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GASTRORETENTIVE: EXPANDING THE FIELD OF CONTROL DRUG DELIVERY

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ABSTRACT

Besides all the novel approaches for the drug delivery, oral delivery approach is still one of the most desirable and preferred routes due to its ease of administration and high patient acceptability. Oral drug delivery depends on the various factors as gastric physiology, drug release, site of absorption and physiochemical properties of drugs. Design of the Gastroretentive dosage is done for the control of gastric retention time for the achievement of desired site specific effect and controlled release of drug over the desired time period. Gastroretentive facilitate the delivery of drug for local action to stomach and proximal part of the small intestine. These systems improve the bioavalability of drug with narrow absorptive window to the upper part of the GIT, unstable at intestinal pH, soluble in acidic pH providing them to reside in stomach for the appropriate time to get absorbed. In the recent year's scientific and technological advancement have been made in the field of gastroretentive drug delivey system. Various approaches for the Gastro retention are floating system, bioadhesive system, swelling and expandable systems, magnetic system, high density system and raft forming system. Recently the controlled drug delivery is leading all other conventional delivery to reduce the frequency of dose and Gastro retentive is one of the safe and easy methods to achieve such effect by prolongation of the gastro retentive time. The need of this review paper was to focus the past and present approaches to achieve the desired gastric retention of the drugs for proper efficacy and therapy.

KEYWORDS: Approaches for Gastric Retention, Floating System, Expandable System, Bioadhesive System, High Density System, Magnetic System.

INTRODUCTION

One of the most widely used delivery system is oral route and the recent approach for improving the patient compliance the work is done to improve its controlled effect so that the frequency of drug will be reduced.[1] Gastroretentive drug delivery system provide the control release of drug with improved bioavailability and therapeutic efficacy.[2] control release drug delivery system(CRDDS) maintain the release of drug at a predetermined rate as determined by the drug pharmacokinetics and desired therapeutic concentration. Factors that affect the control release of drugs are as, physiochemical properties, solubility; intestinal permeability etc.[3] there is always a challenge to maintain the zero-order release products till date beside its history of 15 to 20 years. Study on the physiological control over the body functions and disease states, some drugs as Hormone, Insulin and Nitroglycerin etc shows poor response to zero-order delivery. So while designing such delivery both pharmacokinetics and pharmacodynamics should be considered.[4] for achieving the Gastroretentive delivery the challenge is to modify the gastric emptying time i.e to prolong the gastric retention time of the drugs. Gastric emptying time of drugs depends on the various factors that should be taken in account while designing such dosage forms. Drugs that are locally active, unstable in intestinal environment, having narrow absorption window in the GIT and low solubility at high pH are formulated by gastroretentive approaches.[5] GRDDS is site specific approach especially to stomach or intestine that works by prolonging the gastric residency time(GRT), which improves bioavailability, increases the duration of drug release, reduces drug waste and improves the drug solubility.[6] several gastroretentive drug delivery approaches have been developed as floating drug delivery system, Bioadhesive system, raft forming system, swelling and expandable system, magnetic system, high density system.[7-8] Drugs with limited acid solubility, unstable in gastric environment and drug for colon targeting are unsuitable candidates for the gastoretentive drug delivery system.[16] The key for optimum design is having detail knowledge on gastro intestinal dynamics, Rate and extent of drug absorption from different site of GI tract and Factors affecting the absorption of drugs.[9] Dynamic study of gastrointestinal tract indicates the three main regions which functions for digestion, absorption, secretion, motility and excretion; 1. Stomach 2. Small intestine-duodenum, jejunum, and ileum and 3. Large intestine

The stomach is the depot for the sustained release dosage form which functions to store the food temporarily, grind it and release it tot duodenum that is divided into the three parts: fundus, body and antrum (pylorus). The proximal stomach made up of the fundus and body regions, serves a reservoir for ingested materials while the distal region (antrum) is the major site of mixing motions, acting as a pump to accomplish gastric emptying that occur during both fasting and fed states.

Gastric Motility and Gastric Emptying Rate

Gastric motility is different for the condition of fasting and fed state. During fasting state the interdigestive series of electrical events take place called as inter digestive myoelectric cycle or migrating motar cycle (MMC) that runs every 2 to 3 hours through stomach and intestine. These events are divided into 4 –phases as described by Wilson and Washington.

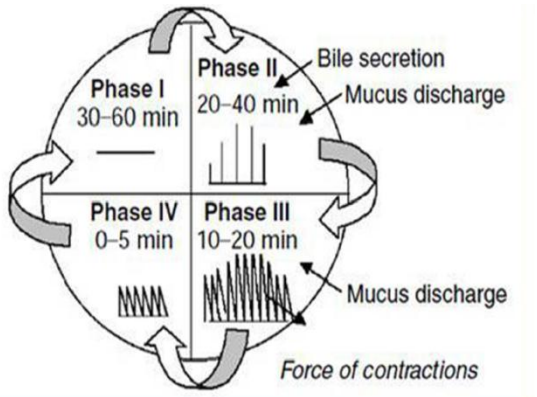

Fig 1: Gastrointestinal motility pattern

Phase-I (Basal Phase or Resting Phase): where the rare contractions take place and lasts from 30-60 min.

Phase-II (Preburst Phase or Secretion Phase): having intermittent action potential and contractions with increased intensity and frequency that last for 20-40 min. bile and mucus secretion occurs.

Phase-III (Burst Phase): it has intense and regular contractions (Strong Electrolytic Waves) for the short period of time for about 10-20 min. due to this force of contractions the undigestive food is swept out of the stomach to small intestine, so this phase is known as the housekeeper wave.

Phase-IV (Transitional Phase): that occurs between phase-I and phase-III for two consecutive cycles that last for 0 to 5 min.

During Fed state, known as digestive motility pattern and similar to the continuous contraction as in Phase II of fasted state, these contraction reduces the size of the food particles to less than 1 mm and are propelled to the pylorous in the suspension form. During the Fed state onset of MMC is delayed that result in slow down of gastric emptying rate.[10-13]

Ideal candidate for the gastoretention[14-15]

1. Stomach as the site of absorption, e.g., amoxocilin, cinnarazine, calcium supplements, chlordiazepoxide.
2. Drugs with narrow absorptive window, e.g., levodopa, riboflavin, methotrexate.
3. Acting locally in stomach, e.g., antacids, misoprostol, drug for H-pylori
4. Having Rapid absorption of drug from GI tract, e.g., tetracycline, ranitidine, metronidazole, metformin HCl
5. Drug that degrade in the colon, e.g., ranitidine, metronidazole, captopril, metformin HCl
6. Drug that disturb normal colonic microbe, e.g., amoxicillin trihydrate, antibiotic against H.plylori
7. Having poor solubility in alkaline pH, e.g., Furosemide, Diazepam

Advantages of gastoretentive drug delivey system[17-19]

1. Increase patient compliance because of sustained drug release with reduced dosing frequency and ease of administration; it benefits the drug with short half-life.
2. Reduce the risk of dose dumping my making the single unit floating unit such as microspheres.
3. Reduce the fluctuation of drug concentration by producing the narrow range to compare of immediate release dosage forms.
4. Reduces the concentration dependent adverse effect by maintaining the constant rate of release of drug within the narrow limit.
5. Benefits the local therapy in stomach and small intestine.
6. Improve the bioavailability of drug by allowing it maximum time for the absorption of drug.
7. Improved selectivity in receptor activation.
8. Minimize the counter activity of drug by slow release of drug into the body leading to higher drug efficiency.
9. Minimize adverse effect to colon by reducing the amount of dug that reaches the colon.

Disadvantages of gastroretentive drug delivey systems[20-21]

1. Not suitable for the drug that causes gastric irritation.
2. Drugs that are unstable in gastric environment cannot be used.
3. It requires a high level of fluid in the stomach so that the dosage form float and work.
4. Not suitable for the drug that have solubility problem in gastric fluid.
5. Drugs with colon release are not suitable.
6. High density system can also be waived out during the house keeping waves.
7. Bioadhesive system may alter it activity as the mucous on the walls of the stomach is in the state of constant renewal.
8. Drugs that are absorbed along the gastric tract and undergo significant first pass metabolism, may not be suitable for floating systems

Factors affecting gastric retention of dosage forms[22-25]

Density: Density of the dosage form must be lower than the gastric fluid (contents) i.e less than 1.004 g/ml to float.

Size and shape

The mean residence time of non-floating dosage from are highly variable and greatly dependend on their size. Smaller unit are emptied during the digestive phase where as the larger units during the house keeping waves, larger size of dosage form are delayed to pass through the pyloric antrum into the intestine causing the higher gastric retention time of that dosage. Size of 9.9 mm in diameter has gastric retention time more than 7.5mm, dosage form having tetra hedron shape residence time is greater than the other device of same size.

Biological factors

Factors as age, gender, posture alters the gastric emptying time. In elderly patient the gastric emptying is slowed. The gastric emptying in women is slower than the men. Effect of posture is generally seen in case of floating systems, such in upright position the system floats to the top of the gastric contents and remained for a longer time with increase gastric retention time(GRT) where as in supine position it GRT is lowered.

Buoyancy effect

Floating dosage form remained buoyant on the gastric contents that increase the gastric retention time while the non floating units sank to the pylorus and is swept out by the house keeping waves during the digestive phase with decrease in gastric retention time.

Fed or unfed state

Under fasting state, the GI motility is characterized by the period of strong mortar activity or the strong myoelectric complex (MMC) that occurs every 2 to 3 hours. When the timing of the formulation administration is same to that of MMC, than the dosage form will be swept out from the stomach along with the undigested food particles, so the GRT become shorter than expected. Different condition is fed state that the MMC is delayed and the GRT is longer.

Nature of meal: Motility pattern is changed for the indigestible polymers or fatty acids to fed state, increasing the gastric emptying time.

Acidity and caloric content of meal: Increase in acidity and caloric (fats) content increase the gastric retention time.

Feeding frequency: Gastric retention time is increased by 400 minutes when successive meals are given compared to the single meal due to low frequency of MMC.

Gastroretentive drug delivey system approaches[26-28]

Classification of GRDDS

1. Floating or Low density system

1.1 Effervescent systems

1.1.1 Gas generating system

1.1.2 Volatile liquid/vacuum system

1.1.2.1 Intra gastric floating gastrointestinal drug delivery system

1.1.2.2 Inflatable gastrointestinal drug delivery system

1.1.2.3 Intragastric osmotically controlled drug delivery system

1.2 Non Effervescent systems

1.2.1 Colloidal Gel Barrier system

1.2.2 Bilayer Floating tablet

1.2.3 Alginate Beads system

1.2.4 Hollow Microspheres (Microballons) drug delivery system

1.2.5 Microporous Compartment system

2. Bioadhesive systems

2.1 Hydration mediated adhesion

2.2 Bonding mediated adhesion

2.3 Receptor mediated adhesion

3. Raft forming system

4. Swellable and Expandable system

5. Magnetic system

6. High density system

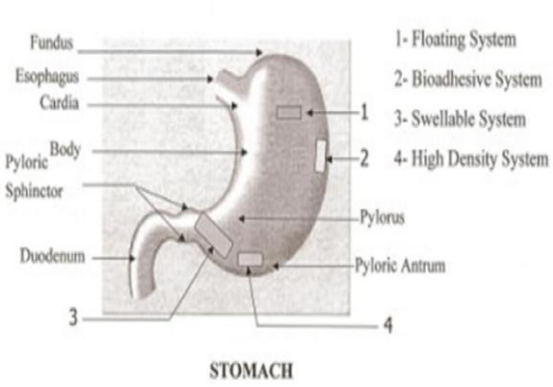

Fig 2: Anatomy of stomach with different gastroretentive drug delivery system

1. Floating or low density system

Here the density of the system is lower than the gastric fluid and remain buoyant in the stomach with increased gastric retention time and prolong the drug release. During the floating of dosage form it release the drug at the predetermined rate. It is further classified as effervescent and non effervescent system.

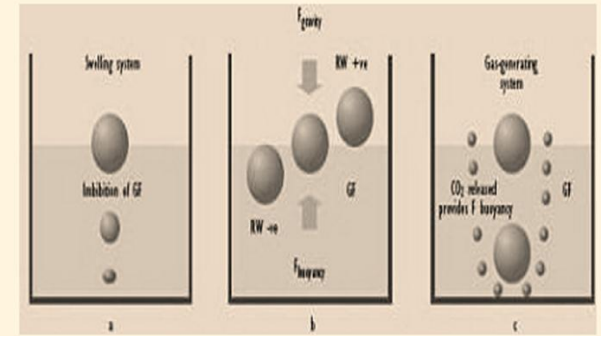

Fig 3: Mechanism of floating system

1.1 Effervescent systems

The system remain buoyant of utilization of the polymer and CO_2 gas production due to the interaction of the compounds like sodium bicarbonate, citric acid or tartaric acid when come in contact with the stomach fluid, these gases are entrapped in the polymer and results in the reduction of density of system making the system to float. Other approach for the effervescent system is use of volatile liquid and vacuum system.

These systems are further classified as

1.1.1 Gas generating system

It utilize the CO_2 gas for the floating of the system.

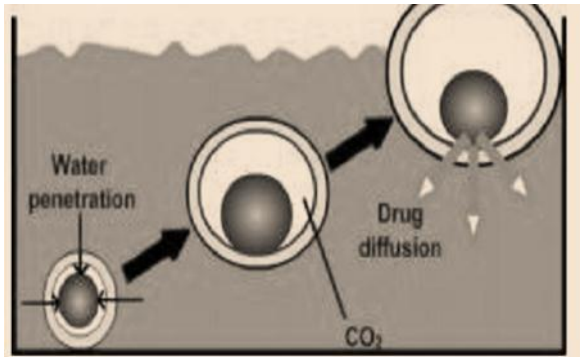

Fig 4: Gas generating system

1.1.2 Volatile liquid/vacuum system

It utilizes the volatile liquid and vacuum system to float the system, further classified as.

1.1.2.1 Intra gastric floating gastrointestinal drug

This system contains a floating chamber which contains vacuum or an inert gas and a microporous compartment enclosing drug reservoir.

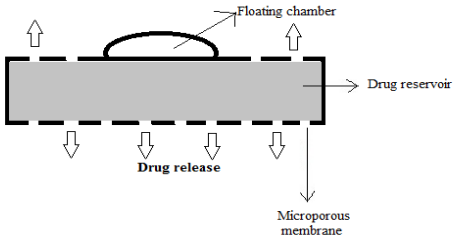

Fig 5: Intra gastric floating gastrointestinal drug delivery system

1.1.2.2 Inflatable gastrointestinal drug delivery system

This system contains inflatable chamber containing liquid ether or cyclopentane which gasifies at body temperature that produce the floating system. The system consists two chamber the first chamber contains the drug and the second chamber contains the volatile liquid. The device may also consist of a biodegradable plug made of PVA, polystyrene etc that slowly dissolve in gastric fluid to release gas and collapse a predetermined time to permit the spontaneous ejection of the inflatable system from the stomach.

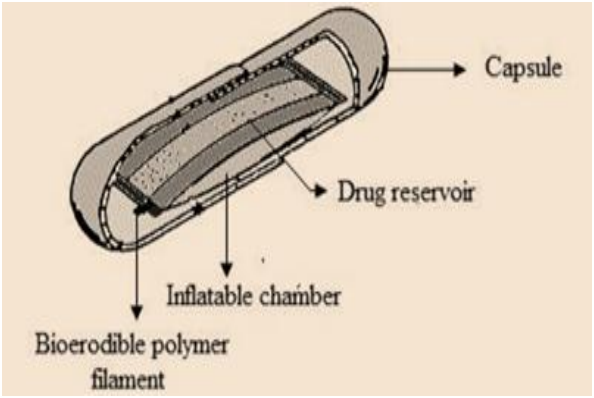

Fig 6: Inflatable gastrointestinal drug delivery system

1.1.2.3 Intragastric osmotically controlled drug delivery system

It is composed of osmotic pressure controlled drug delivery device and an inflatable floating capsule. In the stomach, inflatable capsule disintegrates and release the osmotically controlled drug delivery system which contains two components: drug reservoir compartment and osmotically active compartment.

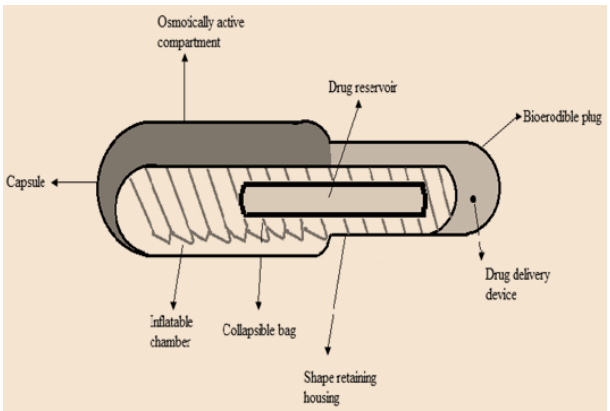

Fig 7: Intragastric osmotically controlled drug delivery system

1.2 Non Effervescent systems

This system is based on the mechanism of swelling of polymer in contact with the gastric fluid and maintains the bulk density of less than one within the outer gelatinous barrier. Buoyancy is achieved by the air trapped within the swollen polymer. Systems are further divided into the followings:

1.2.1 Colloidal gel barrier system (hydrodyanamically balanced systems)

It contains the gel forming hydrocolloids formulated into a single unit dosage form that swells when come in contact with the gastric fluid to form a gel barrier that facilitates the system to remain buoyant.

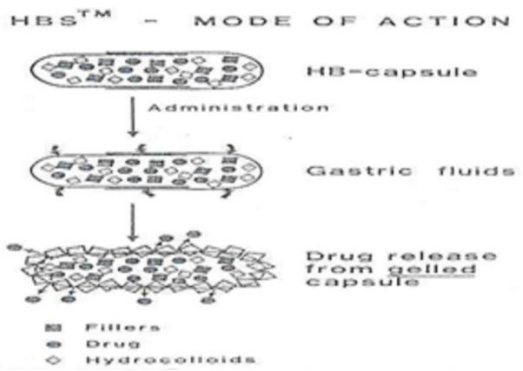

Fig 8: Mechanism of colloidal gel barrier systems

1.2.2 Bilayer Floating tablet

This system consist of two layer, one of the immediate release layer that form the colloid gel barrier when comes in contact with the gastric fluid and other the sustained release layer containing drug and hydrocolloids that remain buoyant in the stomach.

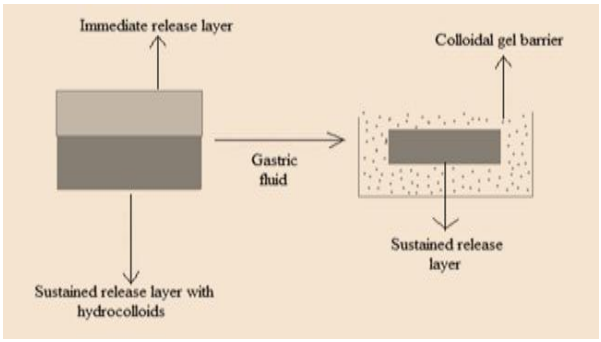

Fig 9: Bilayer Floating tablet

1.2.3 Alginate Beads system

Calcium and low methoxylated pectin or calcium low methoxylated pectic and sodium alginate are used for the formulation of beads, here the spherical beads of approximately 2.5 mm in diameter is prepared by dropping the sodium alginate solution into aqueous solution of calcium chloride, which causes the precipitation of calcium alginate beads. These beads are then separated and dried by air convection and freeze dried, that leads to the formation of porous system which remain buoyant in the stomach for over 12 hours.

1.2.4 Hollow Microspheres (Microballons) drug delivery system

Prepared by the emulsion solvent diffusion method where the drug are loaded in the outer polymer. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated solution of poly vinyl alcohol that is thermally contolled at 40ºc. dichloromethane evaporation forms the internal cavity in the microsphere of the polymer with drug. These formed microsphere float over the surface of an acidic dissolution media containing surfactant for more than 12 hours.

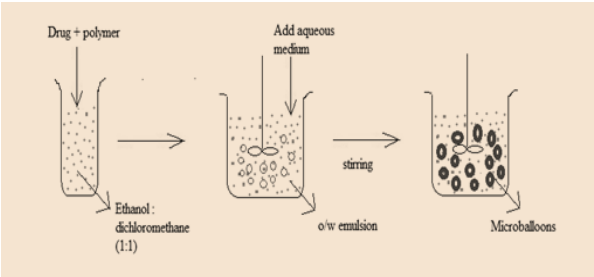

Fig 10: Formation of Microballons

1.2.5 Microporous compartment system

Drug reservoir is encapsulated between the microporous compartment, the walls of drug reservoir are completely sealed with compartment to prevent any direct contact of gastric fluid. The compartment causes to float the system over the gastric fluid. Gastric fluid enters through the aperture, dissolves the drug and carries to the site of absorption.

2. Bioadhesive systems

System consist of the bioadhesive polymer that adhere to the stomach mucosa and prolong the gastric retention time providing site specific absorption. It possess certain limitation to produce gastro retention due to the strong propulsion forces of the stomach wall and continuous production of mucosa by the gastric mucosa to replace the mucous. The polymer used may be natural as sodium alginate, gelatin, gaur gum, etc or the semisynthetic polymers such as HPMC, carbopol, sodium carboxy methyl cellulose. Mechanism of bioadhesion is based on the three mediation:

2.1 Hydration mediated adhesion

Hydrophilic polymer having tendency to absorb large amount of water and become sticky, providing the mucoadhesion. Further the dissolution rate of the polymer controls the gastroretention of the drug.

2.2 Bonding mediated adhesion

Involves the chemical or mechanical bonds due to deposition and inclusion of the adhesive material in the cervices of the mucosa. Chemical bonds involves the ionic or convalent or vander waals forces between the polymer and mucous membrance, among them the hydrogen bonding is most common between the hydrophilic functional group such as the hydroxyl (-OH) and the carboxylic groups (-COOH).

2.3 Receptor mediated adhesion

It occurs between certain polymers and specific receptor sites on the cell surface. The polymers can be cationic or anionic or neutral.

3. Raft forming system

Effective while dealing with antacids and drug delivery for gastrointestinal infections and disorders. These systems contain the gel forming agent and the agent responsible for the formation of CO_2. it involves the formation of viscous cohesive gel in contact with gastric fluids and each portion of the liquid swells forming a continuous layer, so called raft forming system. This raft floats on gastric fluids because of low density created by the formation of CO_2 gas producing gastric retention.

4. Swellable(expandable) system

System consists of polymer that swells by osmotic absorption of water in gastric fluid and prevents its exit for the pylorus. The dosage form remains lodged at the pyloric sphincter for a several hour even in fed condition providing the gastric retentive action. The extensive swelling of the polymer is due to the presence of physical chemical cross links in the hydrophilic polymer network. These cross linking prevents the dissolution of the polymer and hence maintain the physical integrity of the dosage form.

5. Magnetic system

This system consists of small internal magnet inside the dosage form whose elimination is prevented by the strong magnet applied to the region of the stomach providing the gastroretentive action. This system is practically noncompliance to the patient so it has been limited to the practical value.

6. High density system

Based on the principle that high density dosage form sediment down to stomach and retained in the folds of the stomach near the pyloric region which with stand the peristaltic movements of the stomach, finally increase the Gastric retention time. GI transit time can be extended from average 5.8 to 24 hours, depending on the density of the pellets. Zinc oxide, titanium dioxide, iron powder, barium sulphate etc are used to increase the density of dosage form.

Table 1: Drugs that are used as GRDDS[1-5]

Dosage forms	Choice of Drugs
Tablets	Amoxicillin Trihydrate, Acetaminophen, Aspirin, Acetyl Salicylic Acid, Ampicillin, Atenolol, Cefuroxime Axetil, Cinnarazine, Captopril, Ciprofloxacin, Dilitiazem, Domperidone, Furosemide, Flurouracil, Famotidine, Griseofulvin, Ibuprofen, Isosorbide Mononitrate, Metoprolol, Nimodipine, Peritanide, Prednisolone, Quinidine, Ranitidine, Riboflavin, Satalol, Theophylline, Verapamil
Capsules	Chlordiazepoxide Hcl, Diazepam, Furosemide, Levodopa, Misoprostol, Nicardipine, Propanolol, Pepstatin, Verapamil
Granules	Cinnarazine, Diclofenac Sodium, Indomethacin, Flurouracil, Diltiazem, Isosorbide Mononitrate
Powder	Riboflavin, Sotalol, Theophylline And Several Basic Drugs
Films	Cinnarazine, Peritanide, Prednisolone, P-Aminobenzoic Acid, Quinidine,

Main ingredients used in formulation of GRDDS[1-5]

1. Polymers: used for the different purposes as in floating system to increase the buoyancy, bioadhesion, raft forming, swelling of systems are as Acrylic polymer, Calcium alginate, Car-bopol, Eudragit S100 Eudragit RL, Eudragit RS, Eudragit S, Ethyl cellulose, poly methyl meth acrylate, Methocel K4M, Polyethylene oxide, β Cyclodextrin, HPMC 4000, HPMC 100, HPMC K4 M, CMC, Polyethylene glycol, polycarbonate, PVA, Polycarbo-nate, HPC-L, CP 934P, HPC, HPMC, PVP, HPC-H, HPC-M, HPMC K15, HPMC K4, E4 M and Propylene foam, Polyox and Sodium alginate etc.

2. Effervescent agent: that releases the gas when come in contact with the water or acidic fluid of gastric environment such as citric acid, citroglycine, sodium bicarbonate and tartaric acid etc.

3. Inert fatty materials: that causes to increase the gastric retention time (buoyancy) by decreasing the specific gravity of the formulation such as Beeswax, fatty acid and long chain fatty alcohols etc.

4.Release rate retardants: that retards the release of drug from the dosage to provide the control release over the prolong time such as Dicalcium phosphate, Magnesium Stearate and Talc etc. can be used in the concentration between 5% to 60%.

5. Material to lower the density: it provides the system to float in the gastric environment such as Polypropylene foam powder etc.

Evaluation of GRDDS[29-31]

Evaluation of the formulation are done to ensure that the product is prepared as per our design specification and perform the work for what it is desired. During the evaluation the parameter depends the dosage form and the general evaluation is done as per its individual characteristics of the dosage form. Routine test like general appearance, hardness, friability, drug content, weight variation etc needs to be evaluated.

In-vitro method of evaluation

Identification

Drug, polymers and other functional group are identified by the Fourier transform infrared spectroscopy technique.

Particle size and surface characterization

Particle size and size distribution of beads or microspheres are determined in the dry state using optical microscopy method. The external and cross sectional morphology is done by the scanning electron microscope.

Buoyancy lag time or Floating lag time

It is the time taken by dosage form to float on the top of dissolution medium simulated with gastric medium, after it is placed in the medium.

Floating time or Total Floating time

The total time up to which the dosage form float on the dissolution medium, measured by placing the tablets in a 250ml beaker containing 200ml of 0.1N HCl.

Swelling index

Measurement of swelling system, the dosage form is immersed in the simulated gastric fluid and removed out at regular interval, for the measurement of change in dimension that is the thickness and diameter with time.

Swelling index (SI) = $(W_t\text{-}W_O)/_{WO} \times 100$

W_t – weight of the tablet at time t

W_O – initial weight of the tablet

Density

Determined by the displacement method using Benzene as displacement medium.

Water uptake or Weight gain

Here dosage form is immersed in the medium and removed out at regular interval and weight changes are determined with respect to time.

Water uptake (WU) = $(W_t - W_o) * 100 / W_o$

Where, W_t = weight of dosage form at time t

W_o = initial weight of dosage form

In-vitro dissolution test or in-vitro drug release study

This test is done by using USP apparatus with paddle. For the floating dosage form it seen that there is much less paddle force, so the result may be deviated from the actual similar problem may be seen for the swellable dosage form that may stick to the wall of vessel or paddle. In order to prevent such problems modification are done in dissolution assembly as per the dosage form. Samples are withdrawn periodically from the dissolution medium with replacement and then analyzed for their drug content after and appropriate dilution. The test is performed using 900ml of 0.1N HCl, at 37ºc and 100 rpm. A sample of 10ml is withdrawn hourly and analyzed under UV.

In vivo Evaluation

Most cases use the imaging techniques that locate the gastroretentive dosage form in vivo that are as:

X-Ray (Radiology)

This technique is cheap and simple that makes use of incorporation of radio opaque material (Barium Sulphate widely used) inside the dosage form, whose location is tracked by X-ray image. Limitation with the safety issue due to the repeated exposure of X-ray to volunteers.

Gamma Scintigraphy

The radioisotope has to be incorporated into the GRDF in advance. Then, a short time prior to the study, the formulation has to be irradiated in a neutron source that causes it to emit gamma rays. The emitted ray can be imaged using "gamma camera" – a form of a scintillation counter, combined with a computer to process the image and thereby the DF can be tracked in the GI tract.

Gastroscopy

Gastroscopy is peroral endoscopy used with fiber optics or video systems. Gastroscopy is used to inspect visually the effect of prolongation in stomach.

Ultrasonography

It can be used to determine the gastric retention of dosage form but has limitation that it is not traceable at intestine.

Magnetic Resonance Imaging (MRI)

Noninvasive and safe technique that utilizes the incorporation of a super paramagnetic compound such as ferrous oxide enables their visualization by MRI.

CONCLUSION

Gastroretentive drug delivery system are the most desirable approach to deliver the drug as the controlled release for the prolong effect to the upper parts of the Gastrointestinal tract. These systems improve the bioavailability of the drug with narrow absorption window. Beside it several advantages its limitation arises during the IVIVC, although its various successful product are being marketed. Designing of GRDDS requires a thorough knowledge of physiochemical properties of drug and physiochemical events that occur in the gastro intestinal tract. It provides utilization of all the pharmacokinetic and pharmacodynamic parameters. Drug absorption in the GI is variable so by increasing the Gastric retention, the drug are allowed sufficient time for the absorption to assure the proper bioavailability of drugs.

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