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Raft-Forming Agents: Antireflux Formulations

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Gastroesophageal reflux disease (GERD) is caused by excessive reflux of gastric content and duodenal bile into the esophagus, and impaired clearance of refluxate from the esophagus. In this perspective, raft-forming antireflux formulations offer better alternatives to the conventional therapies for treatment of uncomplicated GERD. In addition to the alginate-based systems, various natural polysaccharides have generated interest as raft-forming agents because of their bioadhesive/mucoprotective nature. Inclination of current therapy is towards natural products for healing of the disease, which also underlines the market potential of this class, demanding for thorough investigation and development of evaluation methods with better in vitro–in vivo correlation.

Keywords anti-reflux, agent, raft-forming agent, polysaccharides

INTRODUCTION

"Acid-peptic disorder" is becoming a very common ailment as a result of emerging stressful living conditions. These disorders include a number of medical conditions whose pathophysiology is believed to be the result of damage from acid and peptic activity in gastric secretions (Hoogerwerf & Pasricha).

Gastroesophageal reflux disease (GERD) is a common acid-peptic disorder, which is becoming an obvious reason for increased visits to primary care physicians, gastroenterologists and more recently otolaryngologists. Gastroesophageal reflux is a normal physiological event that may occur as often as once an hour. Population-based studies reveal that more than sixty million American adults experience GERD and heartburn at least once a month, and about 25 million adults suffer daily from heartburn (Richter, 1994). Heartburn is a frequent occurrence during pregnancy where 25% of pregnant women experience daily heartburn and more than 50% have occasional distress (Nebel, Fornes, & Castell, 1976). GERD is very common in infants and children, usually because of immature digestive systems, which may produce recurrent vomiting, coughing, other respiratory problems, or failure to thrive (Geoffrey & Henry, 2003; Jung, 2001). Thus, heartburn and associated reflux symptoms are affecting a major population and causing a large burden to society because of direct and indirect costs (Sandler, Everhart, & Donowitz, 2002). GERD sufferers also have severely impaired health-related quality of life because of symptoms that affect physical, social, and emotional aspects of their lives (Geoffrey & Henry, 2003; Irvine, 2004; Kulig, Leodolter, & Vieth, 2003; Lu, Lang, Chang, Chan, Chan, Luo, & Lee, 2005).

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GASTROESOPHAGEAL REFLUX DISEASE (GERD) AND THERAPEUTIC APPROACHES

GERD (gastroesophageal reflux disease/acid reflux disease) is a clinical condition that develops from chronic exposure of the esophagus to acidic refluxate from the stomach and duodenum and the impaired clearance of acidic refluxate from esophagus. In contrast, heartburn is the symptom of acid in the esophagus, characterized by a burning discomfort behind the breastbone (sternum). GERD patients present common symptoms such as acid regurgitation and heartburn as a result of irritation of esophageal linings by gastric acid. This condition may or may not be associated with inflammation of esophageal mucosa. Other symptoms include esophagitis (reflux esophagitis)—inflammatory changes in the esophageal lining (mucosa), strictures, difficulty in swallowing (dysphagia), and chronic chest pain. Patients could have only one of those findings. However, symptoms of GERD are not only limited to these typical esophageal complaints which could be directly associated with reflux, but the atypical symptoms such as chest pain and otolaryngeal and pulmonary problems are also observed in GERD patients.

Pathophysiology of GERD is very complicated and involves various factors, but the reflux and corrosive action of gastric acid on esophageal mucosa are the key factors leading to irritation, inflammation of esophageal linings, and further complications. Therefore, treatment for GERD is generally targeted for gastric acid neutralization and suppression of gastric acid production and/or secretion (Gregory & Kelly, 1997; Scott & Gelhot, 1999).

Gastric acid is secreted by the parietal cells in the stomach. It plays a vital role in digestion of proteins by activating

pepsinogen, absorption of nutrients like folic acid, ascorbic acid; beta–carotene, various minerals, and prevention of bacterial or fungal overgrowth of small intestine by sterilizing stomach against orally-ingested pathogens. Thus, though gastric acid may appear to be a culprit in developing GERD, the fact cannot be ignored that its presence is essential for body's normal physiology. This perception calls for the appropriate therapeutic action to deal with acid reflux without interfering with body's natural defense system (Gregory & Kelly, 1997).

Looking into this perspective, the most rational approach to alleviate symptomatic GERD would be to minimize the exposure of esophagus to acidic refluxate, to relieve the symptoms, allowing healing of esophagus, and thus preventing further complications.

Therapeutic agents like H_2-receptor antagonists, proton-pump inhibitors act by suppressing the gastric acid secretion, and antacids act by acid neutralization, thus interfering with normal function of gastric acid. In such cases, raft-forming antireflux formulations can prove to be an ideal therapeutic class, which act neither physiologically nor chemically, but exhibit a unique nonsystemic mechanism where they protect the esophageal mucosa by providing a physical barrier between corrosive gastric fluid and esophageal mucosa. They act locally by reducing the contact time of refluxate with esophageal mucosa, exhibiting a mechanism of action, which is distinct from that of antacids, H_2-receptor antagonists and proton-pump inhibitors (Mandel, Daggy, & Jacoby, 2000).

RAFT-FORMING ANTIREFLUX PREPARATIONS

The nonsystemic mechanism of action to alleviate symptomatic GERD separates raft-forming antireflux preparations from other therapeutic classes for the treatment of uncomplicated GERD. Raft-forming antireflux preparations act by forming a viscous, gelatinous neutral barrier on the top of the stomach contents, which for a maximum time remains located at the lower esophageal sphincter (LES) and prevents the acidic gastric content from getting refluxed into the esophagus, giving symptomatic relief to GERD patients. Since this barrier floats on a stomach content like a raft on water, the barrier is called as a raft, and the formulations are called as "Raft-forming antireflux preparations" (Malmud, Charles, & Littlefield, 1979; Mandel et al., 2000; May, Wilson, & Hardy, 1984; Washington, Washington, Wilson, & Davis, 1988).

Apart from this barrier function, these preparations also help in maintaining the pH of esophageal space (lower esophageal sphincter [LES] less acidic or towards the neutral side by offering nearly a neutral-pH-raft, which would be expected to be less damaging to the compromised esophageal mucosa than the corrosive gastric acid. Though the raft may appear to be preventing the entry of corrosive gastric acid into esophagus, it does not act as a cork or a plug blocking the LES, but being a flexible layer, which is viscous and gelatinous in nature, it acts as a movable sealant that precedes the acidic gastric content into esophagus during reflux, protecting esophageal mucosa from acidic environment and while doing so, the raft material also coats the mucosa, offering a soothing protective layer, and thus exhibits a cyto/mucoprotective action.

Unlike the other therapeutic classes for GERD treatment, beneficial action due to raft-forming antireflux preparations is a function of the complete formulation and not a single therapeutic agent, which includes raft-forming agents, nontoxic gas (carbon dioxide) producing agents, and antacids, which act together to obtain a raft. The raft-forming property of this class is attributed to the agents (raft-forming agent), which have an ability to form a gelatinous viscous layer on contact with the acidic gastric content or which can maintain their viscous structure in presence of acidic gastric content, if formed already. These are the polymers producing viscous solutions in aqueous medium. Alginic acid and alginates are the most commonly employed raft-forming agents in antireflux preparations (Malmud et al., 1979; Mandel et al., 2000). However, various other agents have been investigated for their applicability as raft-forming agents, which include guar gum, locust bean gum, carrageenan, pectin, and isapghula (Dettmar, Little, & Baxter, 2003; Field, 1997; Mandlekar, Marathe, & Devarajan, 1997). An equally important feature of a raft is its floatation on the stomach content, which helps it to attain a desired position i.e., at LES, to exhibit its barrier function. It is achieved by including nontoxic gas (carbon dioxide) producing agents in the formulation. These are mainly bicarbonates, which react with gastric acid to liberate carbon dioxide gas, which gets entrapped within the viscous polymer layer converting it into foam, thus imparting buoyancy to the polymer layer formed. Potassium bicarbonate, sodium bicarbonate are the most commonly used bicarbonates. Formulations also typically contain some antacids (for example, aluminium salts like aluminium hydroxide, calcium or magnesium salts) to maintain the pH of the raft on neutral or alkaline side.

RAFT FORMING AGENTS

As a raft-forming agent, various polysaccharides have been explored in several inventions and research, and some of them have been evaluated for their in vivo performance in clinical studies. Though few inventions have also tried semisynthetic polymers such as hydroxy propyl methyl cellulose (HPMC), as raft-forming candidates; natural polysaccharides are still getting a preference over semisynthetic polymers as the therapy based on natural products is increasingly gaining an acceptance among the patients. All these polymers are "generally regarded as safe" (GRAS). Hence their potential as prospective safe therapeutic agents among all age groups including infants, elderly and pregnant women is attracting the attention of the market and the formulator.

Alginic Acid

Alginic acid (and its various salts) is the most widely explored and extensively investigated raft-forming candidate. They are natural polysaccharide polymers isolated from brown seaweed (Phacophycae), and can be classified as dietary fiber. Alginates are block co-polymers of L-guluronic and D-mannuronic acid residues connected by 1:4 glycosidic linkages. The relative proportions of D-mannuronic and L-guluronic acids are species-dependent and can be influenced by growth conditions (Mandel et al., 2000; Figure 1 shows a typical structure for the alginic acid block co-polymer web ref: http://www.lsbu.ac.uk/).

Mechanism of Raft-Formation

In the acid environment of the stomach, both alginate salts and alginic acids precipitate to form a low density, but viscous gel. The gel forms rapidly on exposure to gastric acid, occurring within seconds, and in vivo within a few minutes of dosing (Malmud et al., 1979; Mandel et al., 2000).

Liquid gaviscon is the most popular and simple example of the alginate-based antireflux preparation, which contains sodium alginate and sodium bicarbonate, and no particular antacids; preparation forms a strong floating gel in acidic environment of stomach. The strength of the gel is dependent on various factors. Molecular weight and the ratio of D-mannuronic and L-guluronic acid residues are *intrinsic properties* that influence raft strength. Generally, alginic acids with higher molecular weight and guluronic acid content form rafts with greater visco-elastic strength (Johnson, Craig, Mercer, Chauhan, 1997; Mandel et al., 2000). *Extrinsic factors*, which influence the raft strength, include presence or absence of specific cations. Extrinsic factors became an important part of the formulation development when the alginate-based antireflux preparations were combined with the particular antacids to blend the barrier properties of antireflux preparation with the neutralizing property of antacids. Studies revealed that calcium ions increase the raft strength (Davies, Farr, Kellaway, Taylor, & Thomas, 1994), while the addition of aluminium ions, a common component of many antacid formulations, reduce the raft strength in alginate–based systems (Washington, Washington, Wilson, & Davis, 1986). The ability of calcium ions to increase raft strength is attributed to its ability to crosslink alginic acid polymers, allowing the gel to form an "eggbox" structure which has great inherent strength (Davis et al., 1994; Grant, Morris, Rees, Smith, & Thom, 1973).

Generally alginate/antacids are formulated to include bicarbonate, which acts as a gas generating system. The carbon dioxide bubbles, which are formed in the presence of gastric acid, become entrapped within the gel matrix, converting it into foam and providing buoyancy, which allows the gel to float on the surface of the gastric contents, much like a raft on water, as well as entraps the acid neutralizing capacity, i.e., antacids (Johnson et al., 1997; Mandel et al., 2000). In vitro characterization of raft as a function of molecular structure of alginates and formulation variables, and detailed study of floating of raft as a function of gas-forming agent and alginates has been also performed (Johnson et al., 1997).

Alginate-containing formulations are available in various dosage forms including tablet, chewable tablet, and liquid preparation. The most common composition is a tablet formulation containing alginic acid, sodium bicarbonate, and magnesium trisilicate and aluminium hydroxide, which is when placed in mouth, alginic acid reacts with the sodium bicarbonate in presence of saliva to form a soluble sodium alginate, which in the acidic environment of stomach gets precipitated to form insoluble alginic acid gel, entrapping carbon dioxide bubbles in it, forming a raft floating on the stomach content. In liquid formulations, alginic acid is replaced by sodium alginate to allow the incorporation of alginate and bicarbonate into a single-phase product.

Other therapeutic classes like H_2-receptor antagonists and proton pump inhibitors were studied for their effect on the efficacy of raft-forming agent, when used in combination. Study of effect of cimetidine (H_2-receptor antagonist) pretreatment, omeprazole (proton pump inhibitor) pretreatment on alginate antireflux preparations has been performed which showed no effect of these pretreatments on the raft formation and gastric retention of raft (Dettmar, Little, & Baxter, 2005; Washington, Wilson, Williams, & Robertson, 1993).

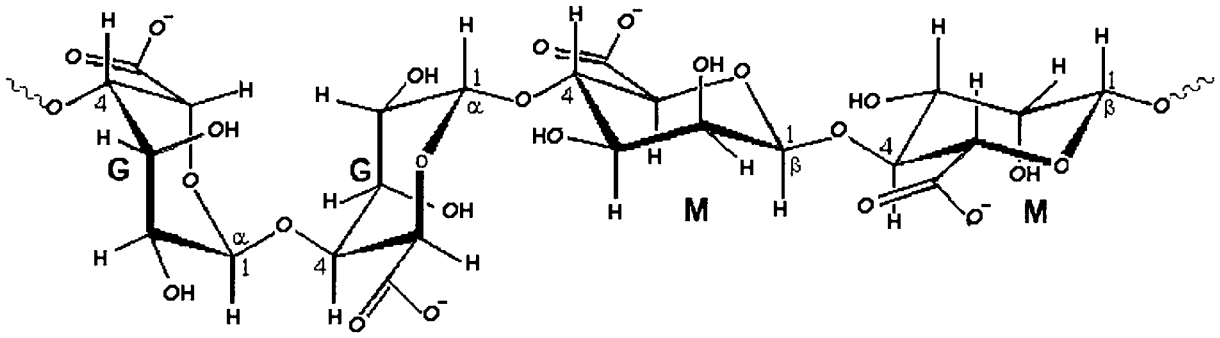

FIGURE 1. Alginic acid structure.

Thus nonsystemic nature of the activity of alginate preparations imparts a favourable safety profile in children and pregnant women (Mandel et al., 2000). Indeed alginic acid has its status of being 'generally regarded as safe' (GRAS). Because of its safety profile and lack of side effects, alginate therapy should be considered where there is a need for daytime protection and treatment.

Other Natural Polysaccharides as Raft Forming Agents

As discussed earlier, the raft formation by alginic acid/alginates involves formation of a gelatinous precipitate of alginate in presence of gastric acid. But other than alginates, there are various natural polysaccharides, which do not possess such property of precipitation, yet they have been considered as potential raft-forming agents, where the bioadhesive property of these polysaccharides is believed to help providing a protective raft layer, with additional advantage of improved bioadhesion and coherence of a raft.

Guar gum, xanthan gum, carrageenan, pectin, locust bean gum are the examples of gums employed as raft-forming agents. These are all potential gelling agents. These polymers are long-chain, straight or branched polysaccharides that contain hydroxyl groups that can bond to water molecules. Apart from forming a gel in gastric fluid, they also act by forming viscous mucilage on dissolution in the mouth as a result of mastication, thus coating the mucous membranes of the esophagus and stomach with the mucilage, thereby protecting them from the inflammatory effects of gastric acids. However, natural dietary fiber such as isapsol husk has been also evaluated as a raft-forming agent in a suspension, which utilizes the gelling behavior of isapgol.

General properties of these polysaccharides including biological source and chemical nature are discussed in brief as follows.

Pectin

Pectin is the second extensively investigated biopolymer after alginates for its efficacy as a raft-forming agent. It is commercially extracted from citrus peels and apple pomace. It consists mainly of galacturonic acid and galacturonic acid methyl ester units that form linear chains (Figure 2, http://www.cybercolloids.net//library/pectin/structure.php). The galacturonic acid chain is partially esterified as methyl esters. The pectin molecules have a molecular weight of up to 150,000 and a degree of polymerization of up to 800 units. The functional properties of pectin are largely determined by the degree of esterification (DE) of the pectin molecules.

Pectin is classified according to its degree of esterification (DE)—pectin with at least 50% DE or greater is high-methoxy (HM) pectin, and the one with DE below 50% is low-methoxy (LM) pectin. These two types of pectin possess different properties; for example, low-methoxy pectin requires calcium to gel, and high-ester pectins are capable of forming gels in aqueous systems with high contents of soluble solids and low pH values. (http://www.foodproductdesign.com/archive/1999/1299ap.Html). Both the types have been studied as raft-forming agents.

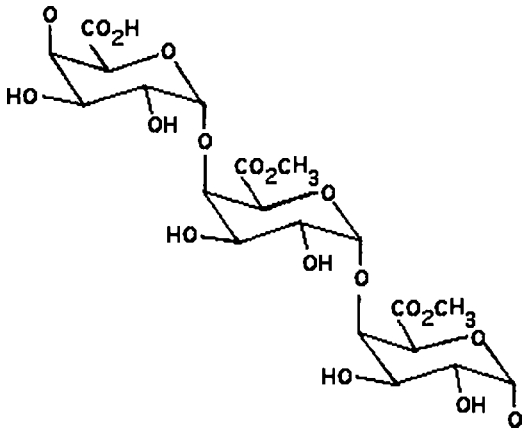

FIGURE 2. Structure of pectin.

Floating behavior of pectin containing antireflux formulation (Aflurax) was studied by gamma scintigraphy (Washington, Wilson, Greaves, & Danneskiold-Samosøe, 1988), which showed that the formulation was localized in the fundal region of the stomach and exhibited an appropriate behavior for an antireflux activity. The efficacy of the raft formed by *pectin* containing antireflux formulation (Aflurax) was further investigated versus a placebo containing the same amount of base in suppressing gastroesophageal reflux where the in vivo study of reflux of the pectin-raft into the esophagus showed a significant reduction in the amount of acid and food reaching the esophagus (Waterhouse, Washington, & Washington, 2000). Apart from relieving symptoms like heartburn in patients with endoscopy – negative GERD (Havelund, Aalykke, & Rasmussen, 1997b), pectin containing antireflux formulation also significantly delayed recurrence of moderate or severe heartburn and erosive esophagitis in GERD, proving its efficacy as maintenance treatment in patients with healed esophagitis (Havelund & Aalykke, 1997a).

Various inventions used pectin as a raft-forming agent in an antacid composition with floating properties for treatment of upper gastrointestinal dyspeptic disorder. Foldager et al. employed low-methoxylated pectin as a raft-forming agent in pharmaceutical composition which was found to alleviate symptoms such as regurgitation, epigastric pain, and nausea (Foldeager, Toftkjor, & Kjornos, 1991). Eccleston et al. used the interaction between alginic acid and pectin *(high methyl)* to form a resilient raft, in the absence of calcium or high concentrations of sugar, under conditions of low pH (Eccleston & Paterson, 2005).

Xanthan Gum: Microbial Polysaccharides or Bio-Fermented Gum

Earlier, xanthan gum was being employed as a stabilizer for alginate-containing raft-forming antireflux suspension where alginate was a raft-forming agent (Rhone, 1992). Later on attempts were taken to combine the bioadhesive property of xanthan gum along with other polysaccharides to obtain a composition having a protecting and healing effect on esophageal mucosa in treatment of GERD where xanthan gum was involved in raft formation (Dettmar, Dickson, Hampson, & Jolliffe, 2003).

Xanthan gum is a polysaccharide produced by a pure culture aerobic fermentation of a carbohydrate with *Xanthomonas campestris* bacteria. Xanthan gum develops a weak structure in water, which creates high-viscosity solutions at low concentration. (Figure 3, http://www.cybercolloids.net/library/xanthan/structure.php). The viscosity remains fairly constant from 0 to 100°C. It is pseudoplastic over broad shear rate and concentration ranges, but imparts a stringy texture. Xanthan gum has excellent solubility and stability under acidic and alkaline conditions and in the presence of salts, and resists common enzymes. Guar and xanthan show viscosity synergy, and when combined with tara or locust bean gum, xanthan gum can form thermoreversible gels above certain concentrations. (http://www.foodproductdesign.com/archive/1999/1299ap.html).

Xanthan gum was employed as a raft forming agent in invention where the formulation also contained an antacid component—hexitol stabilized aluminium hydroxide (Alexitol), and formulation was believed to form a raft by virtue of the ability of Alexitol to produce a viscous mass when mixed with *xanthan gum* under acidic conditions (Brooks, 1994).

Another invention relates to the pharmaceutical compositions having improved bioadhesive properties to provide a protecting and healing effect on the mucosal surface. Bioadhesive characteristic of the formulation is obtained due to xanthan gum, carrageenan and locust bean gum where certain amount of alginate is added to reduce the viscosity of the formulation within consumer acceptance level (Dettmar et al., 2003).

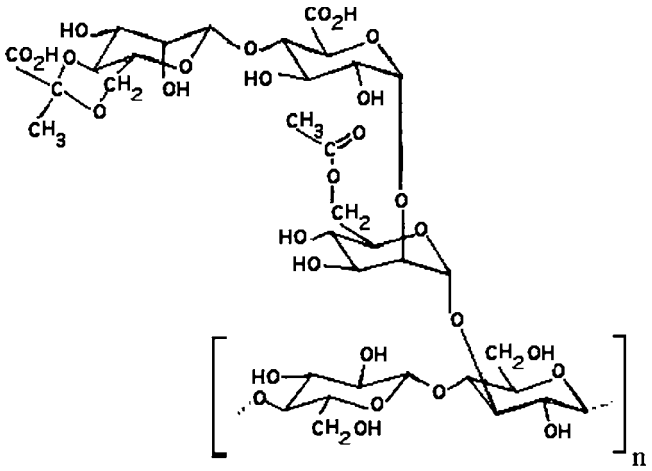

FIGURE 3. Structure of xanthan gum.

Guar Gum: Seed Gum

It is derived from the seed bean plant *Cyamopsis tetragonolobus, fam. leguminosae*. This long-chain, linear molecule of beta-1,4-D-galactomannans with alpha-1,6-linked D-galactose has a molecular weight of approximately 1,000,000 (Figure 4, http://class.fst.ohio-state.edu/FST605/lectures/lect20.html). Guar gum is a cold-water-soluble polysaccharide, and it hydrates easily to produce solutions with a high viscosity at low concentrations. The molecules exhibit interfacial binding, which makes them true emulsifiers. Guar gum has viscosity synergism when combined with xanthan gum (http://www.foodproductdesign.com/archive/1999/1299ap.html).

Guar gum was incorporated in an antacid preparation combining its raft formation property with known antacids and the composition was capable of producing a protective layer containing guar gum (Thomson, 1956). Gayst & Maguire (1982) used polysaccharide gums including guar gum to obtain a formulation for treatment of gastric disorders, wherein the gelation of the gum was inhibited or retarded until after entry into stomach (Gayst & Maguire, 1982).

Locust Bean Gum: Seed Gum

It is obtained from *Ceratonia siliqua.* It is a branched beta-1, 4-D-galactomannan with a high molecular weight (Figure 5, http://www.cybercolloids.net/library/carob/structure.php). This nonionic polymer is only partially soluble in cold water; to fully hydrate, it must be heated. But it swells in cold water. It works synergistically with kappa-carrageenan to form a rigid gel (http:// www.foodproductdesign.com/archive/1999/1299ap.html).

The invention relates to the pharmaceutical compositions having improved bioadhesive properties to provide a protecting and healing effect on the mucosal surface. Bioadhesive characteristic of the formulation is obtained due to xanthan gum, carrageenan and locust bean gum where certain amount

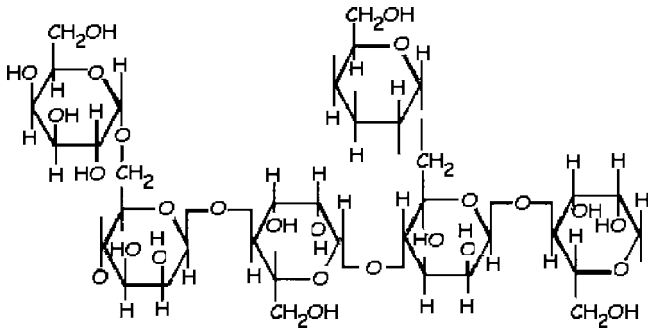

FIGURE 4. Structure of guar gum.

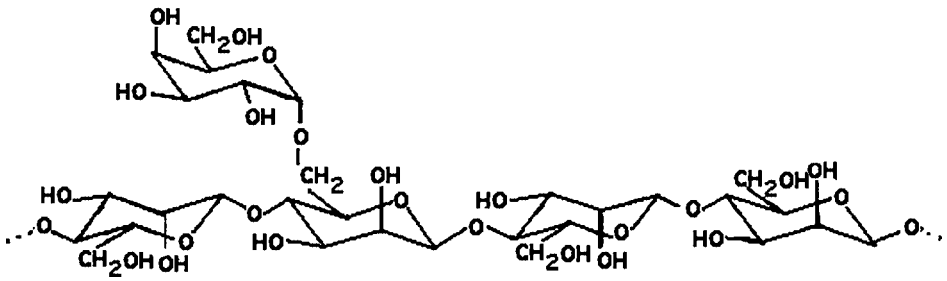

FIGURE 5. Structure of locust bean gum.

of alginate is added to reduce the viscosity of the formulation within consumer acceptance level (Dettmar et al., 2003).

Carrageenans: Seaweed Gum

They are linear sulfated galactans obtained from red seaweeds (*Rhodophyceae*), but since the carrageenan molecule has up to 1000 galactose residues, it has many structures (Figure 6, http://www.cybercolloids.net/library/carrageenan/structure.php). These are usually defined as one of three main types: kappa, iota or lambda. μ, η, and xi fractions have also been identified. These types have different gelling properties and protein reactivities, although they are stable over a wide pH range. Kappa carrageenans produce strong, rigid gels, especially in the presence of potassium ions, while gels made with iota are weaker, with a lesser tendency toward syneresism. Although lambda carrageenans do not gel in water, they interact strongly with proteins to produce a pseudoplastic thickener (http://www.foodproductdesign.com/archive/1999/1299ap.html).

One of the inventions based on carrageenan relates to the dry, water-foamable pharmaceutical compositions, capable of forming a substantially stable foam on contact with water,

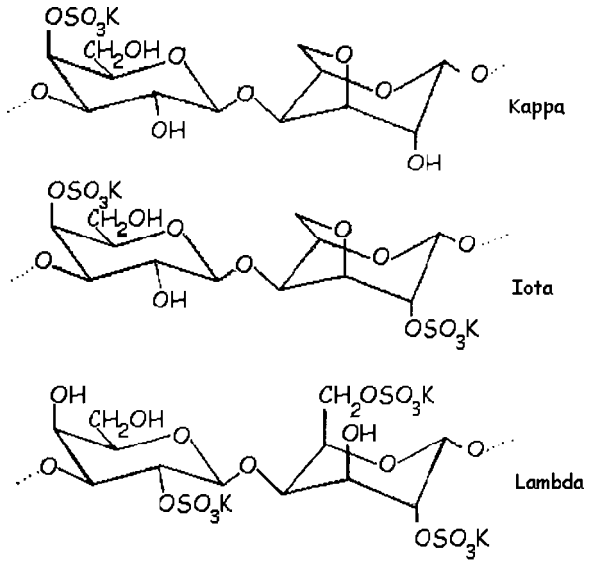

FIGURE 6. Structure of carrageenan.

where the formulation utilized a mixture of water soluble polysaccharide gum (including carrageenan, sodium alginate), effervescent base and a biocompatible gelling salt (Chavkin, 1986).

The invention based on the pharmaceutical compositions containing various natural polysaccharides displayed improved bioadhesive properties to provide a protecting and healing effect on the mucosal surface where bioadhesive characteristic of the formulation is obtained due to xanthan gum, carrageenan and locust bean gum where certain amount of alginate is added to reduce the viscosity of the formulation within consumer acceptance level (Dettmar et al., 2003).

Isapgola (Isapghula)

Isapgol *(Plantago ovata),* an indigenously available natural dietary fiber is official in the Indian Pharmacopoeia. It is made up of polysaccharides; it is popularly used as a bulk laxative. Biological experiments have confirmed its cytoprotective action. A viscous dispersion of isapgol husk in water forms a swollen gel-like mass in acidic medium.

Applicability of isapgol as a raft-forming agent was investigated (Mandlekar et al., 1997). Study was designed to evaluate the possibility of developing a raft-forming antacid suspension using the gelling behavior of isapgol husk, where isapgol was found to be a good raft-forming candidate used in the formulation of raft forming antacid suspensions. The in vivo efficacy of this product in the treatment of gastroesophageal reflux disease, however, needs to be established after extensive clinical trials.

Successful raft formation was found to be influenced by the viscosity of the raft-forming agent; this observation suggested that a whole new range of natural semi-synthetic gums and suspending agents could be used as raft-forming agents in the formulation of antacid suspensions and gels.

IN VIVO FACTORS INFLUENCING/LIMITING PERFORMANCE OF RAFT-FORMING ANTI-REFLUX FORMULATION

Successful raft formation requires sufficient gastric contents to position the formulation in the fundus, where it can prevent

reflux of gastric acid, either by acting as a barrier or by being refluxed preferentially to the gastric contents (Washington et al., 1988). This fact also supports the need for appropriate dosing regimen with respect to food intake. It was observed that, when Gaviscon was administered before meal, ingestion of food caused half of the raft in the fundus to be pushed into the antrum disturbing the raft function, whereas the formulation taken after meal enabled raft-formation and its location in the fundus region providing a barrier against the reflux. Hence, administration of an antireflux agent after meal should be recommended in order to achieve the maximum therapeutic action of the formulation.

Furthermore, *body position and posture* play an important role in achieving raft-forming anti-reflux preparation induced relief from heartburn, since the position of a floating raft and its gastric emptying are greatly influenced by them. Lying on the right side allows the raft to float into the greater curvature and to empty the raft after meal, whereas lying on the left side leads to floating of a raft into pylorus and its emptying ahead of the meal (Johnson & DeMeester, 1981). Some studies of the use of alginic acid in treatment of GERD report an improvement in symptoms when patients are in the upright position. However, alginic acid preparations offer little or no benefit to patients whose GERD symptoms arise principally when they are in the supine position. These findings raise the question about the utility of this therapeutic class when patient is in supine condition, especially when treating nocturnal heartburn (Moss, Washington, Greaves, & Wilson, 1990).

Floating behavior of the raft is greatly influenced by the amount of acid present in the stomach, which reacts with the bicarbonates in a formulation to liberate carbon dioxide, which then gets entrapped in the raft imparting buoyancy to it. However, food present in the stomach reduces the acid available for the raft formation by dilution and by the buffering action of the peptides and proteins present. In addition to this, floating of the raft becomes difficult, when the raft-forming antireflux preparation contains a significant amount of antacid, which compete with bicarbonate for available acid (Washington et al., 1988).

Thus, in order to arrive at an appropriate antireflux formulation, capable of forming strong, cohesive floating raft, in addition to various formulation variables, the above mentioned factors should be also considered and suitable in vivo techniques should be developed to assess the in vivo performance of the formulation.

TECHNIQUES USED FOR IN VIVO STUDY OF RAFT PERFORMANCE

A variety of in vivo imaging techniques, including radiography, scintigraphy, and direct endoscopic visualization have demonstrated the formation and presence of floating rafts from various formulations.

Gamma scintigraphy (noninvasive method). In this technique, a gamma-emitting radioisotope is incorporated into the formulation. Technique allows direct visualization of raft formation and behavior under noninvasive conditions. Malmud et al. utilized the technique to demonstrate the floating behavior of alginate raft (Malmud et al., 1979). Whereas this technique was combined with radio telemetry capsule by May et al., which allowed the visualization of distribution of these preparations within the stomach where alginate formulation was observed to be floating on gastric content, while the conventional antacids showed mixing with gastric contents. The technique being very safe is being used widely in clinical studies (May et al., 1984). X-ray imaging, radiography and direct endoscopic visualization imaging had been employed to allow the visualization of a raft (Goodall, Orwin, & Imrie, 1977; Malmud et al., 1979; Mandel et al., 2000).

Apart from evaluation of an ability of the antireflux preparation to form an effective barrier against reflux, in vivo pH-time profile becomes an important parameter to be evaluated.

pH telemetry allows the assessment of the neutralizing capacity of the preparation in comparison to conventional antacids, which utilized pH-sensitive radio telemetry capsule and it was observed that with alginate preparations, there was a distinct raft-formation and floating on gastric content, which maintained its pH towards neutral side and pH below the raft is at or near basal levels whereas conventional antacids resulted in rise in gastric pH (Goodall et al., 1977; Mandel et al., 2000; May et al., 1984).

These outcomings showed the marked differences between mechanism of action of raft-forming antireflux preparations and conventional antacids underlining the fact that the function of raft-forming antireflux preparations is more of a protective form, and role of antacids incorporated in it is to maintain the pH of raft on neutral side. This fact demands for further investigation of tests for evaluating such type of antireflux formulations.

IN VITRO EVALUATION OF RAFT-FORMING AGENTS

Raft-Strength

In this evaluation, a probe is pulled through a raft causing the rupture of a raft, and the resistance offered by a raft to probe was measured as the breaking strength or raft-strength.

It allows the determination of mechanical strength of a raft. Though it does not exactly represent the stability and durability of a raft in vivo, it is an important parameter to be evaluated in the area of formulation development, as different formulation variables have different effects on raft-strength, plus the parameter also serves as a tool of quality control in assessing batch-to-batch reproducibility of a formulation.

Washington used a microcomputer controlled force balance specially developed for this purpose, which was intended to pull a horizontal wire probe (25 mm long, 0.6 mm diameter) through the raft and relative force required to break the raft was measured in terms of weight applied in grams required to pull the probe (Figure 7). Rafts were formed in situ with the probe

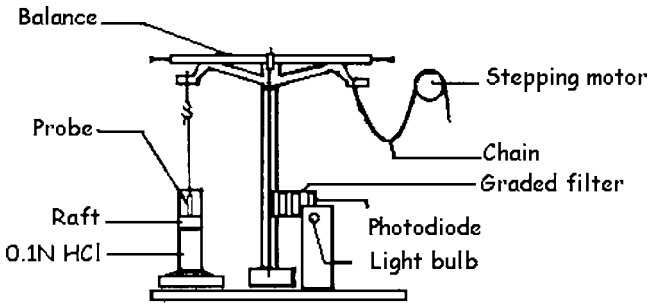

FIGURE 7. Apparatus for measurement of raft-strength.

already placed below the raft. Rafts were allowed to stabilize. The probe was attached to one arm of a beam balance, a chain suspended from the opposite arm of balance supplied the force required to raise the probe. Force was controlled by a stepping motor. Distance traveled by a probe through the raft was measured from the deflection of beam by sensing transmission of a graded optical neutral density filter attached to the beam. Force required to break the raft was measured and results were corrected for the force required, to lift the probe through the same distance in water (Washington et al., 1985a, 1986).

However, the fact that the apparatus has to be individually built from nonstandard pieces of equipment means that reproducibility of results between laboratories is difficult, thus comparison of data is not entirely reliable. This necessitates for the development of a standard method to measure raft-strength.

Use of texture analyzer was investigated as a novel means of assessing the raft characteristics, raft strength being one of them (Figure 8; Hampson, Farndale, Strugala, Sykes, & Dettmar, 2005; Johnson et al., 1997). In texture analysis, rafts were formed with the probe in situ at the start position, i.e., just above the bottom of container. Rafts were allowed to stabilize. Texture analyzer (TA.XT2 texture analyzer) was set up in the tension mode to travel a fixed distance at a constant speed, and resistance offered by a raft to the probe in cycle was obtained as force-time profile. Maximum breaking strength and total area under curve (reflecting the energy required to subject the raft through the probe cycle) were the two parameters chosen to quantitatively describe the raft characteristics.

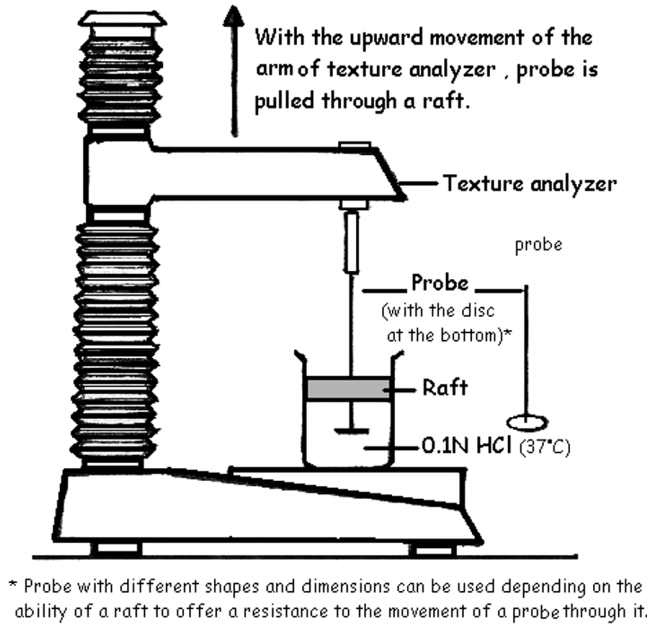

FIGURE 8. Texture analyzer—to measure raft-strength.

The method using texture analyzer showed better applicability in raft characterization, as it also allowed the assessment of the entire breaking process, giving information not only on maximum breaking strength, but also on work involved, plus it also reflected the likely fate of these raft systems as the resistance to deformation may be just as same as rupture strength in an in vivo situation.

Correction of results were necessary in both the methods, as the resistance experienced by a probe—is not the function of only mechanical strength and viscosity of a raft, but also of the surface tension of liquid in which the raft is formed, and the mechanics by which the probe disrupts the surface also play an important role in offering resistance.

Raft-Resilience

Several attempts had been performed to design the tests, which would characterize in vivo stability of a raft in terms of raft-strength, like use of microcomputer controlled force balance, and more reproducible method, i.e., use of texture analysis. Though the raft strength reflects the mechanical strength of raft, it could not be used as a sole indicator of the in vivo stability of a raft. Hence in an attempt to evaluate the in vivo durability and stability of a raft, a method was developed by Hampson et al. (2005).

In this test, rafts formed were subjected to optimum mechanical shaking and then visually assessed for their appearance, coherence, thickness, and integrity over a period of time, at fixed intervals. The last time point, at which a raft was observed i.e., raft resilience, was recorded. The test conditions employed for evaluating this parameter showed better simulation with gastric movements, hence gave better indication of in vivo durability and stability of a raft.

Raft-Resistance

Raft resilience offered better correlation of a raft durability in presence of normal gastric movements, where the rafts were exposed to optimum mechanical shaking and rafts retained their integrity and buoyancy therefore available for its barrier action. But during acid reflux, neutral rafts are preferred to be refluxed into esophagus, preceding the acidic gastric content. Thus during reflux the rafts are forced through relatively narrow lower esophageal sphincter (LES) from top of the stomach content which is much wider. In this case, these rafts are

required to be strong and flexible enough to maintain their integrity and exhibit its barrier action. Hence it would be desirable to assess the performance of the rafts under reflux during transient LES relaxation.

The reflux resistance studies have been briefly reported to assess the raft performance where the rafts formed were forced to either extrude or rupture through a circular orifice (10–20 mm diameter) with similar crosssectional area to that of the relaxed LES and resistance to this simulated reflux was measured using TA.XT2 texture analyzer in terms of maximum force required to extrude or rupture the raft (Jolliffe, Hampson, Campbell, & Dettmar, 2001; Figure 9).

Rafts with greater strength and coherence showed more resistance to the simulated reflux than the weaker rafts, indicating the significance of the "raft-strength" as compared to the parameters such as "raft-volume" or "raft-weight" in resisting the reflux during transient LES relaxation (Hampson et al., 2005).

Raft-Weight, Raft-Volume, and Raft-Thickness

These can be the additional parameters to be evaluated, though they cannot be directly related to the in vivo performance of a raft. These raft-characteristics are greatly influenced by various formulation variables, hence they serve as a useful tool in assessing the effect of formulation variables on raft characteristics, and hence in formulation optimization (Hampson et al., 2005).

Alginate rafts were evaluated for volume and weight where rafts were formed, allowed to stabilize, and excess of subnatent fluid except that which can be retained in raft maintaining its integrity was decanted off, and rafts were weighed. Precaution was taken while handling, weighing the raft since swollen, crosslinked raft material entrapping gas bubbles and considerable amount of fluid in it, contributed to the whole raft structures. Raft volumes were also calculated by correcting for weights of container and fluid, by formula:

$$\text{Raft volume (in mL)} = \left[\begin{array}{l}\text{Weight of container with fluid}\\ \text{to the marked position (level}\\ \text{same as that containing raft)}\end{array} - \text{Weight of empty container}\right] - \left[\begin{array}{l}\text{Weight of container}\\ \text{with raft with fluid}\end{array} - \begin{array}{l}\text{Weight of}\\ \text{empty container}\end{array} - \begin{array}{l}\text{Weight of raft}\\ \text{and container}\end{array}\right]$$

$$= (W_4 - W_1.) - (W_2 - W_1 - W_3)$$

$$\text{Raft weight (in gm)} = \text{Weight of raft and cylinder} - \text{Weight of empty container} = W_3 - W_1.$$

(*All weights were measured in gm or mg).

Studies had been performed to evaluate the effects of alginate molecular structure and formation variables on the physical characteristics of alginate raft systems, measurements of raft thickness being one of them (Hampson et al., 2005). Rafts were allowed to form and thickness of raft was measured for different formulations, keeping the parameters like dimension of container, amount of acid, amount of formulation, time of raft formation constant, then results were compared against the formulation variables. Findings showed marked influence of formulation variables like choice of raft materials, gas-forming agent and presence of cations on thickness of raft.

Thus though the raft thickness does not represent or measure the thickness of a raft in vivo, study of this parameter would definitely help in optimizing formulation, to obtain a stronger raft.

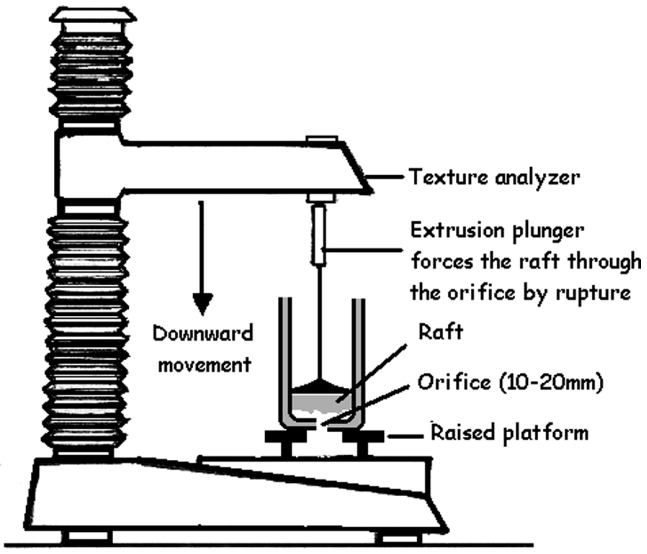

FIGURE 9. Texture analyzer—to measure raft-resistance.

pH-Time Profile

Earlier raft-forming antireflux formulations were considered as antacids where antacids incorporated in the formulation were believed to act by neutralization of the gastric content, combined with simultaneous mucoprotective action by raft-forming agent.

Assuming the role of antacids in antireflux formulations in acid neutralization, variety of in vitro tests had been used to measure the antacid neutralization capacity of formulation, including those tests which measured simply neutralization capacity to those which measured the performance under conditions which bear some resemblance to those occurring in vivo. These included pH –stat methods, the method of Holbert, Noble, & Grote (1947), and the Fuchs test (Fuchs, 1949).

The Rossett and Rice test was the one, which provided some indication of how the antacid may be expected to behave in vivo. In this test, 10 mL of antacid sample was added to 100 mL of 0.3 M hydrochloric acid and pH was measured as further acid was pumped at 4 mL/min with simultaneous stirring (Rossett & Rice, 1954). Furthermore, the concept of replacing

the gastric acid with the fresh one, resembling the in vivo clearance of gastric acid was used by Smyth, Herczeg, Wheatley, House, & Reavey-Cantwell (1976) in modifying the Beekman procedure (Beekman, 1960) which included the important step i.e., pumping reactants out of the reaction vessel at a constant rate, and was found to be showing a good in vitro–in vivo correlation for antacid activity. However, the role of gastric emptying of antacids could not be ignored, which greatly reduced the period of time available for acid neutralization, thus questioning the correlation of in vitro results obtained in above-mentioned conventional tests to in vivo behavior (Jenkins, Hardy, & Wilson, 1983). Also along with the limitation like gastric emptying, the test conditions like agitation was found to be destroying the raft, thereby altering the rate of reaction of the entrapped antacids in a raft. Hence none of the standard test available could be applied to these raft-forming preparations.

Washington et al. investigated the modifications of the Rossett and Rice test in an attempt to mimic the in vivo pH-time profile of a raft in man, for a floating and a conventional antacid formulation. Apparatus used for the original test was modified by the addition of a stationary collar of wide bore glass tubing around the stirrer shaft to prevent vortex mixing of the raft. (See Figure 10), and second pump was introduced to remove the reaction mixture at the same rate (2 mL/min or 4 mL/min). When pH in the raft and that below the raft was recorded using pH electrode, better correlation was observed between pH-time profile and in vivo pH-time profile (obtained by pH telemetry; Washington, Wilson, & Davis, 1985b).

However, when further investigation was done for the evaluation of these preparations, findings of the study suggested that most of the antacids remain associated with the raft without significantly affecting the gastric pH which challenged the purpose of combining the benefits of the barrier with the neutralization of the gastric content beneath, or to increase the neutralization capacity of the raft, by including the antacids in the formulation. Hence to test this hypothesis, Washington et al. investigated the effect of aluminium hydroxide on liquid Gaviscon (which contained raft-forming agent, for example, sodium alginate, and non toxic gas producing agent, for example, sodium bicarbonate, and no antacid). Study involved the measurement of pH in the raft as well as pH below the raft for 3 hr, where liquid Gaviscon raft maintained the pH above 3 for 50 min and no longer neutralized bulk solution, which remained at pH 1–2 and for the raft-forming preparation containing aluminium hydroxide, no significant neutralization of the bulk below the raft was observed, indicating that the majority of the antacids remained associated with the raft, which maintained the pH of the raft towards the neutral side (Washington et al., 1985b).

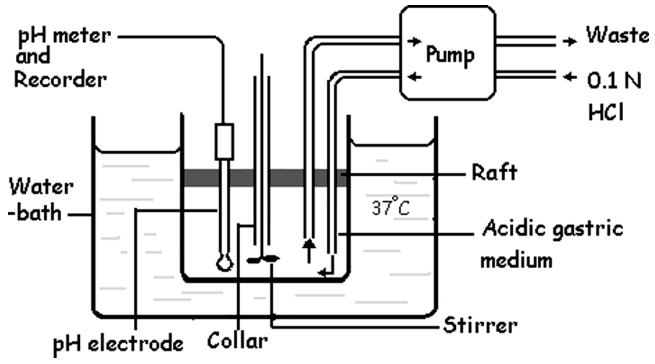

FIGURE 10. Schematic presentation of the apparatus for Rossett and Rice test (with the modifications).

A system resembling the gastric environment was developed by Vatier, Celice-Pinguad, & Farinotti (1998), i.e., "artificial stomach" model (Vatier et al., 1998; see Figure 11). The model was used by Vatier to study the pH variations in the gastric content and at its surface, after adding a therapeutic dose of two alginate-based raft-forming preparations, differing in antacid content, in presence of continuous acid infusion.

The model showed capability

1. of measuring the pH both in gastric contents, using a combined glass electrode, and at its surface, using a surface microelectrode,
2. of simulating the gastric emptying regulation in regard to the intragastric pH in physiological situation, and
3. of controlling the position of the surface microelectrode in regard to gastric volume variations by means of a surface detector system.

The model allowed one to quantify the pH gradient intensity and to anticipate the therapeutic events. It was observed that raft-forming agents decreased the gastric acidity weakly. But by virtue of their ability to induce pH gradient, thereby reducing the total duration for which esophageal pH remains below 4, they helped to alleviate symptoms, also they helped in reducing total number of reflux episodes in infants and children and in patients suffering from GERD as well as in healthy volunteers. Hence pH gradient was considered an important parameter to be evaluated in a study (Vatier et al., 1998).

It could be understood from the in vitro–in vivo studies performed till now that the effectiveness of alginate-based, raft-forming formulations in treating heartburn may not depend on their ability to neutralize bulk gastric contents and precise functional contribution of the antacids to performance is not fully understood.

Yet, the pH-time profile test can be considered as an important assessment of an in vitro raft performance, to obtain a better prediction of in vivo behavior of the raft-forming preparations, and also to study the effect of formulation variables, like antacids or other agents, on the raft-performance.

Creep Viscometry

Established in vitro methods (as discussed earlier) for assessing the strength of rafts are based on the measurement of

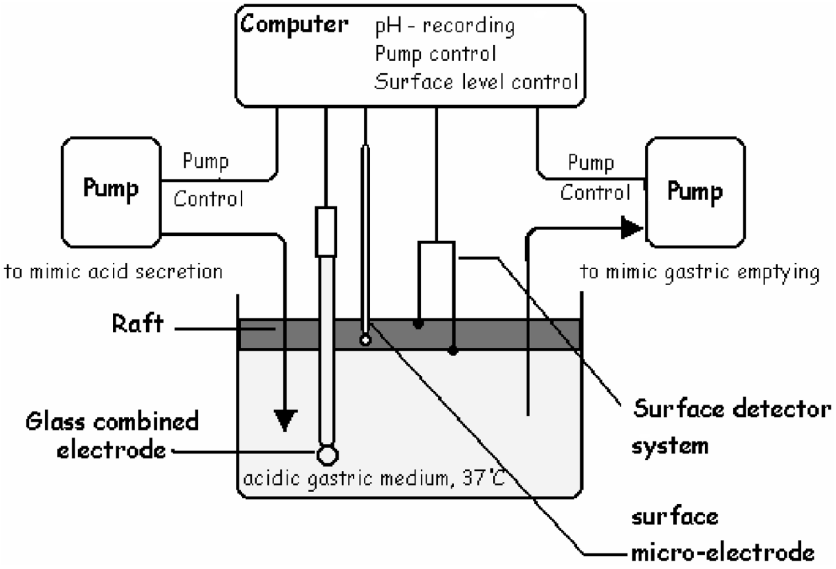

FIGURE 11. Schematic presentation of the computerized "artificial stomach" model.

a force required to disrupt the raft structure. In an attempt to come up with an alternative, nondestructive means for investigating the physical parameter of a raft, investigation was performed to test the applicability of creep viscometry, which is mainly used for visco-elastic structures like, creams and ointment. In this technique shear stresses are applied below the visco-elastic limit of the gel structure, leaving it essentially unaffected. The instantaneous compliance and the Newtonian viscosity were calculated from the creep compliance curves obtained for the rafts, and were used as raft-strength indicators (Hill & Wade, 1993). The study had been performed by Wade and associates using this principle for various alginate-based raft-forming preparations and they found the technique "creep viscometry" useful in raft-characterization of visco-elastic structures like raft.

Successful raft formation was found to be influenced by the viscosity of the raft-forming agent; this observation suggested that a whole new range of natural semi-synthetic gums and suspending agents could be used as raft-forming agents in the formulation of antacid suspensions and gels.

FUTURE PROSPECTS

Acid peptic disorder is becoming a common ailment as a result of emerging stressful living conditions, affecting the quality of patients' life. GERD is one of the commonly experienced acid peptic disorders, by all the age groups—including children, elderly, and pregnant women, which demands for the safe and effective treatment for GERD. Nowadays, inclination of the patients is towards natural products for healing of diseases, because of their safety. Hence therapy based on natural product would be always welcomed in preference to other therapeutic classes- such as H_2-receptor antagonists, proton pump inhibitors, prokinetic agents, and antacids, where each of these agents is accompanied by its side effects. Thus, considering the demand for a safe therapy for all age groups combined with a natural source, i.e., natural polysaccharides as antireflux formulations can be the preferred therapeutic class because of their unique nonsystemic nature.

Future work in this direction should be targeted towards development of suitable in vivo techniques for evaluating the in vivo efficacy of raft forming agents. Furthermore development of a suitable in vitro model correlating well with the in vivo studies would nevertheless be an appropriate futuristic endeavor.

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