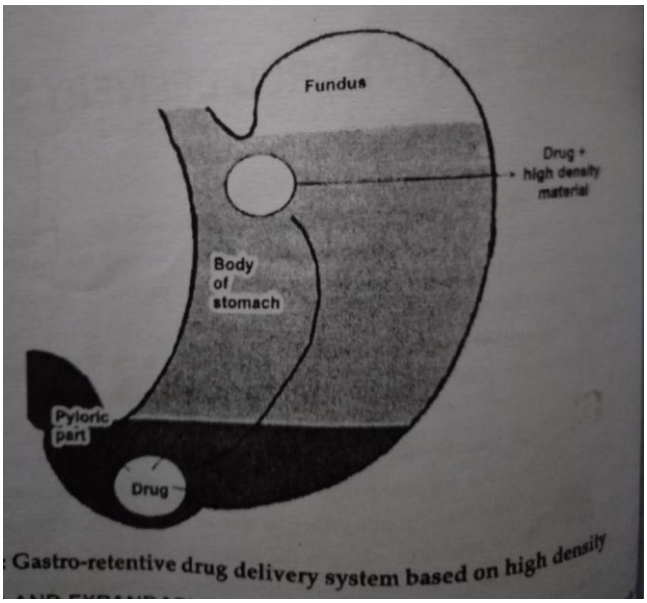


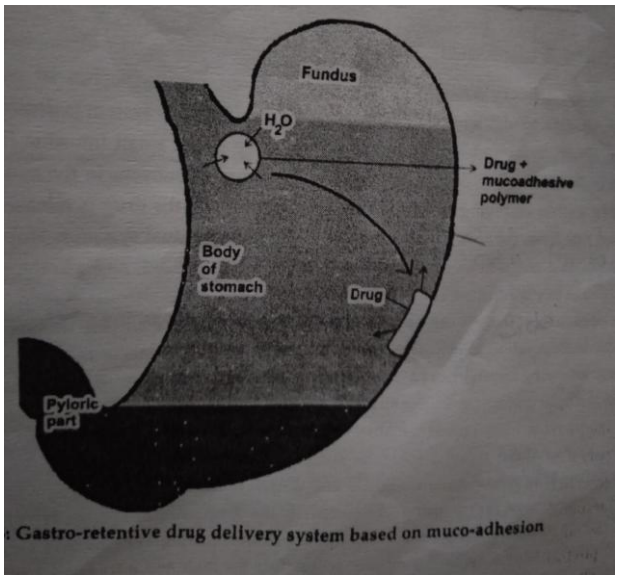
Fig.Formulation of floating hollow microsphere ormicroballoon

Non-Floating System: These gastro retentive drug delivery systems do not float in the stomach however they remain retained there by different mechanism.

High Density System: These systems possess density greater than the gastric fluids due to which the system sinks to the bottom and remains in the stomach. These are formulated by coating drug on heavy inert materials like zinc oxide, titanium dioxide, iron powder, etc.These system ,which have a density of ~3g/cm³.are retained in the stomach and capable of withstanding its peristaltic movement. The materials increase density by up to 1.5- 2.4 gm/cm3. A density close to 2.5 gm/cm3 seems necessary for significant prolongation of gastric residence time



Mucoadhesive/Bioadhesive System: These types of systems adhere to the biological membrane (mucosa) of the stomach and maintain intimate contact with the membrane for a longer time and hence retains in stomach for its prolonged release. These systems are formulated using bio adhesive polymers.Material commonly used for bioadhesion are poly (acrylic acid)(carbopol.polycarbophill),chitosan,Gantrez(polymethyl vinylether/maleic anhydride copolymers),chollestryamine,tragacanth,sodium



Gastro-retentive drug delivery system based on muco-adhesion

alginate,sucralfate,polyethylene glycol,dextran and polylactic acid.

Swelling System: These are a type of non-floating gastro retentive drug deliverysystem which when enters to stomach , swells (due to presence of swell able polymers) to anextent that cannot pass through the pyloric sphincter leading to its retention in the stomach

Expendable System: These systems are capable of expanding and retain in the stomach for longer periods. These are usually formulated as a capsule containing dosageform folded and compact form.

Advantages Of GRDDS-

- Improved bio-availability is expected for drugs that are absorbed readily upon release in the GI tract such ascyclosporine, ciprofloxacin, ranitidine, amoxycillin, captopril,
- Patient compliance by making a once a day therapy.
- Improved therapeutic efficacy.
- Reduces frequency of dosing.
- Targeted therapy for local ailments in the upper GI tract. Delivery of drugs with narrow absorption window in the small intestine region.
- Longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease.
- To avoid the first pass metabolism.
- Excellent accessibility.
- Rapid absorption because of enormous blood supply and good blood flow rates.
- Site-specific drug delivery.
- Minimizing mucosal irritation by drugs, by drug releasing slowly at a controlled rate.

Disadvantages Of GRDDS-

Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted. • The major challenge for a bioadhesive system is the high turnover rate of gastric mucus.

- There is also possibility of esophageal binding with bioadhesive drug delivery system

- Floating systems has limitation, that they require high level of fluids in stomach for floating and working efficiently. So more water intake is prescribed with such dosage form
-

Commonly Used Drug In Formulation Of Gastroretentive Dosage Forms

Dosage form	Drugs
Floating tablet	Acetaminophen,Acetylsalicylicacid, Ampicillin, Amoxicillin trihydrate, Atenolol Captopril, Cinnerzine, Chlorpheniramine maleate, Ciprofloxacin, Diltiazem Fluorouracil, Isosorbide dinitrate, Isosorbid mononitrate, p-Aminobenzoic acid(PABA),Prednisolone, Nimodipine, Sotalol,Theophylline, Verapamil
Floating capsule	Chlordiazepoxide HCl, Diazepam, Furosemide, L-DOPA and Benserazide Nicardipine, Misoprostol, Propranolol, Pepstatin
Floating microshere	Aspirin, Griseofulvin, p-nitro aniline,Ibuprofen, Terfenadine, Tranilast
Floating granules powder film	Diclofenac sodium, Indomethacin, Prednisolone Several basic drugsCinnerzine

Gastroretentive Products Available In The Market

Brand name	Active ingredient
Cifran OD ®	Ciprofloxacin
Madopar ®	L-DOPA and Benserazide
Valrelease ®	Diazepam
Topalkan ®	Aluminummagnesiumantacid
Almagate FlatCoat ®	Aluminum magnesiumantacid
Liquid Gavison ®	Aluminium hydroxide
Conviron	Ferrous sulfate
Cytotec®	Misoprostal

Factors Controlling Gastric Retention Of Dosage Forms

The stomach anatomy and physiology contain parameters to be considered in the development of gastroretentive 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 .
Drug that degrade or unstable in colon. E.g. Captopril,ranitidine HCl, metronidazole , metformin HCl. • Drug that disturb normal colonic microbes, e.g. Amoxicillin Trihydrate,Antibiotic against Helicobacter Pylori.

Conclusion-

Based on the literature surveyed, it may be concluded that gastroretentive drug delivery offers various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper gastrointestinal tract (GIT) and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability.All these gastroretentive drug delivery systems (high density, floating, expandable or unfoldable or swelling, superporous, bioadhesive, magnetic systems etc.) are interesting and present their own advantages and disadvantages. Now, a lot of work is running to develop different types of gastroretentive delivery systems of various drugs. In the future, it is expected that they will become of increasing importance, ultimately leading to improved

efficiencies of various types of pharmacotherapies'.it is necessary to take into consideration the physiological event in the GIT,selection of correct combination of drugs and excipients and design appropriate formulation strategies.

Reference

1. 1.k AK, Maji R & Das B, Gastroretentive drug delivery system: A review, Asian Journal ofPharmaceutical and clinical research, 3 (2010) 1
2. Pawar VK, Kansal S, Garg G, Awasthi R, Singodia D &Kulkarni GT, Gastroretentive dosage forms: A review with special emphasis on floating drug delivery systems,Drug Delivery, 18 (2011) 97.
3. Y. MadhusudanRao, A. V. Jithan, Advances in Drug delivery Vol. II, Pharma. Med. Press,Hyderabad(2011).
4. Novel drug delivery system- Y.W.Chien. Pg no. 1-42
5. Roop K khar, controlled drug delivery, gastroretentive system 4th edition, 202-203
6. Khan F.N, Dehghan H.G, Int J Health Res 2009; 2(1):23
7. Suryawanshi A and Hiremath SP: floating drug delivery system- a review, Americanjournal of pharmatech research 2011; 2(1): 138-53
8. Wu, W, Zhou Q Zhang HB, Ma, G, D, Fu, CD, Studies on mimodipine sustained release tablet capable of floating on gastric fluids with prolonged gastric residence time, Yao, Xue, Xue,Bao, 1997; 32;786Y790
9. Hilton AK, Deasy PB. In vitro and in vivo evaluation of an oral sustained release floating dosage form of amoxicillin trihydrate. Int J Pharm 1992; 86: 79-88.
10. Garg R, Gupta GD. Progress in controlled gastroretentive delivery systems. Trop. J PharmRes 2008; 7(3): 1055-66.
11. .Seth PR, Tossounian J. The hydrodynamically balanced system, a novel drug delivery system for oral use. Drug Dev Ind Pharm 1984; 10: 313-39.
12. .Hwang SJ, Park H, Park K. Gastroretentive delivery systems. Crit Rev Ther Drug CarrierSyst 1998; 15(3): 243-84
13. .Reddy LH, Murthy RS. Floating dosage system in drug delivery. Crit Rev There DrugCarrier System 2002; 19(6): 553-85.
14. Kawashima Y, Niwa T, Takenchi H, Hino T, Itoh Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. J Pharm Sci 1992; 81: 135-40.
15. .Vyas SP, Khar RK. Gastroretentive systems. In: Controlled drug Delivery. VallabhPrakashan, Delhi, India. 2006. p. 197-217.
16. .Clarke GM, Newton JM, Short MD. Gastrointestinal transit of pellets of differing size anddensity. Int J Pharm 1993; 100(13): 81-92.
17. Wu, W, Zhou Q Zhang HB, Ma, G, D, Fu, CD, Studies on biomedicine sustained release tablet capable off floating on gastric fluids with prolonged gastric