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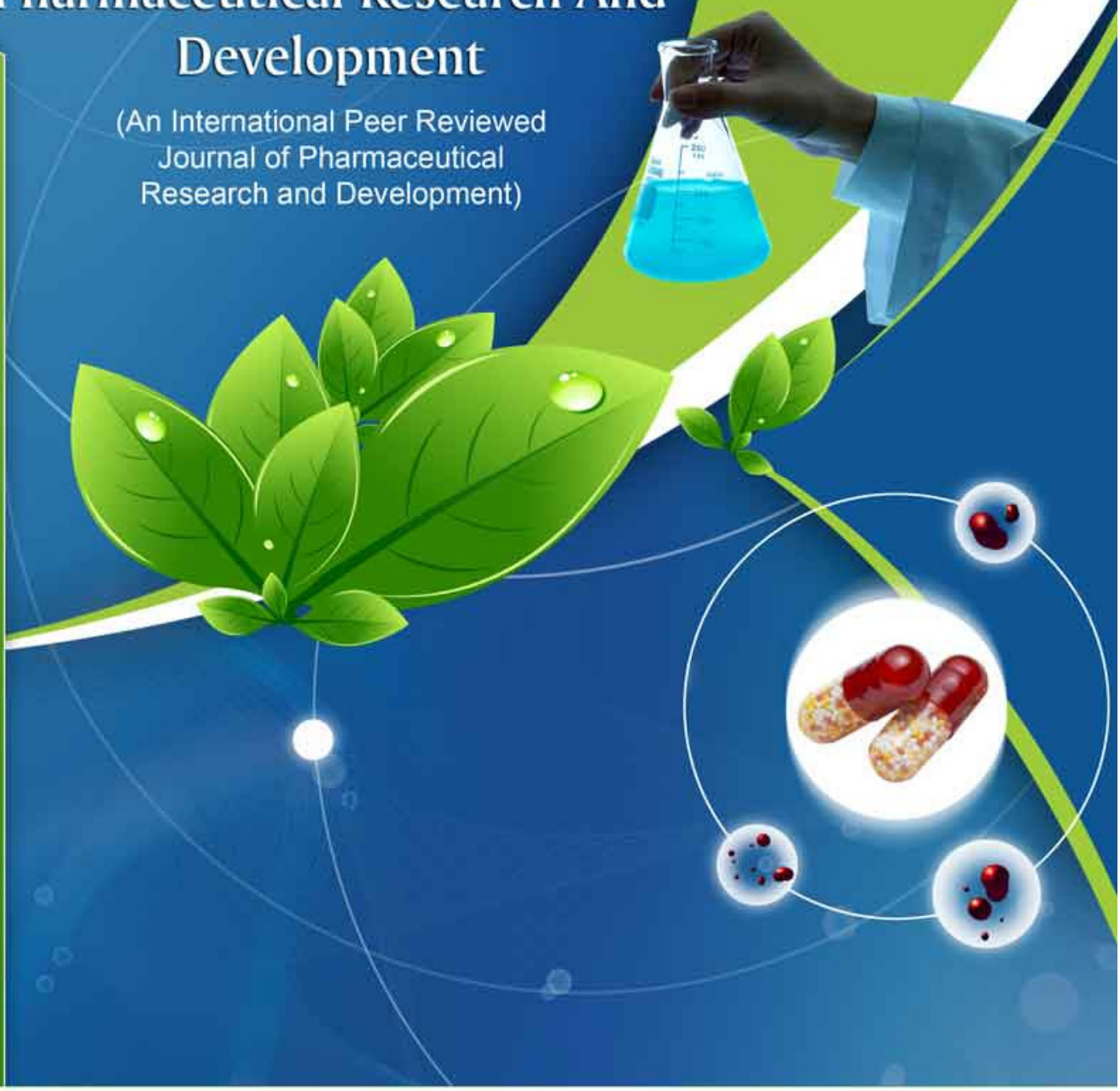

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Review Article

GASTRO-ESOPHAGEAL REFLUX DISEASE (GERD) AND RAFT TECHNOLOGY

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ABSTRACT

Gastro esophageal reflux disease, or GERD, is a digestive disorder that affects the lower esophageal sphincter (LES) as well as the ring of muscle between the esophagus and stomach. Many people of different age group including pregnant womens face the problems of heartburn or acid indigestion and hiatal hernia which are the major symptoms of GERD. Previously doctors preferred diet, lifestyle changes, medication or surgery for treatment of GERD but now a days preferring most advanced therapy that is RAFT. RAFT technology is an alginate/antacid combination used as primary treatments for gastro-esophageal reflux disease (GERD) is the administration of alginate antacid anti-reflux preparations. It acts by forming a physical barrier in the form of a neutral floating gel or RAFT on the inner wall of stomach. Its main advantage over antacid is that provide longer lasting symptom relief and rapid onset of action.

Key Words: *Gastro-esophageal reflux disease, Raft, Alginate*

INTRODUCTION

Gastro-esophageal reflux disease (GERD) includes all the consequences of reflux of acid or other irritants resulting in the regurgitation of gastric acid cause's heartburn or acid indigestion which is a major symptom of GERD. Heartburn causes a burning sensation in the chest, just behind the breast bone or in the epigastria. The pain often rises in the chest and radiates to neck, throat or angle of the jaw. The severity of GERD increases progressively with reflux that is mainly in the postprandial period to that in the upright posture, to that in the supine or that is bipositional reflux. Nighttime reflux leads to severe GERD.

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Although most cases follow a relatively benign course, GERD in some individuals can cause severe erosive esophagitis; serious squeal include stricture formation of Barrett's metaplasia (replacement of squamous by intestinal columnar epithelium), which, in turn, is associated with a small but significant risk of adenocarcinoma The GERD category also encompasses a group of patients that have nonerosive or negative endoscopy reflux disease (NERD). In these patients, esophageal acid exposure may be normal and factors such as visceral hypersensitivity or more proximal reflux of acid or nonacid material may be important. Most of the symptoms of GERD reflect injurious effects of the refluxed acid-peptic content on the esophageal epithelium, providing the rationale for suppression of gastric acid. The goals of GERD therapy are complete resolution of symptoms and healing of esophagitis. With varying levels of evidence, acid reflux has been implicated in a variety of atypical symptoms, including noncardiac chest pain, asthma, laryngitis,

chronic cough, and other ear, nose, and throat conditions. Heartburn is estimated to occur in 30% to 50% of pregnancies, with an incidence approaching 80% in some populations. In the vast majority of cases, GERD ends soon after delivery and thus does not represent an exacerbation of a preexisting condition. Nevertheless, because of its high prevalence and the fact that it can contribute to the nausea of pregnancy, treatment often is required. The generalized therapy is directed towards decreasing gastric acidity, enhancing the lower esophageal sphincter, or stimulating esophageal motility [1].

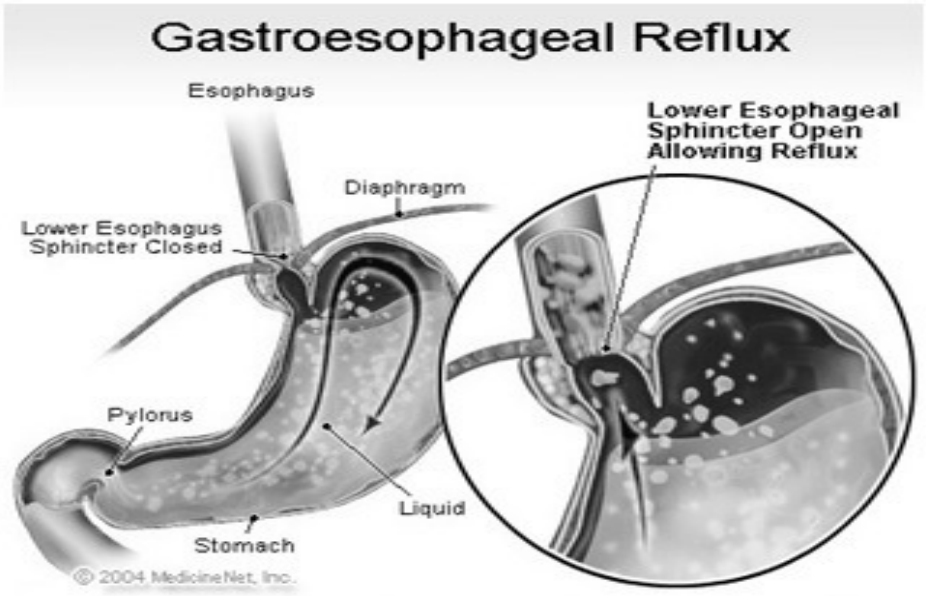

Figure 1: Pathophysiology of GERD

Acid and other refluxed contents

The normal physiology of acid secretion is well understood, and is not discussed here. Reflux of acid is the dominant irritant to the esophagus in the development and progression of GERD, although the presence of bile and other compounds in gastric juice may contribute to the "reflux burden" when combined with the acid or on their own. The reflux burden of acid requires the presence of acid secretion, and is further determined by dysfunction of the gastroesophageal competence mechanism that allows increased reflux, and by decreased esophageal clearance that increases contact time of acid with the mucosa. However, there are a number of relevant issues that arise in regard to gastric acid secretion and the development of GERD.

GERD and Increased Acid Secretion

The reflux of gastric content also includes pepsin and substances such as bile and pancreatic and intestinal enzymes from the duodenum. Although pepsin is activated at a pH <4, and the combination of acid plus pepsin is potentially more injurious to esophageal mucosa than acid alone. The levels of pepsin in gastric juice and the maximum output of pepsin are not different in patients with or without esophagitis. That is, an acid pH is required for the deleterious effects of pepsin to become active. However, in this regard, the presence and amount of gastric acid are still of prime importance.

Incompetence of anti-reflux barrier

The main cause of GERD is incompetence of anti-reflux barrier at the esophago-gastric junction. The anti-reflux barrier includes two

sphincter mechanism viz. Lower esophsgeal sphincter and crural diaphragm that functions as an external sphincter. The peristaltic movements of gastro-intestinal tract are mediated centrally through Vagus nerve conduction and movements of diaphragm by Phrenic nerve conduction (Figure 2).

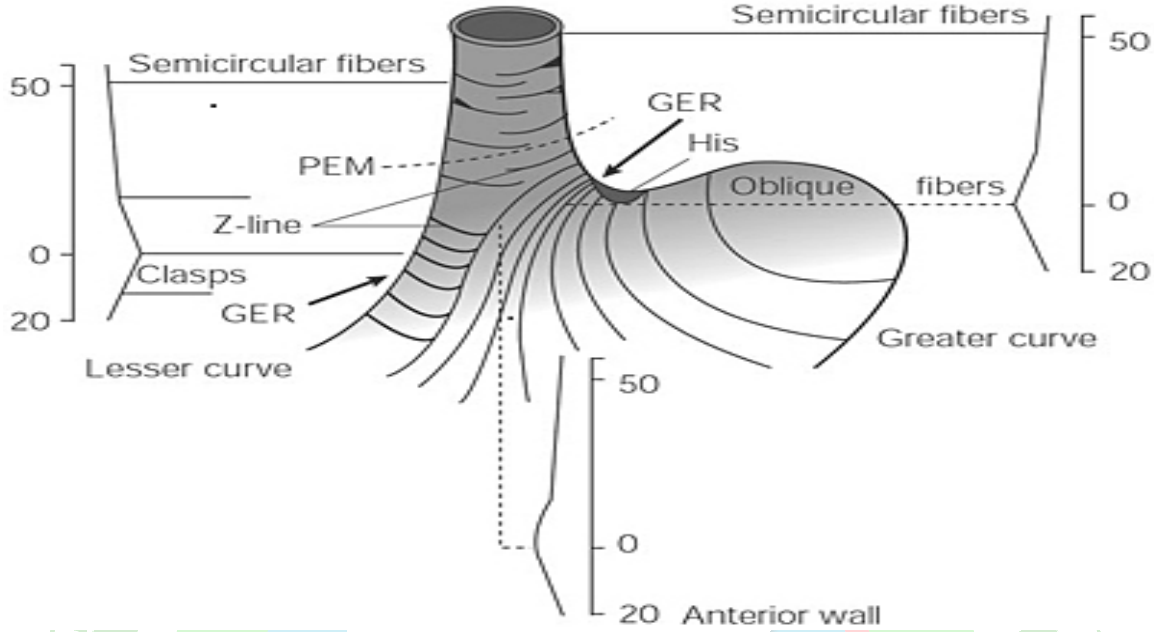

Figure 2: Structure of the lower esophageal sphincter (LES)

GERD occurs when LES pressure is lower than the intragastric pressure, such as in LES hypotension, increased frequency of transient lower esophageal sphincter relaxation (TLESR), when intragastric pressure increases the acid content of the stomach overcomes the LES pressure and comes in contact with esophageal mucosa causing damage to the esophageal mucosal walls. Mucosal defense mechanisms may be overcome by prolong exposure of esophageal mucosa to a pH <4 that may lead to severe and complicated esophagitis.

Esophageal mucosal inflammation may affect nerves and muscles that alter LES function and esophageal body motility. A vicious cycle of inflammation and impaired motility may cause progressive disease. Patient with GERD may develop visible erosive esophagitis; acid and inflammatory mediators may gain access to sensory pathways and produce symptoms either by direct action on nerves or by producing abnormal muscle contraction.

Delayed esophageal clearance

Gastric emptying as determined recently by a standardized technique confirms that delayed emptying is common in GERD patients, present in 26% of patients on the basis of retention at 4 hours. There are cogent reasons to suppose that delayed emptying could lead to GERD, including increased gastric content that could increase the frequency of TLESR and gastric acid secretion. However, there is little evidence to support this conclusion.

THE CONVENTIONAL TREATMENT OF GERD [2]

The conventional treatment of GERD involves the following approaches

- ***Symptomatic relief achieved by use of antacid preparations which increase pH.***

Despite the development of potent medications for the treatment of GERD, antacids remain a mainstay of treatment. Antacids neutralize the acid in the stomach so that there is no acid to reflux. The problem with antacids is that their action is brief. They are emptied from the empty stomach quickly, in less than an hour, and the acid then re-accumulates. The best ways to take antacids, therefore, is approximately one hour after meals or just before the symptoms of reflux begin after a meal. Since the food from meals slows the emptying from the stomach, an antacid taken after a meal stays in the stomach longer and is effective longer. For the same reason, a second dose of antacids approximately two hours after a meal takes advantage of the continuing post-meal slower emptying of the stomach and replenishes the acid-neutralizing capacity within the stomach. Antacids may be aluminum, magnesium, or calcium based. Calcium-based antacids (usually calcium carbonate), unlike other antacids, stimulate the release of gastrin from the stomach and duodenum. Gastrin is the hormone that is primarily responsible for the stimulation of acid secretion by the stomach. Therefore, the secretion of acid rebounds after the direct acid-neutralizing effect of the calcium carbonate is exhausted. The rebound is due to the release of gastrin, which results in an overproduction of acid. Theoretically at least, this increased acid is not good for GERD.

Acid rebound, however, has not been shown to be clinically important. That is, treatment with calcium carbonate has not been shown to be less effective or safe than treatment with antacids not containing calcium carbonate. Nevertheless, the phenomenon of acid rebound is theoretically harmful. In practice, therefore, calcium-containing antacids such as Tums and Rolaids are not recommended. The occasional use of these calcium carbonate-containing antacids, however, is not believed to be harmful. The advantages of calcium carbonate-containing antacids are their low cost, the calcium they add to the diet, and their convenience as compared to liquids. Aluminum-containing antacids have a tendency to cause constipation, while magnesium-containing antacids tend to cause diarrhea. If diarrhea or constipation becomes a problem, it may be necessary to switch antacids or alternately use antacids containing aluminum and magnesium.

e.g. Hydroxides of Calcium, Magnesium and Aluminium in the form of suspensions.

- ***Drugs that inhibit gastric acid secretion.***

Histamine 2 receptor blockers

Although antacids can neutralize acid, they do so for only a short period of time. For substantial neutralization of acid throughout the day, antacids would need to be given frequently, at least every hour. The first medication developed for more effective and convenient treatment of acid-related diseases, including GERD, was a histamine antagonist, specifically Cimetidine (Tagamet).

Histamine is an important chemical because it stimulates acid production by the stomach. Released within the wall of the stomach, histamine attaches to receptors (binders) on the stomach's acid-producing cells and stimulates the cells to produce acid. Histamine antagonists work by blocking the receptor for histamine and thereby preventing histamine from stimulating the acid-producing cells. (Histamine antagonists are referred to as H2 antagonists because the specific receptor they block is the histamine type 2 receptor.) Because histamine is particularly important for the stimulation of acid after meals, H2 antagonists are best taken 30 minutes before meals. The reason for this timing is so that the H2 antagonists will be at peak levels in the body after the meal when the stomach is actively producing acid. H2 antagonists also can be taken at bedtime to suppress nighttime production of acid.

H2 antagonists are very good for relieving the symptoms of GERD, particularly heartburn. However, they are not very good for healing the inflammation (esophagitis) that may accompany GERD. In fact, they are used primarily for the treatment of heartburn in GERD that is not associated with inflammation or complications, such as

erosions or ulcers, strictures, or Barrett's esophagus.

e.g. Ranitidine, Famotidine, Cimetidine, etc.

Proton pump inhibitors

The second type of drug developed specifically for acid-related diseases, such as GERD, were a proton pump inhibitor (PPI), specifically, omeprazole (Prilosec). A PPI blocks the secretion of acid into the stomach by the acid-secreting cells. The advantage of a PPI over an H2 antagonist is that the PPI shuts off acid production more completely and for a longer period of time. Not only is the PPI good for treating the symptom of heartburn, but it also is good for protecting the esophagus from acid so that esophageal inflammation can heal.

PPIs are used when H2 antagonists do not relieve symptoms adequately or when complications of GERD such as erosions or ulcers, strictures, or Barrett's esophagus exist (Figure 3).

e.g. Rabeprazole, Omeprazole, Lansoprazole, etc.

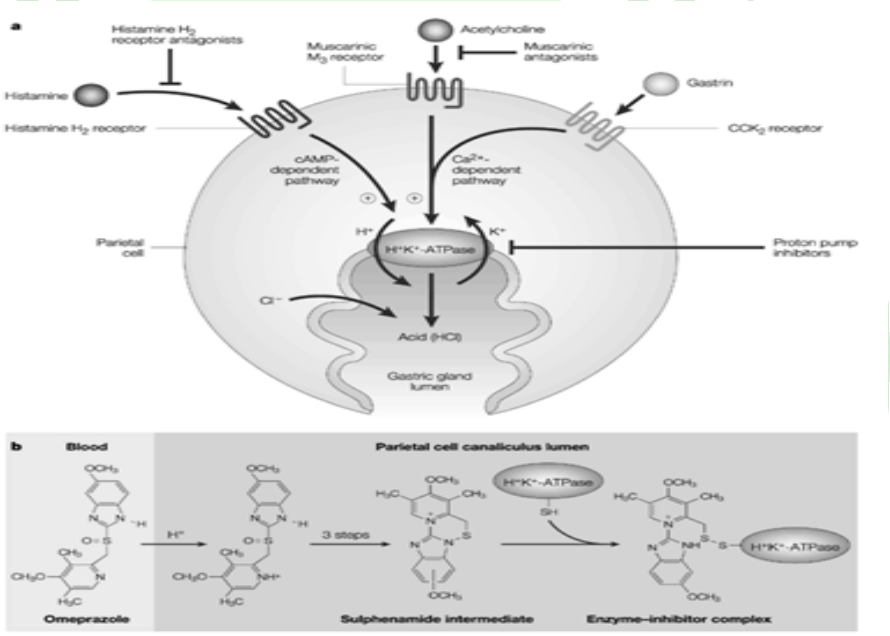

Figure 3: Mode of action of proton pump inhibitor

- ***Prokinetic drugs that decrease gastric emptying time***

Pro-kinetic drugs work by stimulating the muscles of the gastrointestinal tract, including the esophagus, stomach, small intestine, and/or colon. One pro-kinetic drug, metoclopramide (Reglan), is approved for GERD. Pro-kinetic drugs increase the pressure in the lower esophageal sphincter and strengthen the contractions (peristalsis) of the esophagus. Both effects would be expected to reduce reflux of acid. However, these effects on the sphincter and esophagus are small. Therefore, it is believed that the primary effect of metoclopramide may be to speed up emptying of the stomach, which also would be expected to reduce reflux.

Pro-kinetic drugs are most effective when taken 30 minutes before meals and again at bedtime. They are not very effective for treating either the symptoms or complications of GERD. Therefore, the pro-kinetic agents are reserved either for patients who do not respond to other treatments or are added to enhance other treatments for GERD.

e.g. Domperidone, Cisapride, Mosapride, Metoclopropamide, etc

- ***Mucoprotective agents***

The mucoprotective agents do not have acid neutralizing action but they form an inert protective layer on mucosal linings that prevent the contact of gastric acid with the delicate mucosa. Sucralfate is a basic Aluminium salt of sulfated sucrose and polymerises at pH <4. A topical formulation of sucralfate (Pepsigard Light Gel) is available for radiation ulcers.

e.g. Sucralfate, Bismath subgallate. etc

RAFT TECHNOLOGY [3]

One of the primary treatments for gastro-esophageal reflux disease (GERD) is the administration of alginate antacid anti-reflux preparations. These provide a physical barrier on contact with the stomach contents in the form of a neutral floating gel or RAFT. This physical mode of action is quite distinct from the chemical neutralisation of the bulk gastric contents provided by antacids alone, although alginate raft forming preparations have often, mistakenly, been classified as antacids. The advantage of alginate/antacid combinations over antacids alone is that they provide longer lasting symptom relief, even though relief is rapid in both cases. Their rapid onset of action makes them more suitable for self-medication than pharmacologically acting acid suppressants such as H2-receptor antagonists or proton pump inhibitors. Alginate rafts may be formed in liquid products by the action of gastric fluid on a soluble alginate to form an insoluble gel of alginic acid. They may also be formed by the interaction of soluble alginate with metal ions released by acid from an insoluble antacid such as calcium carbonate.

The simultaneous action of gastric acid on a bicarbonate salt produces carbon dioxide, which should ideally be trapped inside the alginate gel to aid buoyancy of the raft. Several features of rafts formed by alginate/antacid anti-reflux preparations are useful in forming an effective long lasting barrier between corrosive gastric fluid and the esophageal mucosa. Such rafts would be expected to be cohesive, buoyant, voluminous, resistant to reflux into the oesophagus and not easily broken up by movement in the stomach. The soluble salts sodium alginate and magnesium alginate are used in liquid alginate/antacid preparations and these can be converted to an insoluble gel of either alginic acid in the acidic gastric conditions or calcium alginate in the presence of calcium ions released by acid. The strength of the gel formed will depend upon both the molecular weight and content of GG blocks in the alginate.

Formulations those are available in market under this technology

- Algicon (Rhone-Poulenc Rorer, UK),
- Gastrocote (Seton Healthcare, UK),
- Gaviscon Advance and Gaviscon Liquid (Reckitt Benckiser Healthcare, UK),
- Gaviscon Liquid Antacid, Regular Strength and Gaviscon Liquid Antacid, Extra Strength, (Glaxo SmithKline Consumer Healthcare, USA),
- Mylanta Heartburn Relief (Warner Lambert, Australia),
- Peptac Liquid (Baker Norton, UK) and
- Rennie Duo (Roche Products, UK).
- Table I elaborates about the RAFT formation speed and character of the products [4].

Table II elaborates about ingredients and acid neutralizing capacity of the marketed formulations.

Alternatives for Alginate Salts

As alignic acid is obtained from biological sources, it comes with the disadvantage of batch to batch variation. This affects the reproducibility of product. Also it carries comparatively high microbial load than that of synthetic polymers. Thus instead of using alignate salts use of other hydrophilic cellulosic polymers like Hydroxy Propyl Methyl Cellulose (HPMC).

New Trend

Role of Interstitial Cell of Cajal [5]

Interstitial cells of Cajal are the group of cells distributed throughout the GIT which work

like pace makers to provide inputs to the enteric neurons. The action of these pace makers is modulated up and down either by vagus, sympathetic system, hormones and peptides from GIT, and also by cytokines. Excitation of ICC leads to contraction while its silence leads to relaxation. Inhibition of ICC causes relaxation of GIT and results in closure of LES, which will curb GERD which achieved by release of Nitric oxide (NO) locally. This can be achieved by use of NO precursors. These precursors are used, as NO is a gas with a very short half life of 2-5 seconds. The nitrates are the precursors of NO that we use for the treatment of angina pectoris are susceptible to first pass metabolism and are of no use [6-9]. Also Sodium nitroprusside is also a precursor but with adverse effect of severe hypotension. So usable NO precursor is the semi essential amino acid Arginine (Figure 4).

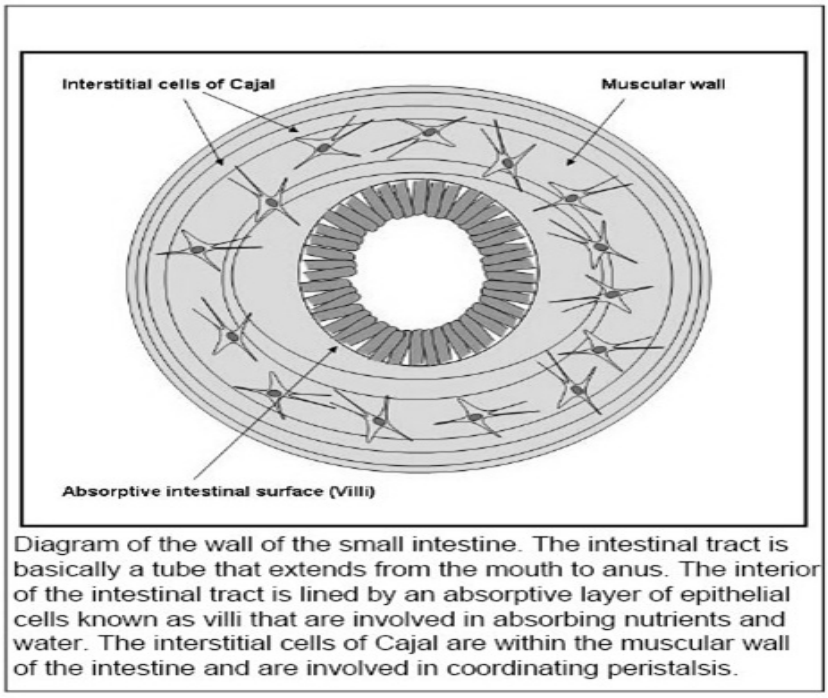

Diagram of the wall of the small intestine. The intestinal tract is basically a tube that extends from the mouth to anus. The interior of the intestinal tract is lined by an absorptive layer of epithelial cells known as villi that are involved in absorbing nutrients and water. The interstitial cells of Cajal are within the muscular wall of the intestine and are involved in coordinating peristalsis.

Figure 4: Interstitial Cells of Cajal

Arginine

Arginine is a semi essential amino acid which by the action of nitric oxide synthases (NOS) is converted into nitric oxide. This enzyme is present throughout GIT. The catalytic reaction takes place as follows [10-13]-

L-arginine + NADPH + H^+ + O_2 ➔ Citruline + Nitric oxide + $NADP^+$

The NO formed in gastro-esophageal tract may diffuse in to the interstitium and will act on Interstitial Cells of Cajal (ICC) on which it has inhibitory action. Inhibition of ICC leads to relaxation of GIT and closening of LES. The effect is more prominent with LES because it possesses more number of ICC. The arginine has half life of almost 45 to 60 minutes so it can release NO for sufficient period of time, to keep the LES closed.

The Predicted Formula

The predicted formula for the desired relief of GERD is as follows in Table 3-

The above formula can be formulated in the form of effervescent tablet with other excipients that are necessary for tabletting.

MECHANISM OF ACTION

The mechanism of action involves the disintegration of tablet by effervescence and release of alginate salt (either Sodium or Magnesium) in stomach, which will convert into either Alginic acid or Calcium alginate

which will absorb water and swell to from a gel like film. The Carbon dioxide released during the effervescence will entrap in the film, making it float on the gastric contents. Mean while the released Arginine will be catalysed by the enzyme Nitric Oxide Synthases and NO will be released. This NO will diffuse through the gastro-esophageal walls and will reach to the Interstitial Cells of Cajal and will inhibit them. This will ultimately result in closure of lower esophageal sphincter and relaxation of GIT. This will prevent the entry of acidic gastric contents in the esophagus thereby preventing the consequences of Gastro-Esophageal Reflux Disease i.e. GERD.

Advantages of the above formulation over the marketed formulation i.e. Gaviscon chewable tablet

- As it is an effervescent tablet its disintegration time is less than the chewable tablet and drug is released rapidly.
- As the disintegration of tablet is achieved in stomach, thus the undesirable effect of carbonate on oral mucosa is prevented.
- Arginine has its own advantages over the Gaviscon which does not contain it.

Table 1: Speed and character of raft formation by product

Product	*Formation speed*	*Flotation*	*Coherence*
Algicon	Immediate	Partial	Poor
Gastrocote	Slow	Partial	Good
Gaviscon Advance	Immediate	Complete	Good
Gaviscon Liquid	Immediate	Complete	Good
Gaviscon Regular Strength (USA)	Slow	Very low	Poor
Gaviscon Extra Strength (USA)	Slow	Very low	Poor
Mylanta Heartburn Relief	Immediate	Complete	Good
Peptac	Slow	Partial	Good
Rennie Duo	Immediate	Complete	Good

Table II: Product active ingredients and ANCs

Product	*Active ingredient listed (mg/maximum dose)*		*Theoretical ANC* (mequiv./maximum dose)*
Algicon	Magnesium alginate Magnesium carbonate $Al(OH)_3$ / $MgCO_3$ Potassium carbonate	1000 700 560 200	35.3
Gastrocote	Sodium alginate Dried aluminium hydroxide Sodium bicarbonate Magnesium trisilicate	660 240 210 120	10.3
Gaviscon Advance	Sodium alginate Potassium bicarbonate	1000 200	6.0
Gaviscon Liquid, Peptac	Sodium alginate Sodium bicarbonate Calcium carbonate	1000 534 320	12.8
Gaviscon Regular Strength (USA)	Magnessium carbonate Aluminium hydroxide	716 190	21.8
Gaviscon Extra Strength (USA)	Aluminium hydroxide Magnesium carbonate	1116 950	48.0
Mylanta Heartburn Relief	Calcium carbonate Sodium bicarbonate Dried Aluminium hydroxide Magnesium hydroxide Alginic acid	500 500 400 400 310	39.7
Rennie Duo	Calcium carbonate Sodium alginate Magnesium carbonate	1200 300 140	28.5

*Where ANC stands for acid neutralizing capacity

Table III: Predicted Formula

Sr. No	*Ingredients*	*Use*
1	Sodium/Magnesium Alginate	In situ film former
2	Sodium carbonate	Effervescent antacid / Floating inducer
3	Arginine	GIT relaxant

CONCLUSION

Gastro-esophageal reflux disease (GERD) includes all the consequences of reflux of acid or other irritants resulting in the regurgitation of gastric acid cause's heartburn or acid indigestion as major symptoms. The goals of GERD therapy are complete resolution of symptoms and healing of esophagitis and alginate/antacid combination also known as Raft technology is the one which can be effectively used for such purpose.

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