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Narrative treatment of GERD: focus on the lower esophageal sphincter (LES) using raft forming *in-situ* gelling system

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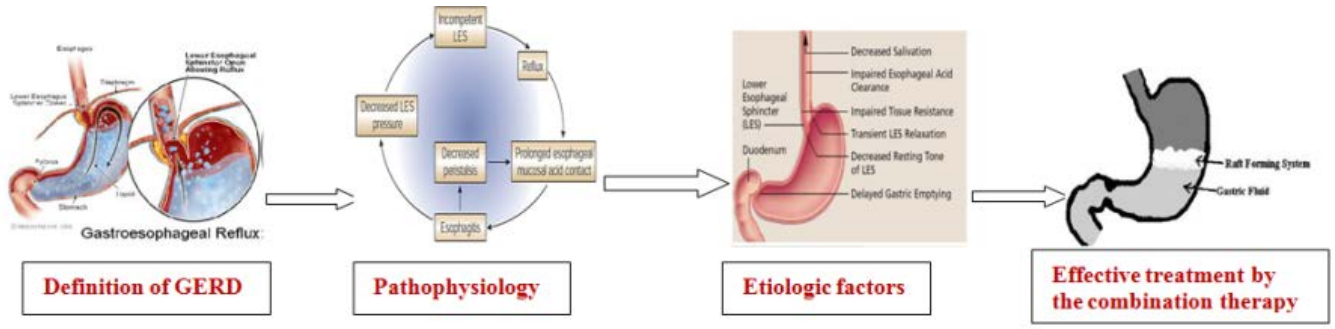
ABSTRACT



Gastroesophageal reflux disease, acidity, and hearts burning are the most common problems, which can be overcome by the raft forming in-situ gel system containing the combination of H_2 antagonist and $GABA_B$ antagonist as well as raft forming agents (alginate, pectin etc.). GERD develops when the reflux of the gastric contents occur into the esophagus which causes various complication into GIT. The main cause of GERD is an abnormal lower esophageal sphincter (LES) pressure and increased reflux during transient LES relaxation. This review mainly focuses on the formulation development for reducing the transient lower esophageal sphincter relaxation (TLESR) rate, attenuating esophageal sensitivity and developing esophageal mucosal protectants. For this purpose $GABA_B$ is used which reduces TLESR rate by 40-50% and reflux episodes by 70%, also increase LES pressure and H_2 antagonist is used as an antisecretory agent in terms of symptomatic relief and mucosal healing. The combined effect of the raft-forming gelling system is more effective. The review also focuses on the physiological factors, physicochemical factors, and formulation factors to be considered in the development of the raft forming system.

Keywords: GERD, Raft, LES, In-situ gel, $GABA_B$ antagonist

INTRODUCTION

Now a day's gastric problems are becoming often the problem to the patients, which can be effortlessly treated by raft forming *in situ* gelling system. This gelling system is in the liquid (sol) form before administration and as it comes in contact with gastric acid gets converted to gel and form raft which floats on gastric contents.[1,2] Raft forming systems are used to treat Gastro-esophageal reflux disease (GERD), peptic ulcer, heartburn, and esophagitis. Anti-reflux raft-forming formulation forms a viscous, gelatinous mass or barrier on the top of the gastric acid contents, at the lower esophageal sphincter (LES) and inhibits the movement of gastric content in the upward position in the esophagus. In gastroesophageal reflux disease, the backward flow of acid from the stomach occurs into the esophagus. When excessive amounts of acid reflux into the esophagus occur people experience heartburn, esophagitis, acid indigestion, mucosal damage or various other problems.[3] At the joint of the stomach and lower end of the esophagus, the circular ring of muscle called the lower

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esophageal sphincter (LES). The LES relaxes after swallowing to allow food to enter the stomach and then contracts to prevent the back-up of food and gastric contents into the esophagus. But sometimes the LES becomes relaxed or weak because the stomach is distended; allowing gastric contents in the stomach to reflux back into the esophagus mostly after meals.[4] So the key etiologic factors are an abnormal LES pressure and increased reflux during transient LES relaxations. In severe disease patients have typically impaired LES resting tone, with a weak sphincter or other factors underlying a persistently reduced LES pressure. This review focused primarily on reducing acid reflux and targeting the direct causes of the disorder, such as transient lower esophageal sphincter relaxation (TLESR), by the use of raft-forming *in-situ* gel system. *The in-situ* gelling system is very reliable. As the use of biodegradable and water soluble polymers for the *in- situ* gel formulations can make them more tolerable and excellent drug delivery systems.[4,5]

Clinical overview of GERD

In Western countries, Gastro-esophageal reflux disease (GERD)is one of the most common GIT disorders.[6] Gastroesophageal includes the stomach and esophagus. Gastroesophageal reflux is the return/ reflux of the GIT contents back up into the esophagus.[7] In normal digestion, when the lower esophageal sphincter (LES) is open, the food passes into the stomach, and when it is close food and GIT fluids are prevented from flowing back into the esophagus.[8] GERD occurs when the LES is weak or relaxes improperly, so the stomach's contents flow up into the esophagus (Figure 1). Hiatal hernias are the abnormalities in the body that may also cause GERD. It occurs when the upper part of the stomach moves up into the chest region.[8, 9]

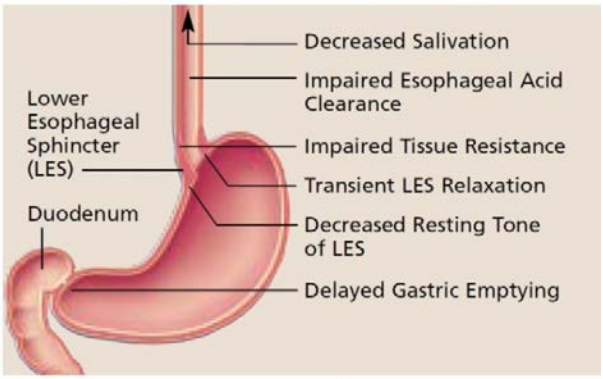

Figure 1: Possible etiologic factors involved in GERD.[9]

Symptoms of GERD

GERD develops when reflux of the stomach contents causes troublesome symptoms.[10] these symptoms may be esophageal or extraesophageal (Figure 2). These complications are also classified into the following category-

Typical symptoms include heartburn, acid regurgitation, dysphagia, odynophagia, nausea, vomiting, dyspepsia, epigastric pain, sleep disorder, reflux esophagitis, Barrett's esophagus development, esophageal adenocarcinoma development, bleeding (in rare cases) etc.

Atypical symptoms include a chronic cough, asthma, non-cardiac chest pain, chronic laryngitis etc.[11]

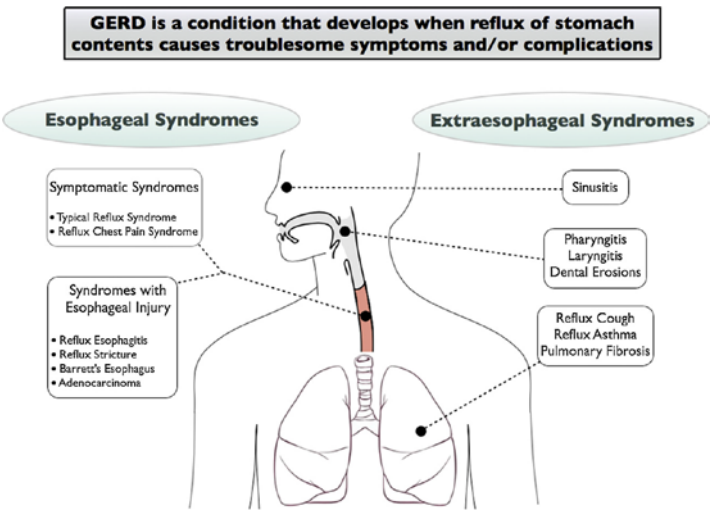

Figure 2: Some esophageal and extraesophageal complications.[12]

Key fact about GERD

- Acid indigestion symptoms are more common among the elderly and pregnant and obese women.
- Over 60 million Americans experience acid indigestion at least once a month and over 15 million Americans experience acid indigestion daily.
- GERD develop in Men and women with equal frequency, but complicated GERD occurs more frequently in men.
- Zollinger-Ellison syndrome - patients have endoscopic esophagitis.[5]

Diagnosis of GERD

Diagnostic testing occurs in the presence of typical symptoms of disease, mainly frequent heart burn and regurgitation. Following diagnostic tests are performed in case GERD:

- Barium Studies
- Esophageal Manometry
- pH Monitoring
- Upper Endoscopy.[5]

Role of lower esophageal sphincter (LES) in GERD

Lower esophageal sphincter is the circular ring of the muscle which is located at the end of gastroesophageal junction or it is the joint between the lower end of the esophagus and the upper end of the stomach[9] (Figure 3 & 4). The Lower esophageal sphincter is 3cm to 4cm long comprising 2 components first is the LES in the distal esophagus (true LES) and other is the crural portion of the diaphragm. Upon swallowing, sphincters are relaxed but relaxation can also occur without swallowing called Transient Lower Esophageal Sphincter Relaxations.[13] Commonly GERD engages resting LES pressures that are within the normal range so this sphincter relaxation is directly related to reflux episodes.[14] the loss of inhibitory mechanisms leads to increased rate of TLESR which is associated with gastroesophageal reflux disease.[15]

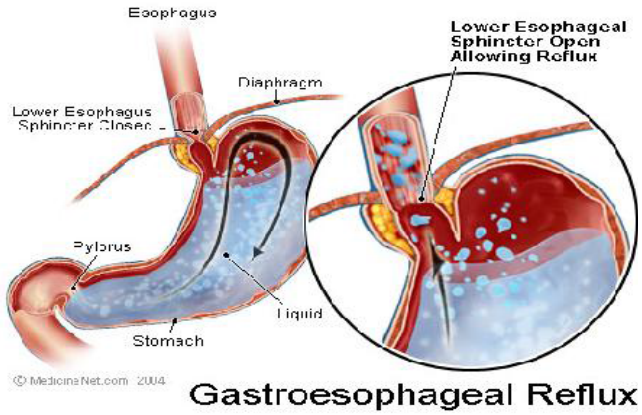

Figure 3: Position of LES and role in acid reflux.[18]

LES and diaphragmatic sphincter compose of myogenic and neurogenic mechanisms which are involved in maintaining LES resting tone.[9, 16] the neurogenic mechanisms maintained tonic or reflux contractions of these sphincters which are vital for their antireflux behavior. Mutilation of these mechanisms cause gastroesophageal reflux disease (GERD).[17]

LES Contraction

A huge number of myogenic, neural, and neurohumoral factors maintained the lower esophageal sphincter tone.[9] There are also different intracellular signaling pathways in the LES, the exclusive pathway may contribute to the tonic contraction of the LES. Constriction of the lower esophageal sphincter prevents the backup or regurgitation of gastric contents into the esophagus. The increased LES pressure is the cause of increases in intra-abdominal pressure.[19] Studies show that the LES abdominal compression reflux is mediated through the vagus nerve and cholinergic system. So in the human being increased abdominal pressure cause contraction of the LES and diaphragmatic sphincter.[14, 19]

LES Relaxations

The relaxation of both the LES and the diaphragmatic sphincter is necessary for the movement of the ingested contents into the stomach. Normally it relaxes to a pressure which is very close to the intragastric pressure. Moreover relaxation, the LES also opens to allow passage of the contents into the stomach.[9] There are various differences between relaxation and opening because LES relaxation process is mediated by neurotransmitters, but the opening is related to bolus pressure, passive or viscoelastic properties of the LES.[19]

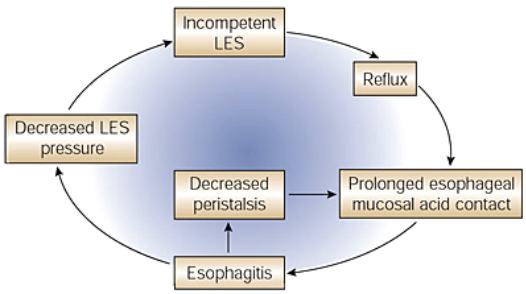

Figure 4: Gastroesophageal reflux disease initiates a vicious cycle of increasing esophageal acid exposure.[20]

Transient Lower Esophageal Sphincter Relaxations (TLESRs)

Transient lower esophageal sphincter relaxations are unprompted, concurrent and non pathological reflux actions.[9] It is the major mechanism of reflux in GERD patient. GERD Patients have an equal frequency of TLESRs compared with normal persons, but the refluxate of GERD patients tend to be more acidic during TLESRs.[21] TLESRs mechanism is characteristically of longer duration than the swallow-induced LES relaxation. Thus, transient lower esophageal sphincter relaxations is not a response as the LES; somewhat it appears as inhibition of a number of structures within and outside of the esophagus due to prolong contact with gastric acid.[22]

Stimuli that elicit Transient Lower Esophageal Sphincter Relaxation

a. Gastric distention
b. Pharyngeal intubation
c. These reflex episodes also depend on the afferent nerve fibers from the pharynx or larynx.[20]

RAFT FORMING SYSTEM

Oral drug delivery is the preferable route of drug delivery due to ease of administration, convenience, more patient compliance etc.[23] but also have some drawbacks i.e. short gastric retention time, non-site specificity. So for maintaining an effective drug concentration in the systemic circulation for a long time or to overcome the drawbacks of conventional oral drug delivery systems, gastro retentive drug delivery system are developed.[24] Raft-forming systems have received much attention for the treatment of gastroesophageal reflux disease, gastrointestinal infection and other related disorders.[25]

The raft-forming mechanism includes that this formulation consists calcium carbonate, sodium or potassium bicarbonate, wherever the bicarbonate is converted to carbon dioxide, in the presence of gastric acid this CO_2 entrapped inside the gel precipitate and it converts into the foam, which floats on the surface of the gastric fluids.[1]The formulation contained antacid components which provide a relatively pH neutral barrier (Figure 5). $CaCO_3$ used as an antacid as well as a raft strengthening agent which releases calcium ions, these ions react with alginate and form an insoluble gel.[26] Alginic acid, alginates, pectin, guar gum, isapgol, carrageenan and locust

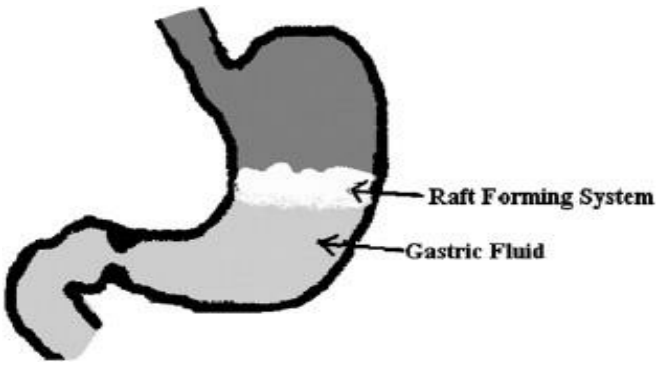

Figure 5: Schematic illustration of the barrier formed by a raft-forming system.[1]

bean gum are the raft forming agents. Alginates and pectin are the most widely used raft forming agents.[27] So overall mechanism is when raft forming formulation comes in contact with gastric fluids it form viscous cohesive gel in which each portion of the formulation swell and form continuous layer called raft.[1,26]

Approaches used for the raft formulation

Raft formation based on the following physical mechanism

Swelling

When the liquid/solid effervescent system comes in contact with gastric fluid gel is formed. *In situ* gel is formed when materials absorb water from the surrounding environment and expanded at the desired space. Swelling occurs when polymer absorbed water which further causes gel formation. Glyceryl mono-oleate is a polar lipid which swells in water to form lyotropic liquid crystalline phase structures.[1, 25]

Diffusion

It involves solvent diffuse from polymer solution into surrounding tissue, which promotes precipitation or solidification of the polymer matrix. Example of such mechanism is N-methyl pyrrolidone.[1]

Raft formation based on the following chemical mechanism

Ionic cross linking

Ion-sensitive polysaccharides such as Na alginate, carrageenan, pectin, and gellan gum undergo phase transition in the presence of various ions such as Ca+, k+, Mg+ and Na+. These polymers falling into the class of ion-sensitive polysaccharides are most widely used in *in-situ* gelation.[5]

Raft formation based on the following physiological stimuli mechanism[27]

Temperature dependent gelling

In situ gelling polymers are liquid (sol) at room temperature (20 °C–25 °C) and when they come in contact with body fluids (35 °C–37 °C), they undergo gelation due to an increase in temperature. These temperature-sensitive hydrogels come in the class of environment-sensitive polymeric systems in drug delivery research, because they go through immediate changes in solubility when increase in environmental temperature (lower critical solution temperature) LCST.[28]

At the, this temperature polymer-water H- bonding becomes critical, compared to polymer–polymer and water–water interactions, and a sudden transition occurs as the solvated macromolecule rapidly dehydrates and changes to a more hydrophobic structures.[29] Polymers such as Poly (propylene oxide), pluronics (polyethylene oxide) poly (propylene oxide)-poly (ethylene oxide), polymer networks of poly (acrylic acid) and polyacrylamide or poly (acrylamide-co-butyl methacrylate) are commonly used for temperature sensitive hydrogels formation.[1,29]

pH dependent gelling

Various pH dependent polymers such as polyvinylacetal diethylaminoacetate (AEA), PAA (Polyacrylic acid, Carbopol) or its derivatives, polyvinylacetal diethylaminoacetate (AEA), polyethylene glycol (PEG) and poly (methacrylic acid) (PMA) mixtures converted sol to gel with change of pH.[1] pH sensitive polymer can be neutral or ionic in nature.[29] In the case of weakly acidic (anionic) groups hydrogel swelling increases as the increase in external pH but in case of weakly basic (cationic) groups its decrease.

Advantages of raft forming formulation

Following are the advantages of the raft forming formulations:

1. It does not interfere with the activity of drug.
2. Can be achieved better patient compliance.
3. Long-duration of action or sustained action can be easily achieved by raft forming system.
4. Therapeutic efficacy and bioavailability improvement and reduction of the dose.
5. Do not interfere with the function of pyloric sphincter.
6. This system is used for the symptomatic treatment of heartburn, oesophagitis and also for Laryngopharyngeal Reflux (LPR).
7. Formed within seconds.[24]

Disadvantages of raft forming formulation

There are some disadvantages associated with raft forming formulations, including:

1. Exposure of certain polymer to radiations (e.g. UV, Visible, electromagnetic, etc.) which can induces the formation of gel within the package.
2. If store at inappropriate temperature or on prolong storage changes in the pH of the system occurs.
3. If formulated in the form of solution which is more susceptible to stability problems, due to chemical degradation (oxidation, hydrolysis, etc.) or microbial degradation etc.[25]

Following factors to be considered for the development of gastroretentive dosage forms/ Raft forming system

Dosage form related factors

Density: The buoyancy of dosage form depends on its density which affects the gastric retention time and also gastric emptying rate. Dosage form floats on the gastric fluid surface if it has low density than fluid whereas high-density systems sink to the bottom of the stomach. For the floating property < 1.0 gm/ cm3 density is required.

Size of dosage form: Size of the dosage form (small, medium, and large units) affects gastric resident time. Gastric resident time increases if larger size of the dosage form is used because the larger size would not allow the dosage form to rapidly pass through the pyloric antrum into the intestine. So the size of the dosage forms is also an important factor affecting gastric retention.

Shape of dosage form: Tetrahedron and ring-shaped devices (48 and 22.5 kilopounds per square inch) are reported to enhance gastric retention time (GRT) 90% to 100% retention at 24 hours compared with other shapes.

Intake food and its nature

Fed or unfed state: In fasting condition GIT have strong motor activity or the migrating myoelectric complex (MMC) occurs in every 1.5 to 2 hours, So MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be very short. On the other hand, in the fed state, MMC is delayed and GRT is significantly longer.

Composition of meal: The rate of gastric emptying for various food materials is in the following order: carbohydrates> proteins> fats. Delayed gastric emptying is observed with a meal that is high in fatty substances.

Physical state and viscosity of meal: Viscous meal increase gastric resident time in comparison to the less viscous meal. Liquid meals take less than one hour to empty while solid meals empty within 6 to 7 hours.

Frequency of feed: when successive meals are given compared with a single meal the gastric retention time can be increase over 400 minutes due to the low frequency of migrating myoelectric complex (MMC).

Temperature of the food: In comparison to body temperature, high or low temperature of the ingested fluid retards the gastric emptying rate.[23]

Patient related factors

Age: Elderly people, have a significantly longer gastric retention time.

Body posture: Gastric emptying is favored while lying on the right side whereas if lying on the left side or on the supine position retards it.

Disease states: Disease likes gastric ulcer, gastroenteritis, diabetes hypothyroidism and pyloric stenosis decrease gastric emptying rate, while duodenal ulcer, hyperthyroidism and partial or total gastrectomy promote gastric emptying rate.

Drugs: Poorly soluble antacids, anticholinergics (atropine, propantheline), tricyclic antidepressants (imipramine, amitriptyline) and narcotic analgesics (morphine) retard gastric emptying, while domperidone, cisapride and metoclopramide (antiemetics) stimulate gastric emptying rate.[5]

Drugs used for the raft forming system

The raft forming system is the potential approach for treatment of GIT disorders. This system is suitable for drugs which are acid soluble.

The criteria of the drug to be considered for the selection of the drug for gastro retentive formulations are as follows:

1. Drugs that act locally in the stomach and absorbed from the stomach and upper part of the gastrointestinal tract.
2. Drugs those are poorly soluble in alkaline medium.
3. Drugs which get degraded in the colon.

Drugs those are not suitable for gastric retention

1. Drugs which are unstable in acidic media.
2. Drugs that have very limited acid solubility.
3. Drugs used for selective release in the colon.

Polymeric approaches for raft forming system

Various polymers are used in gastroretentive drug delivary system for targeted drug delivery to the specific region in the stomach.[25] Following natural and synthetic polymers are used in the formulation of the raft forming drug delivery system-

Natural polymers- Alginic acid, pectin, gellan gum, guar gum, xyloglucan, chitosan etc.

Synthetic polymers- Poly-caprolactone, HPMC, polylactic acid, polylactide-co-glycolide, Methyl cellulose (MC), cellulose acetate phthalate (CAP), Carbopol, Pluronics etc.[31]

Aiginic acid

It is obtained from brown seaweed and marine algae such as *Laminaria hyperborea*, *Ascophyllum nodosum* and *Macrocys tis pyrifera.* It is the unbranched polysaccharides which consist β-D mannuronic acid and α-L-glucuronic acid residues joined by 1, 4-glycosidic linkages.[32] Alginic acid has many different alginate salts and including sodium alginate, calcium alginate magnesium alginate, ammonium alginate, potassium alginate etc. Alginic acid exhibits encouraging biological properties such as biodegradability and nontoxicity. Due to intermolecular binding, its formulation has the ability to form high-viscosity ‘‘acid gel’’ is formed on the hydration of alginic acid, but also its have mucoadhesive properties. Sodium alginate is the most widely used in the floating drug delivery systems. Dilute aqueous solutions of alginates form firm gels on the addition of di and trivalent metal ions. Sodium alginate has been employed in the preparation of gels for the delivery of biomolecules such as drugs, peptides, and proteins.[34]

Pectin

Pectin is the linear polysaccharide obtained from citrus peel, apple pomance, sugar beet pulp etc. plants sources. Pectins are nonstarch polymer mainly comprised of α-(1–4)-linked D-galacturonic acid residues broken up by 1, 2-linked L-rhamnose residues. It willingly forms gels in an aqueous solution in the presence of divalent ions such as free calcium ions, which crosslink the galacturonic acid chains. So the calcium ion is required to produce the gels that are suitable for vehicles for raft forming drug delivery system. The quantities of calcium and citrate ions may be optimized to maintain the fluidity in the stomach. Pectin is commercially available as low methoxy pectin and high methoxy pectin.[25]

Gellan gum

Gellan gum is obtained from fermentation of pure culture of the microbe *Sphingomonas elodea* (*Pseudomonas* species).[34] The chemical structure of the polysaccharide has a tetrasaccharide repeated unit consisting of two glucose residues, one glucuronic acid and other is the rhamnose residue. Its gel forming tendency depends on the temperature and cation induction. The gelation involves three-dimensional network by complexation with cations and hydrogen bonding with water. When administered orally the calcium ions are released

in the acidic medium of the stomach leading to gelation of gellan gum, therefore, forming *in situ* gel.[1, 25]

Chitosan

Chitosan is the natural polymer obtained by alkaline deacetylation of chitin.[35] Chitosan is more useful biodegradable, thermosensitive, polycationic and bioactive polymer. Chitosan is pH dependent cationic polymer, which remains dissolved in aqueous solutions up to a pH of 6.2 if pH exceeding 6.2 leads to the formation of a hydrated gel-like precipitate. Chitosan formulations are instantly becoming buoyant when using in gastro retentive drug delivery system and provide sustained release.[32]

Xyloglucan

Xyloglucan is obtained from seeds of tamarind. It is composed of (1–4)-β-D-glucan backbone chain, which has (1–6)-α-D xylose branches that are partially substituted by (1–2)-β-D-galactoxylose. It is also composed of heptasaccharide, octasaccharide and nonasaccharide oligomers, which differ in the number of galactose side chains. Xyloglucan forms thermally reversible gels on warming to body temperature. Even though xyloglucan itself does not form gel, its dilute solution has been partially degraded by galactosidase and show a thermally reversible sol–gel transition on heating. Xyloglucan has shown a very low gelation time of up to few minutes. Xyloglucan gels can be potentially used for oral, ocular, intraperitoneal, and rectal drug delivery system.[5,32]

Psyllum husk

It is obtained from dried seed coats of *Plantago ovata* (Plantagenaceae). Psyllum husk contains high proportion of hemicelluloses classified as a mucilaginous fiber due to its power ability to form a gel in water. It is most widely used for gastro retentive drug delivery system because it has the ability to prolonged retention of the dosage form in the stomach.[1, 34]

Carbopol

Carbopol is the pH-dependent mucoadhesive polymer, at acidic pH, it remains in solution form but in the alkaline medium it forms a low viscous gel. HPMC is used in combination with carbopol to impart the viscosity of carbopol solution. Various water soluble polymers such as carbopol system- HPMC system, poly (methacrylic acid), poly (ethylene glycol) can come under the category of pH-induced *in-situ* precipitating polymeric systems.[37]

Pluronic F127/ Poloxamers

It consists of more than 30 different non-ionic surface active agents. Pluronics or Poloxamers also endure in situ gelation by change in temperature. Pluronic F-127 was used as an *in situ* gel forming polymer together with mucoadhesive polymers such as Carbopol 934 and hydroxyl propyl methylcellulose (HPMC) to guarantee long residence time at the application site.[38]

DRUG THERAPY

Patient with severe reflux symptoms or with esophagitis require drug therapy. Current drug therapy depends on two categories of drugs:

1. Those drugs that decrease gastric acidity and
2. Those drugs that enhance upper gastrointestinal motility.

Drugs those decrease gastric acidity

Antacids

Antacids provide rapid but short-term symptoms relief by buffering gastric acid. Antacids are a suitable over-the-counter treatment for GERD, but only one-quarter of patients have symptom relief after antacid use.[37] Antacids are best for quick relief of intermittent and relatively infrequent symptoms. Examples of antacids include Magnesium hydroxide, aluminum hydroxide, alginate, $CaCO_3$, $NaHCO_3$, etc.[29]

H_2 blockers

These are drugs that block histamine stimulatory effect on gastric acid secretion, H_2 blockers lower acid secretion by about 70% at standard doses and achieve good symptomatic control in 80% of reflux. H_2 blockers heal the erosions in about 50% of patients. Healing is most reliably achieved in patients with relatively mild esophagitis. Although some patients have better symptomatic responses to one or another of the H_2 blockers, in appropriate doses the various agents appear to be equally effective. The drug choice is often based on physician inclination duration of action of the drug, frequency, drug interactions, and cost. In recent years, H_2 blockers have been released in over-the-counter (OTC) formulations containing lower doses of the prescribed formulations. Examples of H_2antagonist include Ranitidine, Cimetidine, famotidine, nizatidine etc.[29]

Proton Pump Inhibitors

PPIs are drugs that block the final common pathway (gastric H^+/K^+ ATPase) of acid secretion. PPIs block the effects of all three major pathways (histamine, acetylcholine, and gastrin) for acid stimulation. As a result, the acid suppressing capability of PPIs is substantially greater than that of H_2 blockers. In sufficient doses, PPIs are capable of producing a state of achlorhydria in which the stomach produces no acid at all. Patients with typical esophageal symptoms of reflux can be controlled with PPIs.[38] Additionally PPIs heal erosive esophagitis in the most patients, even those with severe esophageal damage.[39] When initial treatment fails, increasing the dose is usually effective. Omeprazole, rabeprazole, Lansoprazole, Esomeprazole, Pantoprazole, Dexlansoprazole are the FDA approved proton pump inhibitor drugs.

Drugs those enhance upper gastrointestinal motility

Prokinetic Agents

These drugs enhance motor activity of the GIT smooth muscle and appear most important influence on gastric motility. Although potentially beneficial for improving the strength of esophageal peristalsis, the resting pressure of the LES, and the strength of gastric contractions. Prokinetic agents are as effective as H_2 antagonist, but less effective than PPIs. In the United States, they tend to be used in combination with an acid-suppressing agent when the latter does not achieve the preferred results. Metoclopramide, domperidone, mosapride, Itopride, cisapride etc are the prokinetic agents.[40]

TLESR REDUCERS

Transient Lower Esophageal Sphincter Relaxations (TLESR) is considered as the major mechanism of GERD which observed in both healthy person and GERD patients. A wide range of receptors are occupied in triggering TLESR, which provides an exclusive opportunity for the development of novel reflux inhibitors. So drug development has focused primarily on gamma-aminobutyric acid B (GABAB) receptor agonists and metabotropic glutamate receptor 5 (mGluR5) antagonists. Examples of this category include Baclofen, Arbaclofen, Lesogaberan etc.20 Arbaclofen placarbil is a prodrug of the pharmacologically active R-isomer of Baclofen. It is efficiently absorbed throughout the upper and lower GIT and has an encouraging tolerability and safety profile across the doses evaluated.[11,21]

Lesogaberan is a new $GABA_B$ agonist that does not cross the blood–brain barrier (BBB). In a recent placebo-controlled crossover study, lesogaberan decreased TLESR by 25% to 30%, increased basal LES pressure by 28% and decreased reflux episodes by 50%. ADX10059 is the only mGluR5 antagonist that reached clinical assessment it is a potent, selective negative allosteric modulator.[39]

EVALUATION PARAMETERS OF THE RAFT FORMING IN-SITU GELLING SYSTEM

In vitro evaluation parameters

pH effect

Formulation was transferred in to simulated gastric fluid at different pH (pH 1.2, 5.8, 1.0N HCl pH 1.2 and pH 5.7) and effect of pH was observed.

Texture analysis

For the determination of the firmness, consistency and cohesiveness of the formulation texture analysis is done for the analysis of the syringeability of sol so the formulation can be easily administered *in-vivo*. For the maintaining an intimate contact with surfaces higher value of adhesiveness of gels is needed.

Sol–gel transition and gelling time

The sol–gel transition temperature can be defined as the temperature at which the phase transition of sol meniscus is first noted which is kept in a sample tube at a definite temperature and then heated at a particular rate. Gel formation is indicated by a lack of movement of meniscus on slanting the tube. Gelling time is the time for first detection of gelation.

Gel strength

It is used to determine gelling property of prepared formulation by the using rheometer. In this evaluation a specified amount of sol is incorporated in a beaker containing gastric fluid to form gel, then a probe of rheometer is slowly push through the gel. So load change on the probe can be measured as a function of depth of immersion of the probe underneath the gel surface.[1]

Viscosity and Rheology

These characteristics of the polymeric formulations, either in sol or in gel form were determined with the different types of viscometers. The viscosity can be determined with Brookfield rheometer or some other type such as Ostwald's viscometer. The viscosity of formulations should be optimum such that no difficulties are envisaged during their administration by the patient.

Raft volume and raft weight

Formulation was transfer in SGF (approx 150 ml) pH 1.2 maintains at 37°C in a pre-weighted beaker (W_1), so raft was formed. Then weight of the beaker and filling was obtained (W_2). After this, raft was decanting off from beaker and the subnatant liquor and weighed (W_3). Than this liquor was removed from beaker and it was refilled with water to the noticeable location and weighed (W_4). Than volume (in ml) and weight (in gms) of each raft was measured by following equation.

$$\text{Raft volume} = (W_4\text{-}W_1) – (W_2\text{-}W_1\text{-}W_3)$$

Raft resilience

Formulation was transfer in SGF (approx 150 ml) pH 1.2 maintains at 37°C in a 200 ml glass jars, raft was allowed to form and developed for 30 min. Then capped jars were placed in a tumble mixer to rotate at 20 rpm, for simulate gastric agitation. Raft resilience resilience was determined as the last time point at which a raft was observed. A raft was dispersed into two or more floating gels at least 15 mm in diameter.

Acid neutralization capacity

The dissolution apparatus 2 (paddle apparatus) was operated at 125 rpm and with 250 ml of 0.02 M HCl solution at 37^0C. 120 ml of formulation dissolved solution was poured into the medium and the pH of the medium was checked incessantly, than after 20 mins, the burette started with continuous titration of 0.1 M HCl solution at a constant speed of 2.0 ml/min until the acidity of medium reached at pH 2.5. The neutralizing capacity and buffering capacity from pH 2.5 to 4.5 was calculated from following equations:

Neutralizing capacity- [(VHcl * THcl) + (Vtr-2 * Ttr)] * W1/W2

Buffering capacity- (Vtr-1 * Ttr) * W1/W2

Where,

VHcl = volume of HCl in the vessel

THcl = the titer of HCl in the vessel

Vtr-2 = the added volume of HCl from the burette until pH 2.5

Ttr = the titer of HCl in the burette

W1 =the weight of intact formulation

W2= the weight of tested quantity of formulation

Vtr-1 = the added volume of HCl from the burette between pH 2.5 and 4.5

Ttr = the titer of HCl in the burette

Raft thickness

The thickness of the raft (after formation in the medium) was calculated at three places by using digital vernier caliper and expressed as mean value.[41]

Floating lag time (FLT)

Floating lag time is the time required for the raft to rise to the surface and float on the medium. It was determined by using paddle dissolution apparatus which contained 900ml SGF (pH 1.2) at 37±0.5°C and at 50 rpm.

Total floating time (TFT)

TFT is the total time for which the raft floats in the dissolution medium including FLT.[42]

***In- vitro* dissolution studies/ Drug release**

It is conducted for a period of 12 hrs using USP type-II (Paddle) dissolution apparatus at 37±0.5°C at 50 rpm using 900 ml of 0.1N HCl/ SGF as dissolution medium. At a different time interval, 1 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the sink condition. After filtration and appropriate dilution, the samples were analyzed by UV/Visible spectrophotometer.

Drug–excipient interaction

To study the compatibility of ingredients Fourier transform infra-red spectroscopy (FTIR) is performed. During the gelation process, the nature of interacting forces can be evaluated by the using FTIR technique. Thermo gravimetric analysis can also be conducted to quantitate the percentage of water in hydrogel. Differential scanning calorimetry can also be used to examine if there are any changes in thermo grams as compared with the pure ingredients used therefore indicating the interactions.[1]

Stability Study

Stability study of *in-situ* gel was done according to ICH (international conference on harmonization) guidelines.The formulation was placed in different environment conditions i.e. in refrigerator at 4 oC for 24 h and in 40 oC, 65% RH the for 24 h. These process was repeated five times, for 10 days. Then these formulations was evaluated for viscosity, in situ gelling capacity, floating lag time, total floating time and in vitro drug release study.[30]

IN-VIVO EVALUATION TEST

Gastroscopy

Gastroscopy is a procedure where a thin, flexible tube (endoscope) is used to look inside the oesophagus, stomach and first part of the small intestine. It is used to check visually the effect of dosage form for prolongation in stomach. By the using gastroscopy we can find detail information of the gastroretentive drug delivery system.

Radiology and scintigraphy

In this method radio-opaque markers are use. Gamma/X-rays scintigraphy helps to detect the location of dosage form in the gastrointestinal tract, so we can envisage and correlate the gastric emptying time and the passage of dosage form in the GIT. Similarly, in case of γ-scintigraphy, the γ-rays are focused on a camera, which helps to examine the location of the dosage form in the GIT.[43]

Magnetic marker monitoring

This method is radiation less and thus not moreover hazardous. It is a method to monitor the passage of an oral dosage form through the intestinal tract. In this technique, formulation is magnetite by incorporating iron powder (Fe_3O_4) inside the formulation. By the very sensitive bio magnetic measurement equipment image of the dosage form can be taken.

^{13}C octanoic acid breath test

This method is cheaper than the other. In this, ^{13}C octanoic acid is incorporated into the formulation and then formulation is introduced in the stomach. So due to chemical reaction, octanoic acid liberates CO_2 gas in the stomach which comes out in breath. The important carbon atom which will come in CO_2 is replaced with ^{13}C isotope. So at the time up to which $^{13}CO_2$ gas is observed in breath can be considered as gastric retention time of the dosage form. When the dosage form moves to the intestine, there is no reaction and no CO_2 release.[5]

Ultrasonography

It is a Diagnosis imaging technique and used to see internal body structures such as muscles, tendons, joints, vessels and internal organs. It intended for use to find a source of a disease or to exclude any pathology. It is used sometimes, because it is not traceable at intestine.[5]

FUTURE PROSPECTS WITH RESPECT TO HERBAL DRUGS

Herbal medicine is the traditional system of medicine, which is use for various health benefits by the curing, mitigation and prevention of diseases. The use of herbals in FDDS is the narrative approach and upcoming field in the pharmacy. The scientists are finding it a big chance to work on GRDDS system.[1] Some of these herbal drugs that can be delivered as floating drug delivery systems are tabulated in table 1:

Name of herbal drugs	GIT Benefits	References
Ginger (*Zingiber officinale* Rosc.)	Dyspepsia, motion sickness, hyper emesis gravid arum and have chemo preventative effect in animal models.	44, 45
Black myrobalan (*Terminalia chebula* Retz)	Treatment of peptic ulcer due to antibacterial activity against strains of *H. pylori.*	44, 45
Turmeric (*Curcumina longa* L.)	Prevent gastric and colon cancers or chemo preventative effects.	30
Berberine *Berberis vulgaris*	Antimicrobial activity against a variety of microorganisms and use in cancer.	1
Licorice (*Glycyrrhiza glabra Linn*)	Most potent effect against strains of *H. pylori*. Bronchitis, indigestion and other irritable GIT disorders.	30
Pepperment (Mentha Piperita)	Effective in heartburn, lower the resting LES pressure and other GERD related symptoms also use for GIT health and motility.	14

Marketed formulations of the raft forming system[5]

Various commercial formulations of the raft forming system are tabulated in table 2.

Table 2. Various commercial formulations of the raft forming system

Brand name	Active ingredients	Company name
Liquid Gaviscon	$Al(OH)_3$(95mg) $MgCO_3$(358mg)	GlaxoSmithKline, India.
Topalkan	Al and Mg mixture	Pierre fabre drug, France.
Almagate Flot-Coat	Al and Mg mixture	Pierre fabre
Bisodol	Na, Ca and light $MgCO_3$	White Hall
Gaviscon advance tablets	Na- alginate, $NaHCO_3$, $CaCO_3$	Reckitt and Colman
Gastrocote	Natural mucilage	Boeringer Mannheim
Gastron	Loperamide hydrochloride	Sanofi Winthrop
Algicon	$Al(OH)_3$-$MgCO_3$-codriedgel, $CaCO_3$, Mg alginate, $MgCO_3$	Rorer

Marketed floating dosage forms[5,46,47]

Various marketed floating dosage form are tabulated in table 3.

Table 3. Marketed floating dosage forms

Brand name	Active ingredients	Company names
MODAPAR	Levodopa, benserazide	Roche Products, USA
VALRELEASE	Diazepam	Hoffmann-LaRoche, USA
CONVIRON	Ferrous sulfate	Ranbaxy, India
CIFRAN	Ciprofloxacin	Ranbaxy, India
OFLIN OD	Ofloxacin	Ranbaxy, India
CYTOTEC	Misoprostal	Pharmacia, USA
PROLOPA	Levodopa, benserazide	Roche Products, USA

Various patented preparations of the raft forming system-

Various patents on the preparation of the raft forming system are tabulated in table 4.

US patent	Formulations	References
US20050063980	Gastric raft composition	48
US5360793	Rafting antacid formulation	49
US20020119941	In situ gel formation of pectin	48
US6777000B2	In situ gel formation of pectin	50
US20110082221	In situ gelling system as sustained delivery for eye	51

CONCLUSION

Drug delivery using various gastro-retentive systems has emerged as an efficient means for controlled delivery,[52] each having their own advantages and disadvantages.[53] Among the various approaches the *in-situ* raft forming system has emerged as an efficient means of enhancing bioavailability and controlling drug delivery.[54,55] It provides stomach specific drug release for longer duration which remains floating on the gastric surface so local action of the drug is increased due to prolonged contact time with the gastric mucosa which leads to improved efficiency and decreased frequency.[56] Thus this system promises to be the potential approach for gastric retention drug delivery system.[57,58] Due to the irregularity of human GIT development of efficient GRDFs is an actual challenge to pharmaceutical technology as the drug delivery system must remain for a sufficient time in the stomach which is not compatible with normal physiology.[59,60] Nowadays, herbal drug delivery[61] and nanoparticles based delivery systems[62] shows potential in the pharmacy field. FDDS for herbals is one of the areas that will find it a great chance to work on GI transit profiles.[44,45] This has given rise to new products with substantial benefits to the patients.

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