CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://zenodo.org/records/11080082

https://www.iajps.com/volumes/volume11-april-2024/18-issue-04-april-24/

Available online at: http://www.iajps.com *Review Article*

A REVIEW ARTICLE ON GASRORETENTIVE DRUG DELIVERY SYSTEM

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Article Received: April 2024 **Accepted:** April 2024 **Published:** April 2024

Abstract:-

The development of formulations based on prolongation of gastric residence has been gaining significant attention of the researchers. Stomach is a major organ of the digestive system and plays a significant role in drug absorption too. The gastrointestinal (GI) tract is highly heterogeneous in nature with wide variation in the pH, size of the segment, structure of the membrane, vascularity and smoothness of inner mucosa, etc. The residence time of the ingested matter, including drugs, is also not uniform throughout. The normal gastric residence time, i.e., around two hours, may not be sufficient for the complete absorption of drugs which are absorbed predominantly from stomach. Moreover, for the drugs acting locally in stomach for conditions such as hyperacidity, peptic ulcer or gastric infection, prolonging the residence time may prove to be advantageous. Medicinal substances, which cause irritation in the intestine or are degraded in the intestinal environment, are preferentially formulated as gastroretentive (GR) dosage forms too. Various strategies such as floating delivery systems, mucoadhesive formulations, high density systems and swelling dosage forms are invariably used to achieve enhancement in gastric residence time. The current chapter endeavors to discuss the stellar merits and limitations of each approach, their evaluation and characterization aspects including gastroretention and bioavailability studies. Each of such systems has also been duly illustrated citing laboratory instances, and/or apt literature reports.

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*Please cite this article in press S.Sameer et al., **A Review Article On Gasroretentive Drug Delivery System**., Indo Am. J. P. Sci, 2024; 11 (04).*

INTRODUCTION:

Gastro retentive drug delivery systems is a type of system which prolongs the residence of administered drug in the gastric region for several hours thereby the bioavailability and solubility of challenging drugs may gets enhanced, and improves the patient compliance. Gastric emptying delaying conceptual mechanisms of mucoadhesion, flotation and sedimentation supports the gastro retentive drug delivery systems1 . Thereby gastro retentive drug delivery systems enhance the absorption of drugs in the gastrointestinal tract drug by improving the contact time with the small intestinal mucosa. Gastric retention-based drug delivery systems in turn provide a newer therapeutic possibilities and substantial benefits for researchers. Gastroretentive drug delivery systems may reduce the drug wastage. Gastro retentive drug delivery systems offer a controlled drug delivery profile with effective plasma zing plasma fluctuations 2.Drugssuitable for gastro retentive drug delivery formulations include drugs that have low absorption in the lower partof the GIT, unstable, poorly soluble at alkaline pH, short half-life, and show local activity at the upper part of the intestine3 . Due to the sustained/controlled release effect gastro retentive drug delivery formulations minimizes the mucosal irritation which may provides a desired plasma drug concentration and prevent drug fluctuations without causing dose dumping. Unstable drugs can also be delivered by this approach. The various approaches utilized in gastro retentive drug delivery system includes extended gastric residence time, low-density(floating), high-density(sinking), expandable (swelling), and mucoadhesive systems. The better understanding on the anatomy and physiology of the stomach (specifically proximal stomach- fundus and body; and the distal stomach-antrum and pylorus) plays a crucial role for the successful development of the gastro retentive dosage form. The critical factors which affect the gastro retentive drug delivery systems are size/ shape/density of gastro retentive formulations. Caloricdensity of the ingested food increases the gastro retentive property, herein the gastric emptying rate also gets affected by the gastroretentive formulations. The other factors related to patient such as gender, age, illness, and emotional state also influences the delivery of gastro retentive formulations. Diseases conditions of Parkinson's disease, diabetes also influence the gastric emptying rate. Elderly patients and males have superior gastric emptying rate compared to females and younger's. In addition factors influencing the delivery of gastro retentive formulations works by accelerating or delaying gastric emptying in other related conditions off earand apprehension, acute /chronic diseases, trauma, drugs, and surgery. The gastroretentive dosage formulation has been regulated by various factors such as polymer types (nonionic, cationic, and anionic polymers), polymer composition, viscosity grade, polymer molecular weight, and drug solubility. density systems etc.

The different mechanisms of gastroretentive drug delivery systems are shown in Approaches of effervescent and non-effervescent systems with the concepts to generate effervescence and concepts of swelling property have been also attempted by researchers. Here in natural, synthetic and semi synthetic polymers are utilized for the development of gastro retentive drug delivery systems. When compared to synthetic/semisynthetic polymers The natural polymers which are naturally available are widely used for gastroretentive drug delivery systems due to the versatile properties of non-toxic, non- irritant, and biocompatible. Therelease mechanism of astroretentivedrugdelivery systemwasshowninFigure. 4.Polymers used in gastro retentive drug delivery systems The development of gastro retentive drug delivery systems involves the role of polymers towards the successful formulation development. In order to afford the floating capacity numerous approaches has been attempted by researchers such as maintaining the hydrodynamically balanced systems, gas-generating systems, raft-forming systems, low-density systems etc 5 . The different mechanisms of gastroretentive drug delivery systems are shown in Figure. 3. Approaches of effervescent and non-effervescent systems with the concepts to generate effervescence and concepts of swelling property have been also attempted by researchers. Here in natural, synthetic and semi synthetic polymers are utilized for the development of gastro retentive drug delivery systems. When compared to synthetic/semi synthetic polymers the natural polymers which are naturally available are widely used for gastro retentive drug delivery systems due to the versatile properties of non-toxic, non-irritant, and biocompatible6 . The release mechanism of gastroretentive drug delivery system was showninFigure.4.Gastroretentive drug delivery systems mechanism Sedimentation Adhesion Swelling Floating Figure 4: Gastro retentive drug delivery system mechanisms Gastroretentive drug delivery Ystem get in contact with the gastric fluids. System gets expanded/swelled Improved gastric retention Drug release either immediate/prolonged release offered Figure 5: Release mechanism of

formulations caloric density factors associated with patien

Gastroretentive drug delivery system Raffi Malik et al; 2015 developed diacerein loaded nanofibers based gastroretentive dosage form in order to improve the solubility of diacerein using Poly L-(lactic acid) by the electrospinning technique. Their developed nanofibers were smooth, discrete, &non- woven. as determined by X-ray crystallography analysis which largely contributes to higher drug solubility in the nanofibers developed. The results of their buoyancy studies demonstrated that the diacerein loaded nanofibers exhibited zero lag time with 61.3% of diacerein release in 30 h facilitating the slow release from the nanofiber. They concluded that the and sulphonic acid of mucus 8 . Su, C et al; 2018 developed complex hydrogels formed with chitosan and ring-opened polyvinyl pyrrolidone as a swellable mucoadhesive gastroretentive drug dosage formulation. Their developed complex gastro retentive metronidazole microparticles using two approaches based on the solubility of the polymer via an aqueous dispersion-based formulations using a hydrophilic polymer hydroxyl propyl methyl cellulose and emulsion-based formulations in case of ethyl cellulose by incorporating chitosan in both the formulations. They observed that all microparticles floated immediately in contact of simulated gastric fluid. Finally they observed that chitosan and hydroxypropyl methyl cellulose based microparticles revealed the best relationship between floating duration and drug release, to wardst he ideal condition for the floating gastroretentive systems10. The mucoadhesive sodium alginate is biocompatible, nontoxic, and biodegradable. Alginates offer better mucoadhesive property. The gelation property of alginate with divalent metal ions such as Ca+2; concept has been applied the gastric residence they observed a better release profile of in simulated gastric fluid(SGFpH1.2).They observed that the mean particle size of the microspheres gets increased upon polymeric concentration gradient and decreased with increase in stirring speed with an entrapment of 51.42−80.46%. Calcium chloride (10 % w/v) present in the formulation supports the extended release of acyclovir. They observed that the optimized acyclovir loaded mucoadhesive alginate microspheres showed (66.42±1.01%). Their results of Gamma scintigraphy analysis revealed the gastroprotection effect of optimized formulation for more than 4h, suitable for gastroretentivesystems11.Hydroxypropylβ-cyclodextrin issue dasa polymer for various pharmaceutical formulations. Hydroxypropyl βcyclodextrin has shown to improve the solubility of lipophilic drugs byf orming a complex between Hydroxypropyl β-cyclodextrin and the drug of choice utilized for the pharmaceutical formulations. The formation of guest-host type complex may enhances the solubility of lipophilic drugs in case of Hydroxypropyl βcyclodextrin.Sharad S. Darandale et al 2012developed Furosemide loaded gastroretentive formulation by polymeric film made up of a bilayer of immediate/controlled release layers folded into a hard gelatin capsule here in furosemide shown narrow absorption window using ethylcellulose,hydroxypropylβcyclodextrin. Here in the gastroretentive retention mechanism works based on the unfolding and swelling of the film and its bioadhesion to the gastric mucosa. Carbopol® 971P NF used in the bilayer film formulation supports optimum drug release, bioadhesion and mechanical properties. The developed film with zig-zag folding in the capsule swell under acidic conditions with immediate release profile for 1 h followed by controlled release characteristics for up to 12 h in acidic medium. They concluded that gastroretentive dosage form may provide controlled release with narrow therapeutic windows12.TheFilmcoatedEudragitbasedpolymerswhicharebeing whitish and faint characteristic odor are resistant to gastric media but solubleinintestinalfluidsabovepH6andshowsmiscibilityinacetone- alcohols, dichloromethane, ethyl acetate and sodium hydroxide. Eudragit polymers shown effective and stable enteric coatings with a fast dissolution in the upper bowel. Eudragit polymers of different grades shown variable release profiles and site specific drug delivery13 . Sivakumar M et al 2002 developed spherical shaped and porous nature gentamycin loaded poly(methyl methacrylate) microspheres for hard tissue repair and regeneration. Shadab Md et al; 2017 developed solvent evaporation technique. They confirmed the presence of characteristic groups and compatible nature of the formulations using 1H-FT-NMR spectroscopy. Their observations of euilibrium swelling studies of microspheres carried out in pH 7.4 phosphate buffer and pH 1.2 gastric medium shown that the developed microspheres were able to float in the pH 1.2 and 7.4 media and gets settled also further they observed a longer period of release. They emphasized that the carboxylic groups of PMMA-F microspheres were coupled with amino groupsofgentamicinusing1-ethyl-3(3-dimethylpropyl) carbodiamide as coupling agent14.The biocompatible and biodegradable aliphatic polyester synthetic polymer Poly (e-caprolactone) is approved by Food and Drug Administration. The hydrophobic crystalline polymer Poly(e-caprolactone) is widely used in drugd elivery systems, sutures, devices, wound dressings and actas an adhesion barrier. The

melting point of Poly (ecaprolactone) melting point is 59–64 °C 15-21 . Umar Farooq et al; 2017 developed Eudragit E 100 and polycaprolactone based floating, metronidazole benzoate microspheres using Polyvinyl alcohol as an emulsifier prepared by oil in water solvent evaporation method in order to improve the enhanced gastric Gastroretentive drug delivery systems novel technologies The novel gastroretentive drug delivery systems reported were non-effervescent systems (single/double layer floating tablets, and micro balloons/hollow microspheres) in which highly swellable cellulose derivatives or gel- forming polymers are used for its formulation development. The gas generating agent and volatile liquids are used in case of effervescent floating systems. This combination of effervescent agents (sodium bicarbonate, calcium carbonate, tartaric acid, and citric acid) and hydrophilic polymers are used in case of effervescent floating systems.

The buoyancy will be exhibited due to the liberated CO2 gas which may elicit the drug release properties. Incase of high density systems the formulations will be developed by enhancing the density of the gastroretentive drug delivery formulation to be greater than that of gastric fluid using excipients such as barium sulfate, zinc oxide, iron powder, and titanium dioxide. Expandable based gastroretentive drug delivery systems drug delivery systems works in such a way by increasing the volume or shape of the formulations. This system works on the principle of plug type system. In case of mucoadhesive based gastroretentive drug delivery systems the adherence towards the gastro epithelial cells will be achieved using natural/synthetic based mucoadhesive polymers (carbopol, chitosan, polyethylene glycol, polyethylene glycol, polyacrylic acid, hydroxypropyl ethyl cellulose etc). The Raft-forming systems based gastroretentive drug delivery systems involves sustained release behavior using effervescent excipients and gel forming polymers. The magnetic based gastroretentive drug delivery systems involves internal magnet to control the delivery. The ion-exchange resin based gastroretentive drug delivery systems involves cationic/anionic based water insoluble Patents in Gastroretentive drug delivery systems The patents in Gastroretentive drug delivery systems includes various approaches in which Vishwanath Sudhir N and epatented a technology of novel gastro-retentive drug delivery system comprising inert core, polymers and plasticizer that floats for an extended period of time over the simulated physiological fluids owing to its low density38 . Hassan Mohammad; 2013patented a technology based pharmaceutical product for retention in the stomach comprising of a sheet of hydrat able polymer which will not pass out of the stomach.Ithasbeenreportedthatgastroretentivefloating drugformulation comprising at least one functionalized natural and/or synthetic calcium carbonate-comprising mineral and at least one pharmaceutically active ingredient and at least one formulating aid wherein said functionalized natural or synthetic calcium carbonate is a reaction product of natural or synthetic calcium carbonate with carbon dioxide and one or more acids, wherein the carbon dioxide is formed in situ by the acid treatment and/or is supplied from an external Advantages

- •Improved drug absorption
- because of increased GRT. Enhanced bioavailability.
- Controlled drug delivery. •Reduced dosing frequency.• Ease of administration
- Better patient compliance.
- Targeted therapy for local allments in the upper GIT. •Reduced fluctuations of drug concentration.
- Deliveryofdrugswithnarrowabsorptionwindowsmall intestine region.
- LON
- Enhanced bioavailability
- Sustained drug delivery/reduced frequency of Dosing
- Targeted therapy for loca lailments in the upper GIT
- Reduced fluctuations of drug concentration • Improved selectivity in receptor activation • Reduced counter-activity of the body

Advantages of GRDDS

Enhances bioavailability.

✓Sustained release of drug by prolonged gastric retention time.✓

Site specific or targeted delivery of drug Reduction in dosing frequency.

✓ Improves patient compliance & Suitable for self-administration. Minimization of side effects

✓ Enhances therapeutic effectiveness.

✓ Local release of drugs to treat stomach and duodenal ulcers, gastritis and esophagitis.

✓Reduced the risk of stomach carcinoma. administered: penicillins,

✓ Various antibiotics, antiviral and antifungal agents can be successfully e.g sulphonamides, quinolones, cephalosporines, aminoglycosides and tetracyclines etc.

Disadvantage

- Retention in stomach is not desirable for drugs that cause gastric lesions/irritations. e.g, NSAIDS.
- Drugs degraded in the acidic environment tof stomach. e.g.insulin.
- Drugs undergo significant first-pass metabolism. e.g. nifedipine.
- Drugs have limited acid solubility .e.g. phenytoin.
- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
- These systems do not offer significant over the conventional dosage forms for drugs, which are absorbed throughout GIT.
- Drugs that may irritates the gastric lining or are unstable in gastric environment should not be formulated in (RDDS.
- Drugs absorbed by GIT will not be suitable for gastric retention system
- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
- Requires the presence of food to delay gastric emptying.
- Drugs which undergo significant first-pass metabolism, may not be desirable for GRDDS. Slow gastric emptying may lead to alter systemic bioavailability.

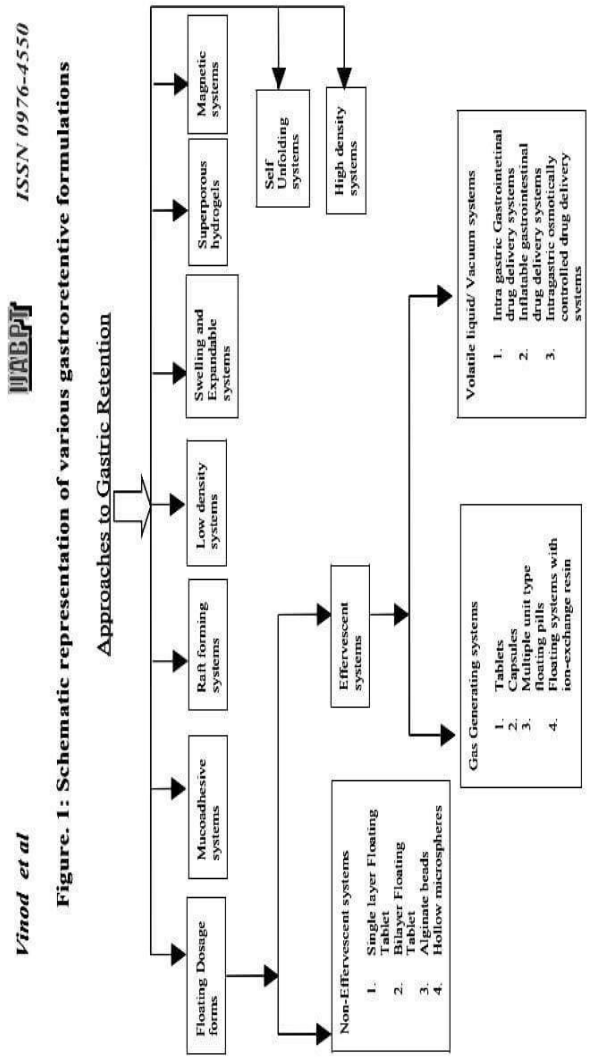

Figure. 1: Schematic representation of various gastroretentive formulations

IAJPI ISSN 0976-4550

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Formulation

Considerations for GRDDS It must be effective retention in the stomach to suit for the clinical demand

1) It must have sufficient drug loading capacity
2) It must be control the drug release profile
3) It must have full degradation and evacuation of the system once the drug release is over
4) It should not have effect on gastric motility including emptying pattern
5) It should not have other local adverse effects(Davis,2005).

Requirements for gastric retention From the discussion of the physiological factors in the stomach it must be noted that to achieve gastric retention, the dosage form must satisfy certain requirements.

One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contraction sand grinding and churning mechanisms. To function as a gastric retention device, it must be resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease.

Factors affecting the gastroretentive system Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time.

These attempts include useof floating dosage forms(gas-generating system sand swelling or expanding systems),mucoadhesive systems, high-density systems, modified shape systems, gastric emptying delaying devices and co-administration of gastric-emptying delaying drugs. Most of these approaches are influenced by a number of factors that affect their bioavailability and efficacy of the gastro retentive system (Sanjay et al., 2003).

Density–Gastric retention time(GRT) is a function of dosage form buoyancy that is dependent on the density.

Size–Dosageform units with a diameter of morethan7.5mm are reported to have an increased GRT compared 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 betterGRT90%to100%retentionat24hourscomparedwithother shapes.

Single or multiple unit formulation–Multiple unit formulations show a more predictable release profile and insignificant impairing of performance 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 coincide swith 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. (Caldwell et al., 1998; Murthy et al., 2000). 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.

Caloric content–GRT canbeincreasedby4 to10 hourswitha meal that is high in proteins and fats (Marvolaetal.,1989)(Mojaverian et al., 1988).

Frequency of feed–TheGRTcanincreasebyover400minuteswhen 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±1.2hours),regardless of the weight, height and body surface.

Age–Elderlypeople,especiallythoseover70,haveasignificantly longer GRT. Posture – GRT can vary between supine and upright ambulatory states of the patient.

Concomitant drug administration–Anti-cholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride can affect floating time.

Biological factors–Diabetes and Crohn's disease, et

Approaches to gastric retention

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas generating systems) (Deshpande et al., 1997). Swelling and expanding systems (Urquhart and Theeuwes, 1984; Mamajek, 1980). Mucoadhesive s systems (Lenaerts, 1990; Lehr, 1994). High density systems (Caldwell et al., 1988).Modified shape systems (Groning andHeum,1989; Bechgaard and Ladefoged, 1978).Gastric emptying delaying devices and co- administration of gastric delaying drugs. Among these, the floating dosage forms have been used most commonly. Floating DDS (FDDS), with low density providing sufficient buoyancy to float over the gastric contents, Bioadhesive systems, enabling the localized retention of the system in the stomach, Swelling and expanding systems,

preventing transit from the gastric sphincter, High density system, remaining in the stomach for longer period of time by sedimenting to the folds of stomach, Superporous hydrogels, and Modified-shaped system A number of other methods like use of passage-delaying agents, magnetically controlled 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. This results in an increased GRT and a better control of fluctuations in plasma drug concentration.
buoyancy and two distinctly different technologies have been utilized in the development of FDDS. 1) Non- Effervescent FDDS 2) Effervescent FDDS 1) Non-Effervescent FDDS The Non- effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as Chitosan and Carbopol

The various types of this system areas:
A. Single Layer Floating Tablets They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains bulk density of less than unity. They are formulated by intimate mixing of drug with low-density enteric materials such as CAP, HPMC.
B. Bi-layer Floating Tablets A bi-layer tablet contain two layer one immediate release layer which releases initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach (Oth et al., 1992).

D.Hollow Microspheres Hollow microspheres (microballoons),loaded with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitatedaqueoussolutionofPVAthatisthermallycontrol ledat400C. The gas phase generated in dispersed polymer drop let by evaporation Effervescent System Effervescent systems -include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO2) gas, thus reducing the density of the system and making it floaton the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporates at body temperature. These effervescent systems further classified into two types. 1. Gas generating systems, 2. Volatile liquid/Vacuum containing systems. like float

International Journal of Applied Biology and PharmaceuticalTechnologyPage:595Availableonlinea twww.ijabpt.comVinod et al ISSN 0976-4550 1. Gas Generating Systems A. Tablets Floating bilayer tablets with controlled release for efficient delivery developed by Ozdemir et al.,2000.Thelowsolubilityofthedrugcouldbeenhanced byusingthekneading
method, preparing a solid dispersion with β cyclodextrin mixed in a 1:1 ratio (SinghandBrahma,2000).Onelayercontainedthepolym ersHPMCK4M,HPMC K100MandCMC(for the control of the drug delivery)and the drug .The second layer contained the effervescent mixture of sodium bicarbonate and citric acid. The in vitro floating studies revealed that the lesser the compression force the shorter is the time of onset of floating, i.e., when the tablets were compressed at15MPa,thesecouldbegintofloatat20minuteswhereasa taforceof32MPa the time was prolonged to 45 minutes. Radiographic studies on 6 healthy male volunteers revealed that floating tablets were retained in stomach for 6 hours and further blood analysis studies showed that bioavailability of these tablets was 1.8 times that of the conventional tablets. On measuring the volume of urine the peak diuretic effect seen in the conventional tablets was decreased and prolonged in the case of floating dosage form. B. Floatingcapsules Floating capsules are prepared by filling with a mixture of sodium alginate and sodium bicarbonate. The systems were shown to float during in vitro tests as a result of the generation of CO2 that was trapped in the hydrating gel network on exposure to an acidic environment. C. Multiple unit type floating pills The system consists of sustained release pills as ‘seeds’ surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapmentofCO2withinthesystem.D.Floatingsystem withIon- Exchange resins A floating system using ion exchange resin that was loaded with bicarbonate by mixing the beads with 1M sodium bicarbonate solution (Shweta Arora et al., 2005). The loaded beads were then surrounded by a semipermeable membrane to avoid sudden loss of CO2. Upon coming in contact with gastric contents an exchange

of chloride and bicarbonate ions took place that resulted in CO2 generation thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads. The in vivo behavior of the coated and uncoated beads was monitored using a single channel analyzing study in 12 healthy human volunteers by gamma radio scintigraphy. Studies showed that the gastric residence time was prolonged considerably (24hours)compared with uncoated beads 1 to 3 hours 2. Volatile Liquid / Vacuum Containing Systems A. Intra-gastric floating gastrointestinal drug delivery system These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoiris encapsulated inside a micro-porous compartment. Table 1: Differentiation between floating and muco adhesive delivery systemsFloating drug delivery system Mucoadhesive drug delivery system 1. FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. 2. Floating of the dosage form can be achieved by two means i.e. either incorporating a gas generating system or volatile liquid/ vacuum system. Examples: Valrelease® , Madopar® HBS, Topalkan® 1. The term bioadhesion is defined as adhesion to biological surface i.e. mucus and/or mucosal surface. In instances when the polymeric system interacts with mucus layer only, it is referred as mucoadhesion.2.Mucoadhesioncanbeachievedbydiffe rentmucin- polymer interactions such as Wetting and swelling of the polymer to permit intimate contact with the biological tissue/interpenetration of Bioadhesive polymer chains and entanglement of polymer and mucin chains/formation of weak chemical bonds/sufficient polymer mobility to allow spreading/ water transport followed by mucosal dehydration B. Inflatable gastrointestinal delivery systems In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated polymeric matrix, encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid.

Intragastric osmotically

Controlled drug delivery system:

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. The osmotic pressure thus created acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate drug release through the delivery orifice.

The floating support is also made to contain abioerodible plug that erode saftera predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.

Bioadhesive drug delivery system

The term bioadhesion is defined as adhesion to biological surface i.e. mucus and/or mucosal surface. In instances when the polymeric system interacts with mucus layer only, it is referred as mucoadhesion. In order to develop an ideal oral bioadhesive system, it is important to have a through understanding of mucosa, bioadhesive polymers and mucin-polymer interactions in the physiological environment. Intestinal mucosa is composed of high molecular weight glycoproteins hydrated and covering the mucosa with a continuous adherent blanket. Mucingly co-proteins are rich with fucose and sialicacid groups at the terminal ends which provide a net negative charge in the acidic environment. The thickness of the mucin gel layer varies in different regions of the GIT with thickness ranging between 50-500 μm in stomach to 15-150μm in the colon. Cohesion of the mucin gel is dependent upon the glycoprotein concentration. Themucuslayer is created biologicallyto play a number of important functions of protecting the

absorption. Various investigators have proposed different mucin-polymer interactions, such asWetting and swelling of the polymer to permit intimate contact with the biological tissue Interpenetration of Bioadhesive polymer chains and entanglement of polymer and mucin chains. Formation of weak chemical bonds Sufficient polymer mobility to allow spreading Water transport followed by mucosal dehydration (Lehr, 1992; Mortazavi, 1993).

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ISSN 0976-4550 As the mucus lay order for a bioadhesive system to be successful; it should release its drug contents during this limited adhesion time

Raft-formingsystems

Here, agel-forming solution (e.g.sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO2 bubbles on contact with gastric fluid. Formulations also typically contain antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidi
Low-density systems

Gas-generating systems inevitably have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter. Low-density systems

Expandable systems

A dosage form in the stomach will withstand gastric transit if it is bigger than the pyloric sphincter (Caldwelletal.,1988).However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus,three configurations are required, a small configuration for oral intake, an expanded gastroretentive form and a final small form enabling evacuation following drug release. Un foldable systems are made of biodegradable polymer; the concept is to make a carrier, such as a capsule, incorporating a compressed system, which extends in the stomach. Caldwell et al., 1988 proposed different geometric forms (tetrahedron, ring or planar membrane (4-lobed, disc or 4-limbed cross form) of biodegradable polymer compressed within a capsule.

Swellable System

Swellable systems are also retained because of their mechanical properties. The swelling usually results from osmotic absorption of water. The dosage form is small enough to be swallowed, and swells in gastric liquids, the bulk enable gastric retention and maintains the stomach in a ‘fed’ state, suppressing housekeeper waves. Super porous hydrogels

Although these are swellable systems, they differ sufficiently fromt he conventional types to warrant separate classification (Chen and park, 2000) with pore size ranging between 10 nm and 10 µm. Absorption of water by conventional hydrogel is very slow process and several hours may be needed to reach an equilibrium state during which premature evacuation of the dosage form may occur. Super porous hydrogel, average pore size >100µm,swelltoequilibriumsizewithin
by a co- formulation of a hydrophilic particulate material, Ac-DiSol (crosscarmellose sodium).

Magnetic system into contact with bioadhesive coated system,

These systems appear as small gastroretentive capsules containing a magnetic material, whose elimination from the stomach is prevented by the interaction with a sufficiently strong magnet applied to the body surface in the region of the stomach. Despite numerous reports about successful tests, the real applicability of such systems is doubtful because the desired results can be achieved only provided that the magnet position is selected with very high precision. Probably, the development of new conveniently applied magnetic field sources will improve this concept.

Self-unfolding systems

The self-unfolding systems are capable of mechanically increasing in size relative to the initial dimensions. This increase prevents the system from passing via the pylorus and provides for its prolonged stay in the stomach. A drug can be either contained in a polymeric composition of the gastroretentive system or included as a separate component. Several methods were suggested to provide for the self-unfolding effect. (1) The use of hydrogels swelling in contact with the gastric juice.(2)Osmotic systems, comprising an osmotic medium in a semipermeable membrane. (3) Systems based on low-boiling liquids converting into a gas at the body temperature. High density systems Gastric contents have a density close to water (1.004 g /cm3). When the patient is upright small high-density pellets sink to the bottom of the stomach where they become entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall. A density close to 2.5 g/cm3 seems necessary for significant prolongation of gastric residence time and barium sulphate, zinc oxide, iron powder, titanium dioxide are used as excipients.

FACTORS CONTROLLING GASTRIC

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 [13]. 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.) [14]. The molecular weight and lipophilicity of the drug depending on its ionization state are also important parameters [15] . 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 [16] . Both positions may isolate the dosage system from the pylorus. A density of<1.0gm/ cm3isrequiredtoexhibitfloatingproperty[17].Shape and size of the dosage form Shape and size of the dosage forms are important in designing in digestible single unit solid dosage forms. The mean gastric residence times of non-floating 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 gastricretention 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[18].Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm [17]. Ring-shaped and tetrahedron-shaped devices have a better gastric residence time as compared with other shapes [19] . Food intake and its nature Food intake, viscosity and volume of food, caloric value and frequency of feeding have a profound effecton the gastric retention of dosage forms. The presence or absence of food in the gastro intestinal 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 [20] . 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 [21] . POTENTIAL DRUG CANDIDATESFORGASTRORETENTIVEDRUGDELIVERYSYSTEMS1) 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, para aminobenzoic acid, furosemide,riboflavinetc.3)Drugs those are unstable int he intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.

4) Drugs that disturb normal colonic microbes e.g antibiotics against Helicobacter pylori. 5) Drugs that exhibit low solubility at high pH values e.g.diazepam, chlordiazepoxide, 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. erythromycinetc.3) Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc. APPROACHES TO ACHIEVE GASTRIC RETENTION High density (sinking) system or non-floating drug delivery system This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content (~1.004gm/cm3).These formulations are prepared by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulphate, zinc oxide and titanium oxide etc [22]. 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[23].But, effectiveness of this system in human beings was not observed [24] and no system has been marketed. Floating drug delivery systems Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability [25]. This delivery systems is desirable for drugs with an absorption window in the stomach or in the upper small intestine [26]. This have a bulk density less then gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly as a desired rate from the system. After release of drug, the residual system is emptied from the stomach . This result in an increased gastric retention time(GRT)and a better control of the fluctuation in plasma drug concentration. The major requirements forfloating drug delivery

system are [22]: • It should release contents slowly to serve as a reservoir. • It must maintain specific gravity lower than gastric contents(1.004–1.01gm/cm3).•It must form a cohesive gel barrier. The inherent low density can be provided by the entrapment of air (e.g. hollow chambers) [27] or by the incorporation of low density materials (e.g. fatty materials or oils, or foam powder) [5, 28, 29]. These following approaches have been used for the design of floating dosage forms of single and multiple-unit systems. Recently a single- unit floating system was proposed consisting of polypropylene foam powder, matrix forming polymers, drug and filler [30]. The good floating behavior of these systems could be successfully combined with accurate control of the resulting drug release patterns. Single- unit dosage forms are associated with problems such as sticking together or being obstructed in the gastrointestinal tract (GIT) which may produce irritation. On the other hand multiple-unit floating systems may be an attractive alternative since they have been shown to reduce the inter-and intra-subject availabilities in drug absorption as well as to lower the possibility of dose dumping [26] . Various multiple-unit floating system like air compartment multiple-unit system [2], hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method [31] ,microparticles based on low density foam powder[5],beads prepared by emulsion gelatin method [32] etc. can be distributed widely throughout the GIT, providing the possibility of achieving a longer lasting and more reliable release of drugs. Based on the mechanism of buoyancy two distinctly different technologies, i.e. non-effervescent and effervescent systems have been utilized in the development of floating drug delivery system 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. In one approach ,intimate mixing of drug with agel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain are lative integrity of shape and a bulk density less than unity within the gastric environment [33]. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl methylcellulose (HPMC) polyacrylates, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates [3]. This system can be further divided into the sub-types: Hydrodynamically balanced systems: Sheth and Tossounian [34] first designated these 'hydrodynamically balanced systems'. These systems contains drug with gel-form in ghydrocolloids meant to remain buoyant on the stomach content. These ares ingle-unit dosage form, containing one or more gel-forming hydrophilic polymers. Hydroxypropyl methylcellulose (HPMC), hydrox ethyl cellulose (HEC), hydroxy propyl cellulose (HPC), sodium carboxymethylcellulose (NaCMC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans oral ginicacid are commonly used excipients to develop these systems [35, 36]. The polymer is mixed with drugs and usually administered in hydrodynamically balanced system capsule. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period. Because, continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form[36].Incorporation of fatty excipients gives low-density formulations reducing the erosion. MadoparLP®,basedonthesystemwasmarketedduringt he1980's [37] . Effective drug deliveries depend on the balance of drug loading and the effect of polymer on its release profile. Several strategies have been tried and investigated to improve efficiencies of the floating hydrodynamically balanced systems[36,37].Micro balloons/Hollow microspheres: Micro balloons / hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion/evaporation methods [38](Figure1) 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 low methoxylated pectin etc. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer polymerratio and the solvent used for formulation. The micro balloons floated continuously over the surface of an acidic dissolution media containing surfactant for>12hours [3].At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple-unit system and good floating. Figure 1. Formulation of floating hollow microsphere or micro balloon Alginate beads: Talukdarand Fassihi[32] recently developed a multiple-unit floating system based on cross- linked beads. They were made by using Ca2+ and low methoxylated pectin (anionic polysaccharide) or Ca2+ low methoxylated pectin and sodium alginate. In this 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 formulation of a porous system, which can maintain a floating force for over 12 hrs. These beads improve gastric retention time (GRT) more than 5.5 hrs[3isbasedontheprincipleoftheencapsulationofadrug reservoir inside a microporous compartment with pores along its top and bottomwalls[40].Theperipheralwallsofthedevicewere completely sealed to present any direct contact of the gastric surface with the undissolved drug. In the stomach the floatation chamber containing entrapped air causes the delivery system to float in the gastric fluid [22].Gastricfluidentersthroughtheaperture,dissolves thedrugand causes the dissolved drug for continuous transport across the intestine for drug absorption. Effervescent (gas generating) systems Floatability can be achieved by generation of gas bubbles. These buoyant systems utilize matrices prepared with swellable polymers suchaspolysaccharides(e.g.chitosan),effervescentcom ponents(e.g.sodium bicarbonate, citric acid or tartaric acid) [40]. The optimal stoicheo metric ratio of citric acid and sodium bicarbonate for gas generationisreportedtobe0.76:1[19].In this system carbon dioxide is released and causes the formulation to float in the stomach Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating dosage forms that generate gas (carbondioxide) when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone (PVP) coated with hydroxy propyl methyl cellulose (HPMC),and floating system based on ion-exchange resin technology etc[3].Bilayer or multilayer system has also been designed [41, 42] . Drugs and excipients can be formulated independently and the gas generating material can be incorporated in to any of the layers. Further modifications involve coating of the matrix with a polymer which is permeable to water, but not to carbon dioxide. The main difficulty of these formulations is finding a good compromise between elasticity, plasticity and permeability of the polymers. Bioadhesive or Mucoadhesive drug delivery systems BioadhesivedrugdelierysystemsareusedasaFigure2.E ffervescent(gasgenerating) systemsFigure3.Drugreleasefromeffervescent(gas generating) systems delivery device within the human to enhance drug absorption in a site-specific manner. In this approach, bio adhesive polymers are used and they can adhere to the epithelial surface in the stomach [43]. Thus, they improve the prolongation of gastric retention. The basis of adhesion in that a dosage form can stick to the mucosal surface by different mechanism. These mechanisms [44, 45] are: 1) The wetting theory, which is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucous layers. 2) The diffusion theory, which proposes physical entanglement of mucin strands the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate. 3)The absorption theory, suggests that bioadhesion is due to secondary forces such as Vander Waalforces and hydrogen bonding. 4) The electron theory, which proposes attractive electrostatic forces between the glycoprotein mucin net work and the bio adhesive material.

Application of GRDDS:

Gastro-retentive drug delivery system offer several applications as follows:

1. Bioavailability: The bioavailability of controlled release GRDDS is significantly enhanced in comparison to the administration of non- GRDDS controlled release polymeric formulations. There are several differentprocesses, related to absorptions and transitof thedrugs in the gastrointestinal tract, that act concomitantly to influence the magnitude of drugs absorption.
2. Site Specific Drug Delivery Systems: These systems are particularly advantageousfordrugsthosearespecificallyabsorbedfor mintestine e.g.Furosemide.Thecontrolled,slowdeliveryofdrugtot hestomach provides sufficient local therapeutic levels and limits the systemic exposuretothedrugs.Itreducesthesideeffectswhicharec ausedby
3. SustainedDrugDelivery.Inthissystem,doselarge andpassingfrom pyloricopeningisprohibited.Newsustainedreleasefloati ngcapsules (HBS) can remain in stomach for prolong periods and hence release the drug in sustained manner for prolong period of time.
4. Enhancement of Absorption:
5. Drugs whichare
6. having poor bioavailability because of site- specific absorption from the upper parts of the GIT are potential candidates to be formulated as floating drug delivery systems, there by maximizing their absorption. By virtue of its floating ability these dosage forms can be retained in the gastric region for prolong period of that drug can be targeted with maximum absorption rate.
7. Minimize adverse activity at the colon:

Retention of the drug in the HBS systems at the stomach minimizes the amount of drug that reaches the colon. Thus, un dersirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDF formulation for betalactam antibiotics that are absorbed only from the small intestine and whose presence in the colon leads to the development of microorganism's resistance

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