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Review Article

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A Raft Forming System: An Novel Approach for Gastroretention

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ABSTRACT

Oral delivery of the drug is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in the formulations but has a drawback of non-site specificity and short gastric resident time. In order to overcome the drawbacks of conventional oral drug delivery systems, several technical advancements have led to the development of gastro retentive drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits. Gastroretentive 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 & highlights advances in this raft forming system. This review attempts to discuss various factors like physiological factors, physicochemical factors and formulation factors to be considered in the development of the raft forming system, different types of smart polymers used for their formulation, mechanism, formulation and development of the raft forming system, studies to evaluate the performance and application of these systems.

Key words: *Gastroretentive form, Raft forming system, Gastric residence time, Gastric emptying time.*

INTRODUCTION

The increased interest in developing oral controlled release dosage forms can be attributed to their ability to maintain an effective drug concentration in the systemic circulation for a long time and offering improved therapeutic advantages such as ease of dosing administration, patient compliance, flexibility in formulation[1].

However, this route has several physiological problems. Including an unpredictable gastric emptying rate that varies from person to person, a brief gastrointestinal transit time (80-12h), and the existence of an absorption window in the upper small intestine for several drugs. These difficulties have prompted researchers to design a drug delivery system which can stay in the stomach for prolonged and predictable period. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs[2].

Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients[3].

Drugs that require to be designed as gastro retentive systems are those acting locally in stomach, primarily absorbed from the stomach, poorly soluble in alkaline pH, absorbed rapidly from the gastrointestinal tract, and that degrades in the colon[4].

Many technological attempts have been made to devise various controlled release gastroretentive drug delivery systems namely, high density (sinking) systems that is retained in the bottom of the stomach,low density (floating) systems that causes buoyancy in gastric fluid, mucoadhesive systems that causes bioadhesion to stomach mucosa, unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach, superporous hydrogel systems, magnetic systems[5].

Among these systems, the raft forming system has been most commonly used as it is one of the most feasible & preferred approaches for achieving a prolonged and predictable drug delivery profile in the GI tract. This system is capable of releasing a drug molecule in a sustained manner affording relatively constant plasma profiles. These hydrogels are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. The goal for designing this system is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of the action, decreasing the dose required or providing uniform drug delivery. The raft forming system also possesses some potential advantages like simple manufacturing processes, better patient compliance and ease of administration[6].

Anatomy and Physiology of stomach

The gastrointestinal tract can be divided into three main regions namely

1. Stomach
2. Small intestine- Duodenum, Jejunum and Ileum
3. Large intestine[7]

The GI tract is essentially a tube about nine meters long that runs through the middle of the body from the mouth to the anus and includes throat (pharynx), oesophagus, stomach, small intestine (consisting of duodenum, jejunum and ileum) and large intestine (consisting of caecum, appendix, colon, and rectum)[8].

The stomach is an organ with a capacity for storage and mixing. The antrum region is responsible for the mixing and grinding of gastric contents[9].

The stomach is anatomically divided into three parts:

- fundus
- body
- antrum (pylorus)[10]

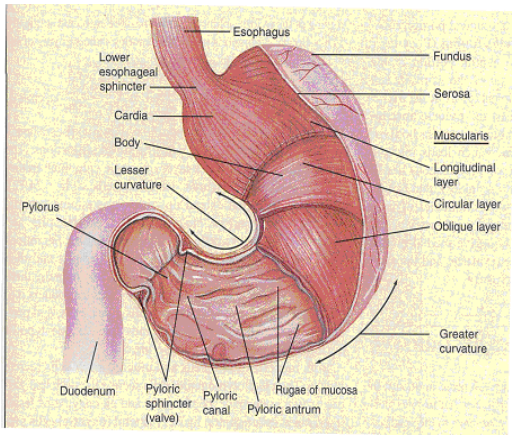

Fig.1: Location of stomach in human body

The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions (Fig. 1). [11]

Gastric emptying occurs both in fasting as well as fed states. In case of fasted state an interdigestive series of electrical events occurs in cyclic manner both through the stomach and small intestine every 2 to 3 hours(Fig.2). The interdigestive myoelectric cycle or migrating myoelectric complex (MMC) governs the activity and the transit of dosage forms[12].

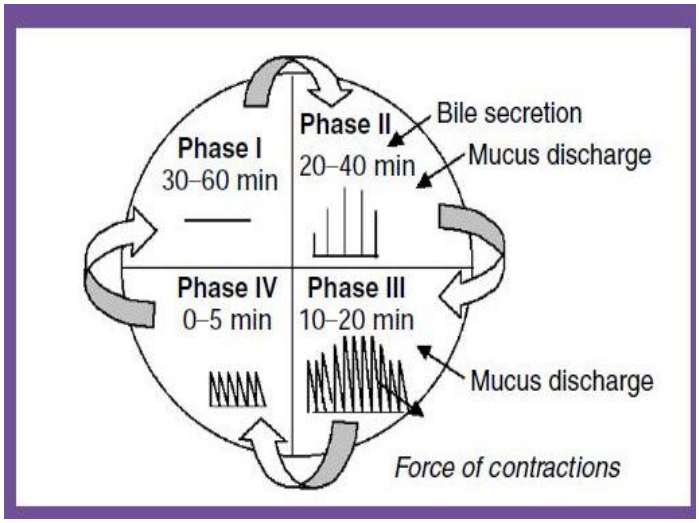

Fig. 2: Gastric motility pattern

It is divided into four phases-

Phase I (Basal phase): the quiescent period, lasts from 40 to 60 minutes and is characterized by a lack of secretary, electrical and contractile activity.

Phase II (Preburst phase): lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses, the intensity and frequency also increases gradually.

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.[13]

Phase IV: transitional phase between phase III and I of two consecutive cycles. It lasts for less than 5 min.[14]

After the ingestion of food, the pattern of contractions changes from fasted to that of fed state. This is known as digestive motility pattern and comprises continuous concentrations as in phase II of fasted state. These contractions result in reducing the size of food particles (> 1 mm), which are propelled towards the pylorus in suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.[15]

Factors affecting gastroretentive drug delivery system

These are various factors to be considered for the development of gastroretentive dosage forms formulation to prolong the dosing intervals and thus improve patient compliance. They are shown below:

Factors related to dosage forms:

Density:

GRT is a function of dosage form buoyancy that is dependent on the density. The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach.

Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach. Both positions may isolate the dosage system from the pylorus. A density of < 1.0 gm/ cm3 is required to exhibit floating property[16].

Size of dosage form:

The size of the dosage form is another factor that influences gastric retention. The mean gastric residence times of non-floating dosage forms are highly variable and greatly dependent on their size, which may be small, medium, and large units. In fed conditions, the smaller units get emptied from the stomach during the digestive phase and the larger units during the housekeeping waves. In most cases, the larger the size of the dosage form, the greater will be the gastric retention time12 because the larger size would not allow the dosage form to quickly pass through the pyloric antrum into the intestine. Thus the size of the dosage form appears to be an important factor affecting gastric retention[17].

Shape of dosage form:

Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilopounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes[18].

Food intake and its nature:

Fed or unfed state:

Under fasting conditions: GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation 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[19].

Nature of meal:

Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.[20]

Caloric content:

GRT can be increased by four to 10 hours with a meal that is high in proteins and fats[21].

Frequency of feed:

The G R T can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC[20].

Patient related factors:

Gender:

Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface[22].

Age:

Elderly people, especially those over 70, have a significantly longer GRT.

Posture:

GRT can vary between supine and upright ambulatory states of the patient[23].

Concomitant drug administration:

Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride[24].

Disease states:

Gastric ulcer, diabetes, hypothyroidism increase GRT. Hyperthyroidism, duodenal ulcers decrease GRT.

Volume of GI fluid:

The resting volume of the stomach is 25 to 50 ml. When volume is large, the emptying is faster. Fluids taken at body temperature leave the stomach faster than colder of warmer fluids[25].

Buoyancy :

On comparison of floating and non floating dosage units, it was observed that regardless of their sizes the floating dosage units remained buoyant on the gastric contents throughout their residence time in the gastrointestinal tract, while the non floating dosage units sank and remained in the lower part of the stomach.

Floating units away from the gastro duodenal junction were protected from the peristaltic waves during digestive phase while the non floating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase.

It was also observed that out of the floating and non floating units, the floating units had a longer gastric residence time for small and medium units while no significant difference was seen between the two types of large unit dosage forms[26].

Raft forming system

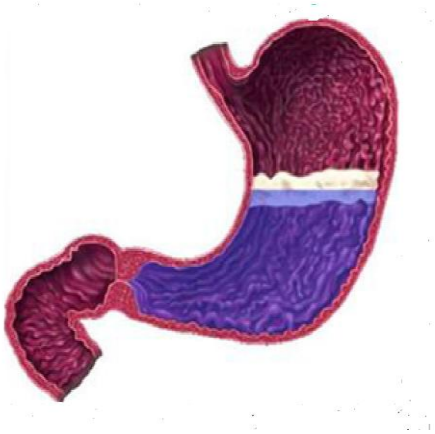

Fig. 3: Schematic illustration of the barrier formed by a raft-forming system

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. Floating Rafts have been used in the treatment of Gastric esophageal reflux disease (GERD)[11].

The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft (Fig.3). This raft floats on gastric fluids because of low bulk density created by the formation of CO_2. 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[28].

An antacid raft forming floating system contains a gel forming agent (e.g. sodium alginate), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft), which when comes in contact with gastric fluids, the raft 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.[25]

A raft‐forming formulation requires sodium or potassium bicarbonate; in the presence of gastric acid, the bicarbonate is converted to carbon dioxide, which becomes entrapped within the gel precipitate, converting it into foam, which floats on the surface of the gastric contents. The antacid components contained in formulations provide a relatively pH‐neutral barrier. Calcium carbonate can be used as an antacid as well as a raft‐strengthening agent. It releases calcium ions, which react with alginate and form an insoluble gel. Various polymers, especially different polysaccharides, have been used in various research works. Alginic acid, alginates and pectin are the most widely used raft‐forming agents. Other polysaccharides are also being used, which include guar gum, locust bean gum, carrageenan, pectin and isapgol[29,30].

Raft forming anti reflux preparation is one of the upcoming new approach to overcame the problem of sevearity of acidity, Peptic ulcer and gastritis problems. They are generally used in the treatment of gastric acid-related disorders, especially GERD, heartburn and oesophagitis[31].

Advantages of raft forming system:

1) They are used for the symptomatic treatment of heartburn and oesophagitis. It can be used in LPR. GERD, Laryngopharyngeal Reflux (LPR) refers to the backflow of stomach contents into the laryngeal and pharyngeal region.
2) It does not interfere with the activity of promotility agent, antisecretory agents such as cimetidine.
3) Rapid and Long-duration of action can easily achieved by raft formation. It may show its action within seconds.
4) It will not interfere with function of pyloric sphincter.
5) Better patient compliance can be achieved and it is well tolerated[32].

Limitation of floating raft forming gastroretentive drug delivery system over other gastroretentive drug delivery system:

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

Drugs suitable for raft forming system:

1) Drugs with narrow absorption window in GIT, e.g., Riboflavin and Levodopa[33].
2) Drugs that primarily absorbed from stomach and upper part of GIT, e.g., Calcium supplements, chlordiazepoxide and cinnarazine. [34]
3) Drugs that act locally in the stomach, e.g., Antacids and Misoprostol[35].
4) Drugs that degrade in the colon, e.g., Ranitidine HCl and Metronidazole.
5) Drugs that disturb normal colonic bacteria, e.g., Amoxicillin Trihydrate[36].

Approaches used for the formulation of the raft forming drug delivery system

Raft forming drug delivery systems are a revolution in oral drug delivery. These systems are liquids at room temperature but undergo gelation when comes in contact with body fluids or change in pH. These have a unique property of temperature dependent and cation-induced gelation. Gelation involves formation of the double helical junction zones followed by aggregation of the double helical segments which form three dimensional networks by complexation with cations and hydrogen bonding. [37]

Different approaches based on their mechanisms used for triggering the raft formation in the GIT are as follows.

Raft formation based on physical mechanism

Swelling:

Formation of a gel occurs when the liquid effervescent system comes in contact with gastric fluid. In situ formation of gel occurs when materials absorb water from the surrounding environment and expand to

occur at the desired space. Swelling of the polymer occurs by absorption of water which further causes formation of the gel. Certain biodegradable lipid substance such as myverol 18–99 (glycerol mono-oleate), is a 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[38].

Diffusion:

Diffusion is the method which involves diffusion of a solvent from polymer solution into surrounding tissue, which further results in precipitation or solidification of polymer matrix. Solution of polymer that can be used for such mechanism is N-methyl pyrrolidone (NMP)[39]. Raft formation based on chemical mechanism

Ionic cross linking:

There are various polysaccharides that undergo phase transition in the presence of various ions. Polysaccharides falling into the class of ion-sensitive ones are most widely used[40]. Ion sensitive polysaccharides such as carrageenan, gellan gum (Gelrite®), pectin, and sodium alginate undergo phase transition in the presence of various ions such as K^+, Ca^+, Mg^+ and Na^+. Various polysaccharides undergo gelation in the presence of various monovalent, divalent cations. Alginic acid undergoes gelation in the presence of divalent/polyvalent cations like Ca^{2+} due to the interaction with guluronic acid block in alginate chains. K-carrageenan forms rigid, brittle gels in response to small amount of K^+, i-carrageenan forms elastic gels mainly in the presence of Ca^{2+}. Gellan gum commercially available as Gelrite® is an anionic

polysaccharide that undergoes in situ gelling in the presence of mono- and divalent cations, including Ca^{2+}, Mg^{2+}, K^+ and Na^+. Gelation of the low-methoxy pectin can be caused by divalent cations, especially Ca^{2+}. [41]

Raft formation based on physiological stimuli mechanism

pH dependent gelling:

Formation of gel in the system also occurs due to change in the pH of the medium. Various pH dependent polymers are used which cause the formation of in situ gel in the system. Various polymers such as PAA (Carbopol®, carbomer) or its derivatives, polyvinylacetal diethylaminoacetate (AEA), mixtures of poly(methacrylic acid) (PMA) and poly(ethylene glycol) (PEG) show change from sol to gel with change of pH.[42] 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. Mixtures of poly(methacrylic acid) (PMA) and poly(ethylene glycol) (PEG) also have been used as a pH sensitive system to achieve gelation[42]. pH sensitive polymer can be neutral or ionic in nature. The anionic networks contain negatively charged moieties, cationic networks contain positively charged moieties, and neutral networks contain both positive and negatively charged moieties. In the case of anionic polymeric network containing carboxylic or sulphonic acid groups, ionization takes place, as the pH of the external swelling medium rises above the pKa of that ionizable moiety.

Temperature dependent gelling:

These hydrogels are liquid at room temperature (20 °C–25 °C) and undergo gelation when in contact with body fluids (35 °C–37 °C), due to an increase in temperature. This approach exploits temperature-induced phase transition. Some polymers undergo abrupt changes in solubility in response to increase in environmental temperature (lower critical solution temperature, LCST)[43,44]. At the LCST, hydrogen bonding between the polymer and water becomes unfavorable, compared to polymer–polymer and water–water interactions, and an abrupt transition occurs as the solvated macromolecule quickly dehydrates and changes to a more hydrophobic structure.[45] Alternatively, some amphiphilic polymers that self-assemble in solution, show micelle packing and gel formation because of polymer–polymer interactions when

temperature is increased[46]. Temperature-sensitive hydrogels are probably themost commonly studied class of environment-sensitive polymer systems in drug delivery research. Polymers such as pluronics (poly(ethylene oxide)– poly(propylene oxide)–poly(ethylene oxide) (PEO–PPOPEO Triblock), polymer networks of poly(acrylic acid) (PAA) and polyacrylamide

(PAAm) or poly(acrylamide-co-butyl methacrylate) are commonly used for temperature sensitive hydrogels formation[47.] A positive temperature-sensitive hydrogel has an upper critical solution temperature (UCST), and such hydrogel contracts upon cooling below the UCST. Polymer networks of poly(acrylic acid) (PAA) and polyacrylamide (PAAm) or poly(acryl amide-co-butyl methacrylate) have positive temperature dependence of swelling[48].

Polymers used for formulation

Pectin

Pectins are a family of polysaccharides, in which the polymer backbone mainly comprises α- (1-4)-D-galacturonic acid residues(Fig.4). Low methoxypectins (degree of esterification <50%) readily form gels in aqueous solution in the presence of free calcium ions, which crosslink the galacturonic acid chains in a manner described by egg-box model . Although the gelation of pectin will occur in the presence of H^+ ions, a source of divalent ions, generally calcium ions is required to produce the gels that are suitable as vehicles for drug delivery. The main advantage of using pectin for these formulations is that it is water soluble, so organic solvents are not necessary in the formulation. Divalent cations present in the stomach, carry out the transition of pectin to gel state when it is administered orally. Calcium ions in the complexed form may be included in the formulation for the induction of pectin gelation. Sodium citrate may be added to the pectin solution to form a complex with most of calcium ions added in the formulation. By this means, the formulation may be maintained in a fluid state (sol), until the breakdown of the complex in the acidic environment of the stomach, where release of calcium ions causes gelation to occur[49].

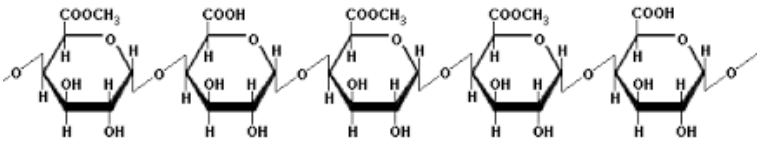

Fig. 4: Structure of Pectin

Alginic Acid

Alginic acid is a linear block copolymer polysaccharide consisting of β-D-mannuronic acid and α-L-glucuronic acid residues joined by 1,4-glycosidic linkages(Fig. 5). The proportion of each block and the arrangement of blocks along the molecule vary depending on the algal source. Dilute aqueous solutions of alginates form firm gels on addition of di and trivalent metal ions by a cooperative process involving consecutive glucuronic residues in the α-Lglucuronic acid blocks of the alginate chain. Alginic acid can be chosen as a vehicle for formulations, since it exhibits favorable biological properties such as biodegradability and nontoxicity[50].

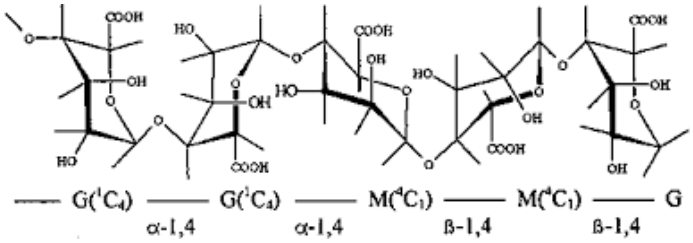

Fig. 5: Structure of Alginic Acid

Gellan Gum

Gellan gum (commercially available as Gelrite™ or Kelcogel™) is an anionic deacetylated exocellular polysaccharide secreted by Pseudomonas elodea with a tetrasaccharide repeating unit of one α-L-rhamnose, one β-D-glucuronic acid and two β-D-glucuronic acid residues (Fig.6). Gellan gum produces temperature dependent or cations induced in situ gelling.Chemical structure of the polysaccharide has a tetrasaccharide repeat unit consisting of two glucose (Glc) residues, one glucuronic acid (GlcA) residue, and one rhamnose (Rha) residue. These are linked together to give a tetrasaccharide repeat unit[51].

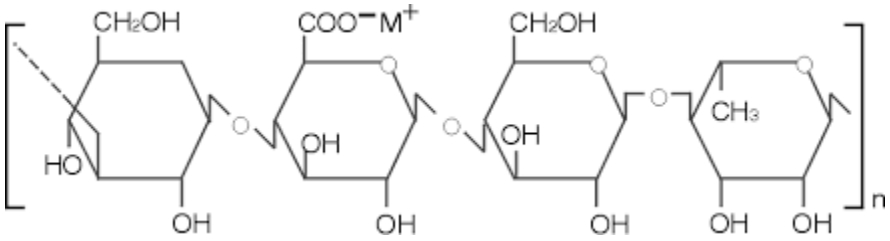

Fig. 6: Structure of Gellan Gum

Xyloglucan

Xyloglucan is a polysaccharide derived from tamarind seeds and is composed of a (1-4)-β-Dglucan backbone chain, which has (1-6)-α-D xylose branches that are partially substituted by (1-2)-β Dgalactoxylose(Fig.7). When xyloglucan is partially degraded by β-galactosidase, the resultant product exhibits thermally reversible gelation by the lateral stacking of the rod like chains. The sol-gel transition temperature varies with the degree of galactose elimination. It forms thermally reversible gels on warming to body temperature. Its potential application in oral delivery exploits the proposed slow gelation time (several minutes) that would allow *in situ* gelation in the stomach following the oral administration of chilled xyloglucan solution[52].

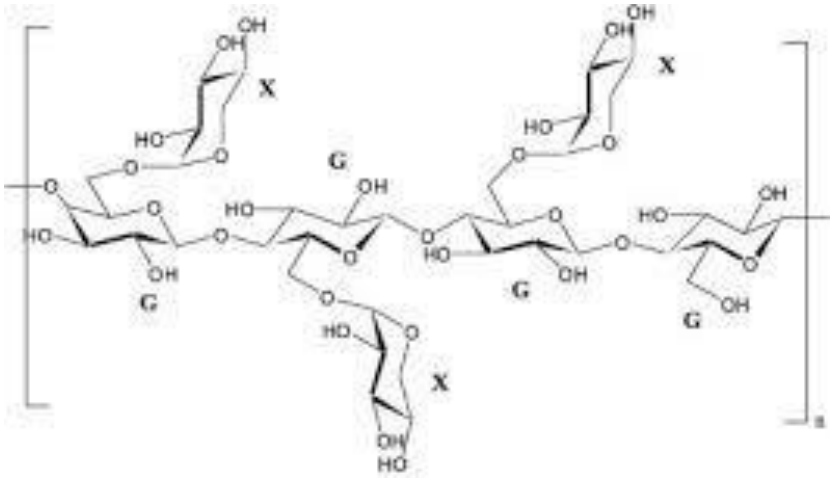

Fig. 7: Structure of Xyloglucan

Chitosan

Chitosan is a cationic polysaccharide consisting copolymers of glucosamine and N-acetyl glucosamine, these are natural polymer obtained by deacetylation of chitin (Fig.8). It is non toxic, biocompatible, biodegradable polysaccharide and having bioadhesive, antibacterial activity[30]. Chitosan aqueous solution forms a hydrated gel, like precipitate, at pH exceeding 6.2.[53]

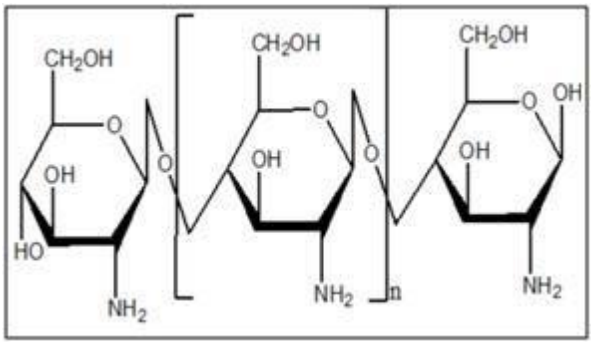

Fig. 8: Structure of Chitosan

Carbopol

It is Mucoadhesive polymer that increases the formulation's mechanical strength, but also increases surface interaction with the ocular tissue and consequently contact time. Carbopol shows a solid-to-gel transition in aqueous solution as the pH is raised above its pKa of about 5.5; therefore, to have an easy administration, an acidic pH would be needed before carbopol phase transition.

Evaluation parameters of the raft forming system

***In vitro* evaluation parameters**

Texture analysis:

Texture analysis is done to determine the firmness, consistency and cohesiveness of the formulation. This analysis mainly indicates the syringeability of sol so the formulation can be easily administered *in-vivo*. Higher value of adhesiveness of gels is needed to maintain an intimate contact with surfaces like tissues[54,55].

Sol–gel transition and gelling time:

Raft forming system is an effervescent liquid which involves the formation of viscous cohesive gel in contact with gastric fluids. The sol–gel transition temperature may be defined as the temperature at which the phase transition of sol meniscus is first noted when kept in a sample tube at a specific temperature and then heated at a specified rate. Gel formation is indicated by a lack of movement of meniscus on tilting the tube. Gelling time is the time for first detection of gelation as defined above. [48]

Gel strength:

This is used to determine gelling property of prepared formulation. This parameter can be evaluated using a rheometer. In this test a specified amount of gel is prepared in a beaker, from the sol form. Gel containing beaker is raised at a certain rate, then pushing a probe of rheometer slowly through the gel. The changes in the load on the probe can be measured as a function of depth of immersion of the probe below the gel surface[42,56].

Viscosity and rheology:

This is an important parameter to be evaluated for the raft forming system. The viscosity and rheological properties of the polymeric formulations, either in solution or in gel made with artificial tissue fluid (depending upon the route of administrations) were determined with a different viscometer. The viscosity can be determined with Brookfield rheometer or some other type of viscometers such as Ostwald's viscometer. The viscosity of formulations should be such that no difficulties are envisaged during their administration by the patient[56,57].

Drug–excipient interaction study:

Fourier transform infra-red spectroscopy and thermal analysis. Fourier transform infra-red spectroscopy is performed to study compatibility of ingredients. During the gelation process, the nature of interacting forces can be evaluated using this technique. This technique employs potassium bromide pellet method.

Thermo gravimetric analysis can also be conducted for in situ forming polymeric systems to quantitate the percentage of water in hydrogel. Differential scanning calorimetry can also be used to observe if there are any changes in thermo grams as compared with the pure ingredients used thus indicating the interactions[58].

***In-vitro* drug release:**

Raft forming system is administered orally, thus drug release study is carried out using a different method. Any of the following method can be used to determine in-vitro drug release.

• The in-vitro drug release of the in situ raft forming system can be carried in 0.1 N HCl from 0 to 8 h by USP type V (Paddle over-disk) at 50 rpm. The dissolution medium used is 900 ml of simulated gastric fluid (0.1 mol l−1 HCl, pH 1.2) and temperature is maintained at 37 ± 0.2 °C. Ten ml of the formulation was placed into a Petri dish (4.5 cm i.d.)which can be kept in the dissolution vessel and simulated gastric fluid is carefully added to the vessel avoiding any disturbance of the Petri dish. At each time interval, a precisely measured sample of the dissolution medium is pipette out and replenished with fresh medium. Drug concentration in the aliquot can be determined spectrophotometrically. Each study will be conducted in triplicate. The plot of % Cumulative drug release v/s time (h) can be plotted[59].

• The in-vitro drug release of the raft forming system is carried in 0.1 N HCl from 0 to 8 h by USP type-II apparatus at 50 rpm. The dissolution medium used is 900 ml of simulated gastric fluid (0.1 mol l−1 HCl, pH 1.2) and temperature is maintained at 37 ± 0.2 °C.

• The release rate of the drug from sustained release suspension can be determined by slightly modifying USP dissolution testing apparatus I by covering the basket with muslin cloth at 50 rpm. This speed was slow enough to avoid the breaking of gelled formulation and is maintaining the mild agitation conditions believed to exist in vivo. The dissolution medium used is 900 ml of 0.1 N HCl, and temperature was maintained at 37 °C. A sample (5 ml) of the solution is withdrawn from the dissolution apparatus from 0 to 8 h of dissolution.The samples are filtered through a 0.45 μm membrane filter and analyzed[60].

• The drug release studies are carried out by using the plastic dialysis cell. The cell is made up of two half cells, donor compartment and a receptor compartment. Both half cells are separated with the help of a cellulose membrane. The sol form of the formulation is placed in the donor compartment. The assembled cell is then shaken horizontally in an incubator. The total volume of the receptor solution can be removed at intervals and replaced with the fresh media. This receptor solution is analyzed for the drug release using analytical technique [61].

Floating/buoyancy test:

It is 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) which is 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 termed as 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)[62].

***In-vivo* evaluation test**

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[63].

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.

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[64].

^{13}C octanoic acid breath test:

^{13}C 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 $^{13}CO_2$ 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[64].

Marketed formulations of raft forming system

Alginate-based raft-forming formulations have been marketed world-wide under various brand names, including Gaviscon . Gaviscon is a thick creamy suspension that is available in two flavors. Peppermint and aniseed flavors. It is quite pleasant to taste but a lot of people cannot bear the taste of aniseed. Gaviscon Advance is an extra strength treatment for heartburn, esophagitis and gastro esophageal reflux disease also known as GERD. The Gaviscon liquid is a thick suspension that on swallowing slides down the esophagus into the stomach. It forms a barrier over the top of the stomach contents preventing the acid from rising into the esophagus[65,66].

CONCLUSION

In conventional dosage forms, oral drug delivery of drugs with narrow absorption window in gastrointestinal tract is often limited by poor bioavailability due to incomplete drug release and short residence time at the site of absorption. To overcome this drawback, novel drug delivery system has been developed which leads to increase in oral absorption of these drugs.

Controlled release gastroretentive dosage forms (CR-GRDF) enable prolonged and continuous input of the drug to the upper parts of the gastrointestinal (GI) tract and improve the bioavailability of medications that are characterized by a narrow absorption window. Based on the literature surveyed, it may be concluded that gastroretentive drug delivery offers various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper gastrointestinal tract (GIT) and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability. And hence, it can be concluded that these dosage forms serve the best in the treatment of diseases related to the GIT and for extracting a prolonged action from a drug with a short half-life.

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