IJP (2018), Vol. 5, Issue 6 **(Review Article)**

Received on 16 February, 2018; received in revised form, 21 March, 2018; accepted, 30 March, 2018; published 01 June, 2018

IN-SITU RAFT FORMING SYSTEM: A REVIEW

S. S. Raut * and H. A. Shinde

NGSPM's College of Pharmacy, Anjaneri, Nashik - 422213, Maharashtra, India.

Keywords:

Raft forming system, Gastro retentive drug delivery system, Floating drug delivery system, Gastrointestinal track, Gastric residence time, Altered physiological conditions

Correspondence to Author:
S. S. Raut

NGSPM's College of Pharmacy, Anjaneri, Nashik - 422213, Maharashtra, India.

Email: shilpaborate16@gmail.com

ABSTRACT: Oral delivery of drug is the most preferable drug delivery due to the ease of administration, patient compliance and flexibility in the formulations. In recent era various technologies have been made in research and development of controlled release oral drug delivery system to overcome various physiological difficulties such as variation in gastric retention and emptying time. Conventional oral dosage forms pose low bioavailability problems due to their rapid gastric transition from stomach, especially in case of drugs which are less soluble at alkaline pH of intestine and locally acting drugs in stomach get rapidly emptied. So, frequency of dose administration in such cases is increased. Gastro retentive drug delivery system is facing many challenges which can be overcome by upcoming newly emerging approach *i.e*. raft forming system. The present study provides valuable information and highlights advances in this raft forming system. Different types of smart polymers used for their formulation have also been summarized. The review focuses on the mechanism, formulation, development and system optimization aspects of the raft forming system and also highlight parameters which may lead to response variations in altered physiological conditions are discussed as well.

INTRODUCTION: Raft forming system is one of the floating drug delivery system. Floating drug delivery system is retained in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids. Floating drug delivery system (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. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased gastric residence time and a better control of fluctuations in plasma drug concentration [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.IJP.5(6).337-349

Article can be accessed online on: www.ijpjournal.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.IJP.5(6).337-349

In raft forming systems have been widely investigated as vehicles for prolonged drug delivery. This interest has been sparked by the advantages shown by raft forming polymeric delivery systems such as ease of administration and reduced frequency of administration, improved patient compliance and comfort. Raft formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange.

So, raft forming system via different route such as oral, nasal, ophthalmic etc can be formulated. Various natural and synthetic polymers such as gellan gum, alginic acid, xyloglucan, pectin, chitosan, poly (DL lactic acid), poly (DL-lactide-co-glycolide) and polycaprolactone are used for formulation development of raft forming drug delivery systems. Gastro retentive raft forming system helps to increase bioavailability of drug compared to conventional liquid dosage form. The raft formed from raft forming system, being lighter than gastric fluids, floats over the stomach contents

or adhere to gastric mucosa due to presence of bioadhesive nature of polymer and produce gastric retention of dosage form and increase gastric residence time resulting in prolonged drug delivery in gastrointestinal tract.

This review attempts to discuss stomach specific raft forming system in detail including formulation factors to be considered in the development of raft forming system. Also, different types of smart polymers, their mechanisms of gel formation from the sol form [2, 3]. Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, where in each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO_2.

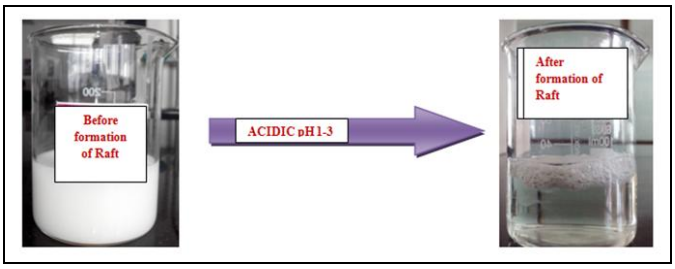

FIG. 1: SCHEMATIC REPRESENTATION OF RAFT FORMING SYSTEM

Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense and float on the gastric fluids an antacid Raft forming floating system. The system contains gel forming agent (*e.g.* alginic bicarbonate, calcium carbonate, mannitol and a sweetener. These ingredients were granulated, and citric acid was added to the granules. The formulation produces effervescence and aerates the raft formed, making it float acid), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids.

The raft thus formed floats on the gastric fluids and prevents the reflux of the gastric contents (*i.e.* gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus. A patent assigned to Reckitt and Colman Products Ltd., describes a raft forming formulation for the treatment of *Helicobacter pylori* (*H. Pylori*) infections in the GIT [2, 3].

Basic Anatomy of Stomach and its Physiology of Stomach: During past 4 decades, the idea of gastro retention is known to researchers and is popularly cultured Davis, in 1968, 1st described the concept of floating drug delivery system. To understand the approaches for gastro retention it is necessary to overview gastric physiology and gastric motility.

Anatomy: Human stomach has a resting volume of 25 - 50 ml, which can distend up to 1500 ml following a meal. The stomach is a J-shaped organ. It is located in the upper left hand portion of the abdomen, just below the diaphragm. It occupies a portion of the epigastria and left hypochondria region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Since the drugs are absorbed in the upper small intestine, it will be beneficial to develop the dosage forms that reside in that region.

Anatomically stomach is divided into 3 parts:

Fundus: The superior part of the stomach, this lies above the imaginary horizontal plane passing through the cardiac orifice.

Body: The body or corpus is the central part of the stomach. This lies between the fundus and the antrum and it is the largest part of the stomach.

Antrum: This lies in the imaginary transpyloric plane and to the right of the angular notch (incisura angularis). It joins the pyloric canal on its right.

The main function of fundus and body is storage whereas that of antrum is mixing or grinding. The fundus also exerts a steady pressure on the gastric contents, pressing them towards the distal stomach (**Fig. 2**). To pass through the pyloric valve into the small intestine, particles should be of the order of 1-2 mm. The antrum does this grinding. The stomach has limitation of short residence time [23, 24, 25, 26].

Physiology: The physiology and disease state of stomach has a direct effect on design of controlled drug delivery system because drug is absorbed from and enters into site of action. Factors such as pH, nature and volume of gastric secretions and

gastric mucosa play an important role in drug release and absorption [24].

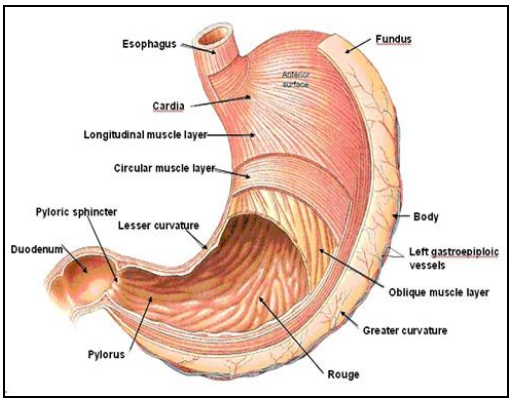

FIG. 2: ANATOMY OF HUMAN STOMACH [23]

pH: The stomach has acidic pH due to secretion of HCl, favours absorption of acidic drugs if they are soluble in gastric fluids since they are unionized in large extent in such a pH. The pH of stomach in fasted condition is about 1.5 to 2 and in fed conditions it is usually 2 to 6. A large volume of water administered with oral dosage form changes the pH of stomach to pH of water initially [24, 28].

Gastric Mucosa: The surface of the gastric mucosa is layer of simple columnar epithelial cells called surface mucous cells. The mucosa contains a lamina propria and a muscularis mucosa. Stomach lumen and mucous neck cells are secrets mucus. Parietal cells produce intrinsic factor and hydrochloric acid. The mucous, parietal and chief cells from stomach secrets 2000 - 3000 ml gastric juice per day. Gastric glands include a type of endocrine cell, the G cell, which stimulates several aspect of gastric activity [23].

TABLE 1: ANATOMICAL DIFFERENCE BETWEEN DIFFERENT REGIONS OF THE GIT [24, 25]

Particulars	Stomach	Small intestine	Large intestine	Rectum
pH range	1-3	5-7.5	7.9-8.0	7.5-8.0
Length (cm)	20	285	110	20
Diameter (cm)	15	2.5	5	2.5
Surface area (m^2)	0.1-0.2	200	0.15	0.02
Blood flow (L/min)	0.15	1.0	0.02	-
Transit time (hrs.)	1-5	3-6	6-12	6-12

Gastric Secretion: Acids, pepsin, gastrin, mucus and some other enzymes are the secretions of the stomach. Normal adults produce a basal secretion up to 60 ml with approximately 4 mM of hydrogen ions every hour. Other potent stimulators of gastric acid are the hormones like gastrin, peptides, amino acids and gastric distension [23].

Gastrointestinal Transit Time: Food content remains in each segment of the gastrointestinal tract for different periods of time. The time a dosage form takes to traverse the stomach is usually termed the 'gastric emptying rate' **Table 2**. Since most of the drugs are absorbed from the upper part of intestine, the total effective time for the drug absorption is 3-8 hrs [24].

TABLE 2: TRANSIT TIME OF FOOD IN EACH SEGMENT OF THE GASTROINTESTINAL TRACT [24]

Segment	Liquid	Solid
Stomach	10-30 min	1-3 h
Duodenum	<60 sec	<60 sec
Jejunum and ileum	3 h ± 1.5 h	4 h ± 1.5 h
Colon	-	20-25 h

Gastric Motility: Gastric motility is also a key factor in stomach specific drug delivery. Thorough knowledge of motility is prerequisite for developing a retentive form of drug. Gastric motility differs in fasting and fed states. In fasting states, an Inter-digestive myoelectric motor complex (IMMC), a 2 h. cycle of peristalsis is generated which progresses to ileocecal junction. It consists of 4 phases.

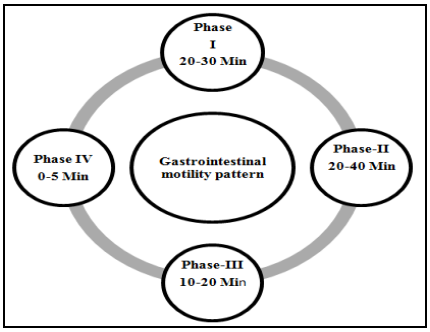

FIG. 3: SCHEMATIC REPRESENTATION OF THE INTERDIGESTIVE MOTILITY PATTERN [4, 25]

Phase I: Also called quiescent period with rare low amplitude contractions, lasting for 30- 60 min.

Phase II: It comprises of intermediate amplitude contractions with bile secretion, lasting for 20 - 40 min.

Phase III: Also called Housekeeper waves, it forms of very high amplitude contractions offering maximum pyloric opening and efficient evacuation of stomach contents. It lasts for 10 - 20 min. with a frequency of 4-5/min.

Phase IV: Transitional phase between phase III and I of two consecutive cycles. It lasts for less than 5 min.

In fed states, motility is induced 5-10 min after ingestion and persists as long as food remains in stomach, typically 3-4 hr. Activity is same as phase II of IMMC. Gastro retentivity of drug was required to increase the bioavailability of drug and to reduce the undesirable effects caused by exposure of drug to other regions of GIT [3, 23, 24, 26].

Factor Affecting on RFS:

Factors Related to Dosage Form:

Size of the Dosage Form: To allow the dosage form to pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm. In most cases, the larger the dosage form the greater will be the GRT. Due to the larger size of the dosage form, it could not quickly pass through the pyloric antrum into the intestine. Small-size tablets leave the stomach during the digestive phase while the large-sized tablets are emptied during the housekeeping waves[2, 3, 4, 9].

Shape of Dosage Form: Ring-shaped and tetra hedron-shaped devices have a better gastric residence time as compared to other shapes [2, 3, 4, 9].

Density of Dosage Form: Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to the bottom of the stomach. Both positions may isolate the dosage system from the pylorus. A density of b1.0 g/cm^3 is required to exhibit floating property. However the floating tendency of the dosage form usually decreases as a function of time, as the dosage form gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium [2, 3, 4, 9].

Food Intake and its Nature:

Fed and Unfed State: Under fasting conditions, the gastrointestinal motility is characterized by periods of strong motor activity or MMC that occurs every 1.5 to 2 h. The MMC sweeps the 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 expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer [1, 2, 9].

Food Intake and Nature of Food: Food intake, viscosity and volume of food, caloric value and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the gastrointestinal tract influences the gastric retention time of the dosage form. Usually the presence of food in the gastrointestinal tract improves the gastric retention time of the dosage form and thus, the absorption of drugs increases by allowing its stay at the absorption site for a longer period [1, 2, 3].

Calorie Content: The rate of gastric emptying primarily depends on the caloric contents of the ingested meal. It does not differ for proteins, fats, carbohydrates as long as their caloric content is the same. Generally an increase in acidity, osmolarity, and caloric value slows down gastric emptying. GRT can be increased between 4 and 10 h with a meal that is high in proteins and fats [9].

Frequency of Feed: The GRT can increase by over 400 min when successive meals are given compared with a single meal due to the low frequency of MMC [2, 3].

Patient Related Factors:

Gender: Gastric emptying rate may differ in male and female. Generally the gastric emptying in women was slower than in men [1, 2, 3, 4].

Age: Elderly people, especially those over 70 years have a longer gastroretentive time. Thus gastric emptying time is slowed down [1, 3, 4].

Posture: The effect of posture on gastric residence time, found no significant difference in the mean gastric residence time for individuals in upright, ambulatory and supine state. In the upright position, the raft forming systems floated to the top of the gastric contents and remained for a longer time, showing prolonged gastric residence time. But the non-floating units settled to the lower part of the stomach and underwent faster emptying as a result of peristaltic contractions, and the floating units remained away from the pylorus. However, in supine position, the floating units are emptied faster than the nonfloating units of similar size [4, 7].

Concomitant Drug Administration: 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*. metoclopramide,

cisapride) can alter gastro retention of oral dosage forms. anticholinergics like atropine and propan-theline increase gastric residence time. Drugs like metoclopramide and cisapride decrease gastric residence time [7, 10].

Disease State: In gastric ulcer, diabetes, and hypothyroidism there is an increase in gastric residence time. In the case of hyperthyroidism and duodenal ulcers there is a decrease in gastric residence time [3, 4].

Volume of the GI Fluid: The resting volume of the stomach is 25 to 50 ml. The volume of liquids administered affects the gastric emptying time. When the volume is large, the emptying is faster. Fluids taken at body temperature leave the stomach faster than colder or warmer fluids [9].

Effect of Gastrointestinal Fluid: On comparison of the floating and non-floating units, it was concluded that regardless of their sizes the floating units remained buoyant on the gastric contents throughout their residence in the GIT, while the non-floating units sink and remained in the lower part of the stomach. Floating units away from the gastro-duodenal junction were protected from the peristaltic waves during the digestive phase while non-floating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase [7, 10].

pH: Variation of gastric pH occurs because of number of physiological factors and patient related factors like diseases, diet, disease, presence of gases, age, pathological conditions, drugs, as well as intra- and inter-subject variation. This variation in pH may significantly influence the performance of orally administered drugs.

About 20% of the elderly people exhibit either diminished (hypochlorohydria) or no gastric acid secretion (achlorohydia). Pathological conditions such as pernicious anemia and AIDS may significantly reduce gastric acid secretion leading to elevated gastric pH.

In addition, drugs like H2 receptor antagonists and proton pump inhibitors significantly reduce gastric acid secretion. These things affects mechanism of the raft formation in the individuals. It means that the formation of raft varies according to the stomach pH of the patient at the time of administration of the formulation [1, 2, 8, 9].

The Design of the Raft Forming System: The formulation of the raft forming system depends on the physicochemical properties of the drug molecule, the diseased condition for which treatment is required, the patient population and the marketing preference. Physicochemical factors include molecular weight, lipophilicity and molecular charge; an anatomical and physiological factor includes membrane transport and pH of tissue fluid; formulation factors include pH, gelation temperature, viscosity, osmolarity, and spreadability. To achieve the gastric retention of the dosage form, the dosage form must be able to satisfy the following criteria. They are as follows:

- The drug should be released slowly from the system.
- The dosage form must be able to withstand the force exerted by peristaltic waves in the stomach and the constant contractions, grinding and churning moments.
- Should maintain specific gravity lower than gastric contents (1.004-1.01 g/cm^3).
- The dosage form must remain in the stomach for a prolonged period of time.
- Better patient compliance.
- Easy for administration for the patient.
- After the release of the drug the device should be easily evacuated from the stomach [2, 3, 4, 8].

Ingredients used in the Formulation of the Raft Forming System: An appropriate candidate should be selected for the formulation of controlled release gastroretentive formulation. Various ingredients used in the formulation of such system are gel forming agent and alkaline bicarbonates or carbonates which are responsible for the formation of a less dense system which float on the gastric fluids [9].

Drugs Selection Criteria for the Raft Forming System: Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The raft forming system is the potential approach for heart burn and esophagitis. This system is suitable for acid soluble drugs that are poorly soluble or unstable in intestinal fluids.

Various drugs that can be used for the raft forming system are summarized in **Table 3** with their category.

Thus the criteria of the drug to be considered for the selection of the drug for gastro retention are as follows:

- Drugs acting locally in the stomach *e.g*. Antacids and drugs for *H. Pylori viz*., Misoprostol
- Drugs that are primarily absorbed in the stomach *e.g*. Amoxicillin
- Drugs those are poorly soluble at alkaline pH *e.g*. Furosemide, Diazepam, Verapamil, *etc*.
- Drugs with a narrow window of absorption *e.g*. Cyclosporine, Methotrexate, Levodopa, *etc*.
- Drugs which are absorbed rapidly from the GI tract. *e.g*. Metonidazole, tetracycline [1, 12, 13, 16, 17, 18].

TABLE 3: DRUGS USED FOR THE RAFT FORMING SYSTEM [1, 12, 13]

S. no	Category	Drugs
1	Antacids	Aluminum hydroxide, Aluminum phosphate, Magnesium silicate, Magnesium hydroxide, Calcium carbonate
2	H2 receptor antagonist Proton pump inhibitor	Cimetidine, ranitidine, loxatidine, famotidine, nizatidine, Omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole
3	Anti-cholinergic	Oxyphenonium, propantheline, telezepine, pirenzepine
4	Anti-helicobacter pylori drugs	Amoxicillin, clarithromycin, tetracycline, metronidazole, tinidazole, colloidal bismuth

The Criteria of the Drug that are not Suitable for Gastric Retention are:

- Drugs that have very limited acid solubility.
- Drugs that suffer instability in the gastric environment.
- Drugs intended for selective release in the colon.

Polymer Used for Formulation: Various polymers are employed in floating drug delivery systems so as to target the delivery of the drug to a specific region in the gastrointestinal tract *i.e*. stomach. Various natural and synthetic polymers are used in the formulation of the raft forming drug delivery system. Natural polymer such as alginic acid, guar gum, gellan gum, xyloglucan, pectin, chitosan *etc*. and synthetic polymer such as poly (DL lactic acid), poly (DL-lactide-co-glycolide) and poly-caprolactone, HPMC *etc*. are used for formulation development of the raft forming drug delivery system.

A polymer used for in situ gels should have the following characteristics:

- It should be biocompatible.
- It should have pseudo plastic behaviour.
- The polymer should be capable of increasing the viscosity with increasing the shear rate [9, 12].

Sodium alginate: Sodium alginate is a widely used polymer of natural origin. Chemically, it is alginic acid salt, consisting of -L-glucuronic acid and -D-mannuronic acid residues connected by 1,4-glycosidic linkages. Solution of alginates in water form firm gels in presence of di-or trivalent ions (*e.g*. calcium and magnesium ions). Alginates salts, specifically, sodium alginate is mostly used for preparation of gel forming solution, for delivery of the drugs and proteins.

Alginate salts are considered most favourable because of biodegradable and non toxic nature, with additional bio- adhesive property. Sodium alginate is a salt of alginic acid - a linear block copolymer polysaccharide consisting of β- D-mannuronic acid and α-L-glucuronic acid residues joined by 1,4-glycosidic linkages. Aqueous solutions of alginates form firm gels on addition of di- and trivalent metal ions. The results indicated that the alginates form compact structures when the ionic radical of the cation are lower. Sodium alginate has been employed in the preparation of gels for the delivery of bio molecules such as drugs, peptides and proteins.

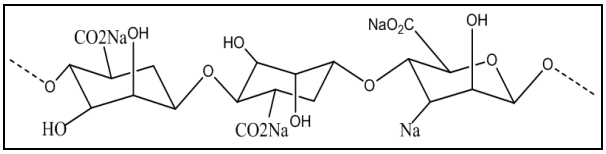

FIG. 4: CHEMICAL STRUCTURE OF SODIUM ALGINATE

Pectin: These are plant origin anionic characteristics can be divided into two polysaccharides isolated from the cell wall of most plants and basically

consist of -(1-4) -D-galacturonic acid residues. Pectin undergoes gel formation in presence of medium, a stiff gel is produced. The gelling capacity divalent ions (*e.g*. Ca) which causes cross linking of the is determined on the 2^+ basis of stiffness and time galacturonic acid units (ionic cross linking) and also in the period for which gel remains, as such. Presence of the H^+ ions (pH dependent gelling).

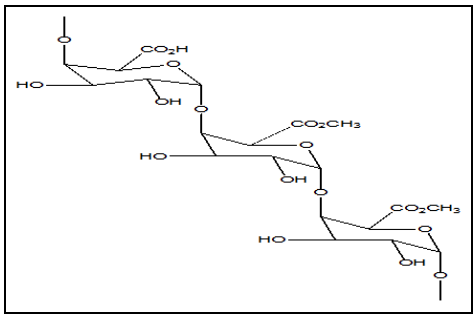

FIG. 5: CHEMICAL STRUCTURE OF PECTIN

Pectin is a complex poly saccharide comprising mainly esterified D-galacturonic acid residues in an a-(1-4) chain. The acid groups along the chain are largely esterified with methoxy groups in the natural product. The hydroxyl groups may also be acetylated. Pectin gelatine types: high-methoxy and low-methoxy gelation. Gelation of high methoxy pectin usually occurs at pH < 3.5. Low-methoxy pectin is gelled with calcium ions and is not dependent on the presence of acid or high solids content.

Gellan gum: Gellan gum (FDA approved) secreted by the *Sphingomonas elodea (Pseudomonas elodea)* and chemically is anionic deacetylated polysaccharide with repeating tetrasaccharide units composed of -D-glucuronic acid (1 unit), -L-rhamnose (1 unit) and -D-glucuronic acid (2 units) residues. Gellan gum undergoes gel formation due to change in temperature or due to presence of cations (*e.g*. Na^+ K^+, Ca^{2+}).

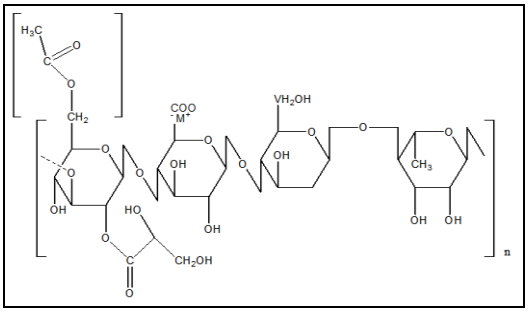

FIG. 6: CHEMICAL STRUCTURE OF GELLAN GUM

Gellan gum is an anionic deacetylatedexocellular polysaccharide secreted by *Pseudomonas elodea* with a tetra- saccharide repeating unit of one α-L-rhamnose, one β-D-glucuronic acid and two β-D-glucuronic acid residues. It is a water soluble polysaccharide. It forms a gelvia formation of double helices, followed by their ionic cross-linking.

Xyloglucan: It is a plant based polysaccharide obtained from seeds of tamarind. Chemically, this polysaccharide composed of a chain of (1-4)- -D-glucan having (1-6)-D xylose units as branches which have partial (1-2)- - D - galactoxylose substitution. Xyloglucan, itself, does no undergo gel formation but dilute solutions partly degraded by galactosidase exhibit gelling properties on heating (temperature dependent gelformation). Besides the use in oral drug delivery, it is also being used for ocular and rectal drug delivery.

Xyloglucan has shown a very low gelation time of up to few minutes. Xyloglucan is a polysaccharide derived from tamarind seeds and is composed of a (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. Xyloglucan is composed of heptasaccharide, octasaccharide and nona-saccharide oligamers, which differ in the number of galactose side chains. Although xyloglucan itself does not gel, dilute solutions of xyloglucan which has been partially degraded by galactosidase exhibit a thermally reversible sol-gel transition on heating.

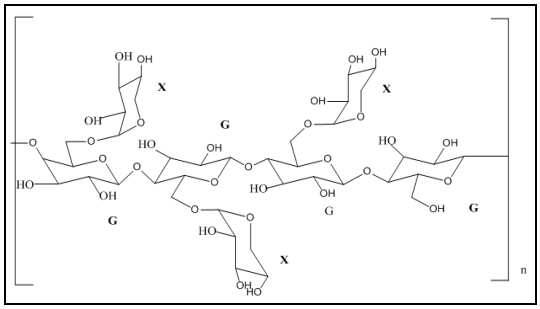

FIG.7: CHEMICAL STRUCTURE OF XYLOGLUCAN

Xanthan gum: Xanthan gum is a high molecular weight extra cellular polysaccharide seeds and is composed of a (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. Xyloglucan is composed of heptasaccharide, octa-

saccharide and nonasaccharideoligamers, which differ in the number of galactose side chains. Although xyloglucan itself does not gel, dilute solutions of xyloglucan which has been partially degraded by galactosidase exhibit a thermally reversible sol-gel transition on heating.

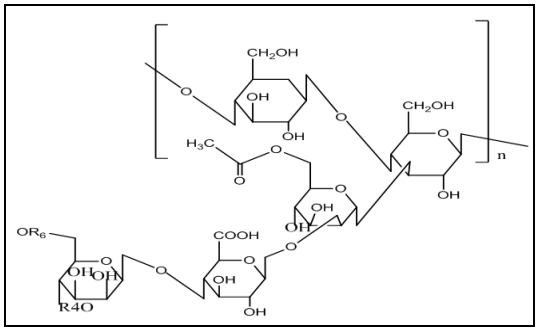

FIG. 8: CHEMICAL STRUCTURE OF XANTHAN GUM

Pluronic F-127: Poloxamers or pluronic (marketed by BASF Corporation) are the series of commercially available difunctional triblock copolymers of non-ionic nature. They comprise of a central block of relatively hydrophobic polypropylene oxide surrounded on both sides by the blocks of relatively hydrophilic poly ethylene oxide. Due to the PEO/PPO ration of 2:1, when these molecules are immersed into the aqueous solvents, they form micellar structures above critical micellar con-centration.

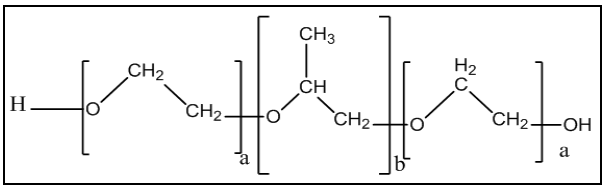

FIG. 9: CHEMICAL STRUCTURE OF PLURONIC F-127

They are regarded as PEOPPO- PEO copolymers. Chemically they are Oxirane, methyl-, polymer with oxirane or α-Hydro-ω- hydroxypoly (oxyethy-lene) a poly (oxypropylene) b poly (oxyethylene) a block copolymer. The pluronic triblock copolymers are available in various grades differing in molecular weights and physical forms. Depending upon the physical designation for the grades are assigned, as F for flakes, P for paste, L for liquid. Pluronics or Poloxamers also undergo in situ gelation by temperature change.

Chitosan: Chitosan is a biodegradable, thermo sensitive, polycationic polymer obtained by alkalinedeacetylation of chitin, a natural component of shrimp and crab shell. Chitosan is a biocompatible pH dependent cationic polymer, which remains dissolved in aqueous solutions up to a pH of 6.2. Neutralization of chitosan aqueous solution to a pH exceeding 6.2 leads to the formation of a hydrated gel like precipitate. The pH gelling cationic polysaccharides solution are transformed into thermally sensitive pH dependent gel forming aqueous solutions, without any chemical modification or cross linking by addition of polyol salts bearing a single anionic head such as glycerol, sorbitol, fructose or glucose phosphate salts to chitosan aqueous solution.

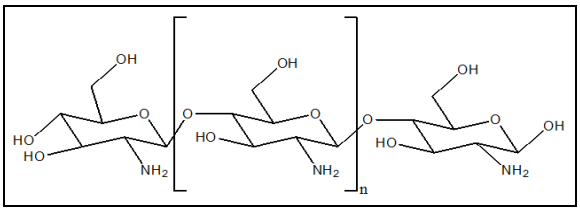

FIG. 10: CHEMICAL STRUCTUREOF CHITOSAN

Carbopol: Carbopol is a well known pH dependent polymer, which stays in solution form at acidic pH but forms a low viscosity gel at alkaline pH. HPMC is used in combination with carbapol to impart the viscosity to carbopol solution, while reducing the acidity of the solution.

Various water triblock copolymers consisting of poly (oxyethylene) and poly (oxypropylene) units that undergo changes in solubility with change in environment temperature. Pluronic ™ F 127. A 25-40% aqueous solution of this material will gel at about body temperature, and drug release from such a gel occurs over a period of up to one week [1, 10, 12, 15, 29].

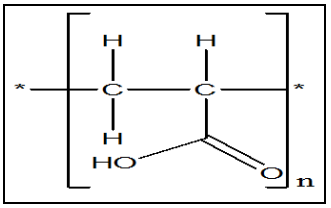

FIG. 11: CHEMICAL STRUCTURE OF CARBOPOL

Different Approaches for RFS System: There are four broadly defined mechanisms used for triggering the in raft formation of biomaterials: Physiological stimuli (*e.g.*, temperature and pH), physical changes in biomaterials (*e.g.*, solvent exchange and swelling) chemical reactions (*e.g.*, enzymatic, chemical and photoinitiated poly-merization).

Raft Formation Based on Physical Mechanism:

Swelling: Raft formation may also occur when absorbs water from surrounding environment and expand to occur desired space. One such substance is myverol 18-99 (glycerol mono-oleate), which is polar lipid that swells in water to form lyotropic liquid crystalline phase structures. It has some bioadhesive properties and can be degraded *in-vivo* by enzymatic action [2, 3].

Diffusion: This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N- Methylpyrrolidone (NMP) has been shown to be useful solvent for such system [2, 3].

Raft Formation Based on Physiological Stimuli:

Thermally Trigged System: Temperature sensitive hydrogels are probably the most commonly studied class of environment-sensitive polymer systems in drug delivery research. The use of biomaterial whose transitions from sol-gel is triggered by increase in temperature is an attractive way to approach *in-situ* formation. The ideal critical temperature range for such system is ambient and physiologic temperature, such that clinical manipulation is facilated and no external source of heat other than that of body is required for trigger gelation. A useful system should be tailorable to account for small differences in local temperature, such as might be encountered in appendages at the surface of skin or in the oral cavity.

Three main strategies are exists in engineering of thermoresponsive sol-gel polymeric system. For convenience, temperature-sensitive hydrogels are classified into negatively thermosensitive, positively thermosensitive, and thermally reversible gels. Negative temperature-sensitive hydrogels have a lower critical solution temperature (LCST) and contract upon heating above the LCST. Polymers with low critical temperature (LCST) transition between ambient and physiologic temperature is used for this purpose. One of the most extensively investigated polymers that exhibit useful LCST transition is poly(N- isopropylacrylamide) (PNIP AAm). PNIPAAM is a water soluble polymer at its low LCST, but hydrophobic above LCST, which result on precipitation of PNIPAAM from the solution at the LCST.

A positive temperature-sensitive hydrogel has an upper critical solution temperature (UCST), such hydrogel contracts upon cooling below the UCST. Polymer networks of poly (acrylic acid) (PAA) and polyacrylamide (PAAm) or poly (acrylamide-co-butyl methacrylate) have positive temperature dependence of swelling. The most commonly used thermoreversible gels are these prepared from poly (ethylene oxide) -bpoly (propylene oxide) -b-poly (ethylene oxide) (Pluronics®, Tetronics®, polo-xamer [19, 20, 21].

pH Dependent Gelling: Another formation of Raft is based on Change in pH. Certain polymers such as poly-vinylacetal diethylaminoacetate (AEA), Mixtures of poly (methacrylic acid) (PMA) and poly (ethylene glycol) (PEG) shows change from sol to gel with change of pH. The polymers with a large number of ionizable groups are known as polyelectrolytes. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups [22].

Raft Formation Based on Chemical Reactions:

Ionic Crosslinking: Polymers may undergo phase transition in presence of various ions. Some of the polysaccharides fall into the class of ion-sensitive ones. Gellan gum commercially available as Gelrite ® is an anionic polysaccharide that undergoes in situ gelling in the presence of mono- and divalent cation, including Ca^{2+}, Mg^{2+}, K^{+} and Na^{+}. Gelation of the low-methoxy pectin can be caused by divalent cations, especially Ca^{2+}. Likewise, alginic acid undergoes gelation in presence of divalent/ polyvalent cations *e.g.* Ca^{2+} due to the interaction with guluronic acid block in alginate chain [1, 8, 9].

Alginic acid + ca $^{++}$ ⟶ Interaction with guluronic acid block in alginate ⟶ Formation of Raft

Enzymatic Cross-linking: Raft formation catalysed by natural enzymes has not been investigated widely but seems to have some advantages over chemical and photochemical approaches. For example, an enzymatic process operates efficiently under physiologic conditions without need for potentially harmful chemicals such as monomers and initiators. Intelligent stimuli-responsive delivery systems using hydrogels that can release insulin have been investigated. Cationic pH sensitive polymers containing immobilized insulin and

glucose oxidase can swell in response to blood glucose level releasing the entrapped insulin in a pulsatile fashion. Adjusting the amount of enzyme also provides a convenient mechanism for controlling the rate of gel formation, which allows the mixtures to be injected before gel formation [5, 6, 7].

Photo-polymerization: A solution of monomers such as acrylate or other polymerizable functional groups and initiator such as 2,2 dimethoxy-2-phenyl acetophenone, camphor Quinone and ethyl erosin can be injected into a tissues site and the application of electromagnetic radiation used to form gel designed readily to be degraded by chemical or enzymatic processes or can be designed for long term persistence *in-viv*o. Typically long wavelength ultraviolet and visible wavelengths are used. A photo polymerizable, biodegradable hydrogels as a tissue contacting material [5, 6, 7].

Advantages of Floating Raft Forming System:

- Raft forming system forms a low density viscous layer on gastric contents and hence provides more effective surface area than a tablet. These lead to more drug release and improve bioavailability.
- Floating obtained faster than the other floating dosage form.
- Improve patient compliance by making a once a day therapy.
- Improve therapeutic efficacy.
- Easy to administer to a patient.
- It increases the contact time of drug at the site of maximum absorption (stomach).
- It provides advantages such as the delivery of drugs with narrow absorption in the small intestinal region.
- Reduction in plasma level fluctuation.
- Target stomach specific drug delivery system like *H. pylori* induced gastric ulcer [2, 4, 8, 14].

Limitation of Floating Raft Forming System:

- These systems are formulated in the form of solution which is more susceptible to stability problems. These are due to chemical degradation (oxidation, hydrolysis, *etc*.) or microbial degradation.
- The formulation must be stored properly because if the formulation is not stored properly it may cause stability problem. This is due to change in the pH of the system on prolonged storage or on storing inappropriate temperature conditions.
- Exposure of certain polymer to radiations (e.g. UV, Visible, electromagnetic, *etc*.) induces the formation of gel within the package [2, 4, 8, 14, 28].

Evaluation Parameter of RFS:

***In-vitro* Evaluation:**

Physical Appearance: The clarity of formulated solution and Raftl was determined by visual inspection under black and white background [3, 10].

pH: The pH was measured of RFS using a calibrated digital pH meter at 25°C. All measurements of pH are made in triplicate [3, 10].

Viscosity Measurement of RFS: Viscosity of the raft forming solution was determined with a Brookfield viscometer (Model No Brookfield DVE -LV viscometer Version 10.0) using a 20 ml aliquot of the sample. Measurements were performed using appropriate spindle number and the temperature was maintained at 25 ± 1 ^{O}C. All measurements were made in triplicate [3, 9].

Buoyancy Study: It was determined in order to measure the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. Test is usually performed in SGF (simulated gastric fluid, 0.1N HCl) which was maintained at 37 °C. The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remains buoyant were measured. The time for which the dosage form continuously floats on the dissolution media is floating time. The time taken for dosage form to emerge on the surface of the medium is called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remains buoyant is called Total Floating Time (TFT) [3, 9].

Gel Strength: The gel strength apparatus was fabricated in house using a measuring cylindrical of 1.2 cm radius and a bore of 0.1 mm at its base. A needle 2 cm in length was used to which a nylon threads was tied. Solution (10 ml) is taken in the cylinder with temporarily sealed bore followed by addition of 50 ml 0.1 N HCl for raft formation. After raft formation the HCl is drained off by opening bore leaving the Raftl mass formed. The

needle was rested on to surface of the raft. At the free end of the thread a light weight pan is attached to which the weight was added. The gel/raft strength is reported in terms of weight required to pass the needle probe through the formed raft mass. The gel/raft strength is calculated using this formula [3, 9, 10].

$$\text{Gel Strength} = M \times g / a \quad \ldots\ldots\ldots\ldots\ldots \quad (1)$$

Where,
M = Weight at which needle passes through the formed gel mass
g = Gravitational force
a = Area of surface

Measurement of Water Uptake by the Raft: The water uptakes by the raft of the selected formulations of sodium alginate were determined by a simple method. In this study raft formed in 40 ml of 0.1 N HCl (pH 1.2) was used. From each formulation the raft portion from the 0.1 N HCl was separated and the excess HCl solution was blotted out with a tissue paper. The initial weight of the raft taken was weighed and to this raft10 ml of distilled water was added and after every 30 minutes of the interval water was decanted and the weight of the Raft was recorded and the difference in the weight was calculated and reported [7, 38].

$$\% \text{ water uptake} = W2 - W1 / W1 \times 100 \quad \ldots\ldots\ldots \quad (2)$$

Where,
W1 = initial weight of gel (10 ml)
W2 = weight of swollen matrix after 16 h.

Drug Content: Accurately, 1 ml of RFS was added to appropriate amount of 0.1N HCl to yield solution containing strength of 1000 µg/ml. From that 10 µg/ml solution was prepared by diluting stock solution. Determine drug content using above stock solution [17].

***In-vitro* Drug Release Study:** The release rate of drug was determined using USP apparatus 2 at 50 rpm. This speed slow enough to avoid breaking of raft formulation and is maintaining mild agitation condition exist *in-vivo*. The dissolution medium used is 900 ml of simulated gastric fluid (0.1 N HCl) and temperature is maintained at 37 ^{o}C. A sample is withdrawn at every 60 min time interval. The sample is analyzed and % cumulative release is calculated [9, 17].

***In-vivo* Evaluation:**

Radiology and Scintigraphy: It involves the use of radio-opaque markers. X-ray/Gamma Scintigraphy helps to locate dosage form in the gastrointestinal tract (GIT), thus one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. Barium sulfate is widely used as Radio Opaque Marker. Here the inclusion of a radio-opaque material *i.e.* $BaSO_4$ into a solid dosage form enables it to be visualized by X-rays at different intervals to determine gastric retention.

Similarly inclusion of γ-emission of radionuclide in a formulation allows indirect external observation using a scintiscanner. In case of γ-scintigraphy, the γ-rays emitted by the radionuclide are focused on a camera, which helps to monitor the location of the dosage form in the GIT. 99Tc is widely used as the emitting material [29, 36].

Gastroscopy: Gastroscopy is peroral endoscopy used with fiber optics or video systems. Gastroscopy is used to inspect visually the effect of dosage form for prolongation in stomach. It can also give the detailed evaluation of the gastroretentive drug delivery system [37].

Magnetic Marker Monitoring: In this technique, dosage form is magnetically marked with incorporating iron powder inside the dosage form. Image of the dosage form can be taken by very sensitive bio-magnetic measurement equipment. Advantage of this method is that it is radiation less and thus not too much hazardous [29, 37].

13C Octanoic Acid Breath Test: 13C octanoic acid is incorporated into the gastroretentive drug delivery system and the system is introduced in the stomach. In the stomach due to chemical reaction, octanoic acid liberates CO_2 gas which comes out in breath. The important carbon atom which will come in CO_2 is replaced with 13C isotope.

So the time up to which $13CO_2$ gas is observed in breath can be considered as gastric retention time of the dosage form. As the dosage form moves to the intestine, there is no reaction and no CO_2 release. So this method is cheaper than the other [37].

Patented Formulations of RFS: Patent Formulations are as follows:

TABLE 4: PATENTED FORMULATIONS [30, 31, 32, 33, 34]

S. no.	US Patent	Formulations
1	US20120009275	*In-situ* forming hydro gel wound dressing containing antimicrobial agents
2	US20050063980	Gastric raft composition
3	US5360793	Rafting antacid formulation
4	US20020119941,35]	*In -situ* gel formation of pectin
5	US20110082221	*In -situ* gelling system as sustained delivery for eye

Marketed Formulation of RFS: Various marketed preparation of RFS are as follows.

TABLE 5: MARKETED FORMULATION OF RFS [9, 25]

S. no.	Brand name	Drug
1	Liquid Gaviscon	Aluminium hydroxide and magnesium stearate
2	Topalkan	Aluminium hydroxide and magnesium stearate
3	Conviron	Ferrus sulphate

CONCLUSION: Development of efficient gastro-retentive system for stomach specific drug delivery is real challenge. So, in order to produce the desired gastro retention various approaches have been employed, out of which floating drug delivery system has emerged as most promising technique. RFS is one of the approaches of floating drug delivery system which undergo raft formation in acidic stomach conditions and provide stomach specific release of drug for longer duration while being buoyant on the gastric fluid surface.

As the system remains in stomach for longer duration local action of drug due to prolonged contact time to gastric mucosa is increased. This leads to less frequent dosing and improved efficiency of treatment. Raft forming system is not only helpful for sustained drug delivery but also convenient for pediatric and geriatric patients. This system is helpful as an alternative of oral solid dosage form with the advantages of liquid dosage form. Sustained and prolonged release of the drug, good stability and bioavailability characteristics make the raft forming system very suitable candidate for gastric retention of the drug. Thus the raft forming system promises to be the potential approach for gastric retention drug delivery system. Development of RFS provide opportunity of line extension for marketplace; wide range of drugs.

ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: Nil

REFERENCES:

1. Shah P, Bhimani B and Patel U: Brief review of polymers use in raft forming system. International Journal of Pharmaceutical Research and Bio-science 2014; 3(5): 437-448.
2. Doshi N: In *situ gel*: a novel approach of gastro retentive drug delivery. Asian Journal of Pharmaceutical Sciences and Research 2013; 3(3).
3. Vishvadeep P, Akshay P, Henil P, Jay P, Ravi P and Upendra P: A review on *in-situ* gelling system: Novel approach for stomach specific drug delivery. International Journal of Pharmaceutical Research and Bio-science 2014; 3(2): 466-480.
4. Bhavsar DN, Varde NM, Sini S, Shah VH and Upadhyay UM: Advances in GRDDS: Raft forming system a review. Journal of Drug Delivery and Therapeutics 2012; 2(5): 123-128.
5. Chaturved S, Kumari P, Singh S and Agrawal V: Approaches to increase the gastric residence time: floating drug delivery systems- a review. Asian J Pharm Clin Res 2013; 6(3): 1-9.
6. Ramya DD, Abhirami M, Brindha R, Gomathi S and Vedhahari BN: *In-situ* gelling system - potential tool for improving therapeutic effects of drugs. International Journal of Pharmacy and Pharmaceutical Sciences 2013; 5(3).
7. Lovenish B, Pramod KS and Rishabha M: A short review on gastro retentive formulations for stomach specific drug delivery: special emphasis on floating *in-situ* gel systems. African Journal of Basic and Applied Sciences 2011; 3(6): 300-312.
8. Samar ES: Floating systems for oral controlled release drug delivery. PhD Theses, Pharmazie der Freien Universität Berlin, Juli 2010.
9. Vipul D, Prajapati, Girish K, Tohra AK and Bhumi SZ: Raft forming system-an upcoming approach of gastro-retentive drug delivery system. Elsevier, Journal of Controlled Release 2013; 168: 151-165.
10. Kalia N, Nirmala and Harikumar SL: *In-situ* gelling system: A review. Journal of Drug Delivery and Therapeutics 2014; 4(4): 93-103.
11. Vinod K, Santhosh V, Anbuazaghan S, David B and Padmashri A: Sandhya, S. Approaches for gastrotentive drug delivery systems. International Journal of Applied Biology and Pharmaceutical Technology 2010; 1(2).
12. Singh A, Dubey V and Arora V: Role of natural polymers used in floating drug delivery system. Journal of Pharmaceutical and Scientific Innovation 2012; 11-15.
13. Nirmal HB, Bakliwal SP and Pawar SP: *In-situ* gel: new trends in controlled and sustained drug delivery system. International journal of pharm Tech Research 2010; 2(2): 1398-1408.
14. Nikita D: Floating drug delivery system. Journal of Current Pharmaceutical Research 2011; 7(1): 6-20.
15. Shreeraj S, Pratik U, Darsh P and Jinal S: *In-situ* gel: A Novel approach of gastroretentive drug delivery. Asian Journal of Biomedical and Pharmaceutical Sciences 2012; 2(8): 01-08.
16. Jayswal B, Yadav V, Patel K, Patel B and Patel P: Formulation and evaluation of floating *in-situ* gel based

gastro retentive drug delivery of cimetidine. International Journal for Pharmaceutical Research Scholars 2012; 1(2).
17. Sanket C, Dron M, Ravi P, Jay P, Rahul D and Sunita C: Formulation and evaluation of floatable *in-situ* gel for stomach-specific drug delivery of ofloxacin. American Journal of Advanced Drug Delivery 2013.
18. Rishad R, Chhagan N, Dashrath M and Nurudin P: Development of a novel floating *in-situ* gelling system for stomach specific drug delivery of the narrow absorption window drug baclofen. Iranian Journal of Pharmaceutical Research 2010; 9(4): 359-368.
19. Sapra P, Patel D, Soniwala M and Chavda J: Development and optimization of in situ periodontal gel containing levofloxacin for the treatment of periodontal diseases. Journal of Scientific and Innovative Research 2013; 2(3): 608-627.
20. Asija R, Patel N, Shah S, Asija S and Barupal A: Sustain ophthalmic delivery of levofloxacin from a pH triggered *in-situ* gelling system. International Research Journal of Pharmacy 2012; 3(4).
21. Akhani J and Modi C: Formulation development and evaluation of *in-situ* gel for vaginal drug delivery of antifungal drug. An International Journal of Pharmaceutical Sciences, Pharma Science Monitor 2014 Sup-1, 5(2).
22. Patel D, Patel, DK and Patel C: Formulation and evaluation of floating oral *in-situ* gelling system of amoxicillin. International Scholarly Research Network, Pharmaceutics 2011.
23. Tortora GH and Derrickson B: Principle of anatomy and physiology, Wiley International, Edition 11th, 902-940.
24. Brahmankar DM and Jaiswal SB: Biopharmaceutics and pharmacokinetics- A Treatise. Vallabh Prakashan, Edition 2nd, 2009; 63-71.
25. Jain NK: Progress in controlled and drug delivery system. CBS Publishers and Distributers Pvt., Ltd., 76-97.
26. Ross and Wilson: Anatomy and physiology in heath and illness, Edition 12th, 294-308.
27. Singh S, Singh J, Muttu MS, Balasubramaniam J and Mishra B: Gastroretentive drug delivery system of metoclopride hydrochloride: Formulation and *in-vitro* evaluation. Current Drug Delivery 2007; 4: 269-275.
28. Sathish D, Himabhindu S, Shravan K and Rao Y: Floating drug delivery system for prolonging gastric residence time: A review. Current Drug Delivery 2011; 8: 494-510.
29. Caragh S, Pillay V, Choonara YE and Toit LC: Current Drug Delivery 2009; 6: 451-460.
30. Gillian E and Ronald P: An alginate, a pectin and an antacid, such as sodium or potassium bicarbonate; gastrointestinal reflux disease, US 20050063980 A1, 2004.
31. Bruktawit T: *In-situ* forming hydrogel wound dressings containing antimicrobial agents US 20120009275 A1, 2011.
32. William J: Rafting antacid formulation, US5360793, 1994.
33. Yawei N and Knneth M: *In-situ* gel formation of pectin, US 20020119941, 2002.
34. Gillian E and Ronald P: Gastric raft composition, US 20050063980, 2005.
35. Claire H and Stephane J: *In-situ* gelling systems as sustained delivery for front of eye, US20110082221, 2011.
36. Rathee P, Jain M, Garg A, Nanda A and Hooda A: Gastrointestinal mucoadhesive drug delivery system: a review. J. Pharm. Res 2011; 4: 1448-1453.
37. Soni R, Patel A, Patel R, Patel M, Patel K and Patel N: Gastroretentive drug delivery systems: a review, Int. J. Pharma World Res 2011; 2: 1-24.
38. Panwar P, Chaurasiya D, Jain G and Sheorey R: Formulation and evaluation of oral floatable *in-situ* gel of diltiazem HCl. Intrnational Journal of Novel Drug Delivery Technology, 2012.

How to cite this article:
Raut SS and Shinde HA: *In-situ* raft forming system: a review. Int J Pharmacognosy 2018; 5(6): 337-49. doi link: http://dx.doi.org/10.13040/IJPSR.0975-8232.IJP.5(6).337-49.