Raft-forming Polysaccharides for the Treatment of Gastroesophageal Reflux Disease (GORD): Systematic Review

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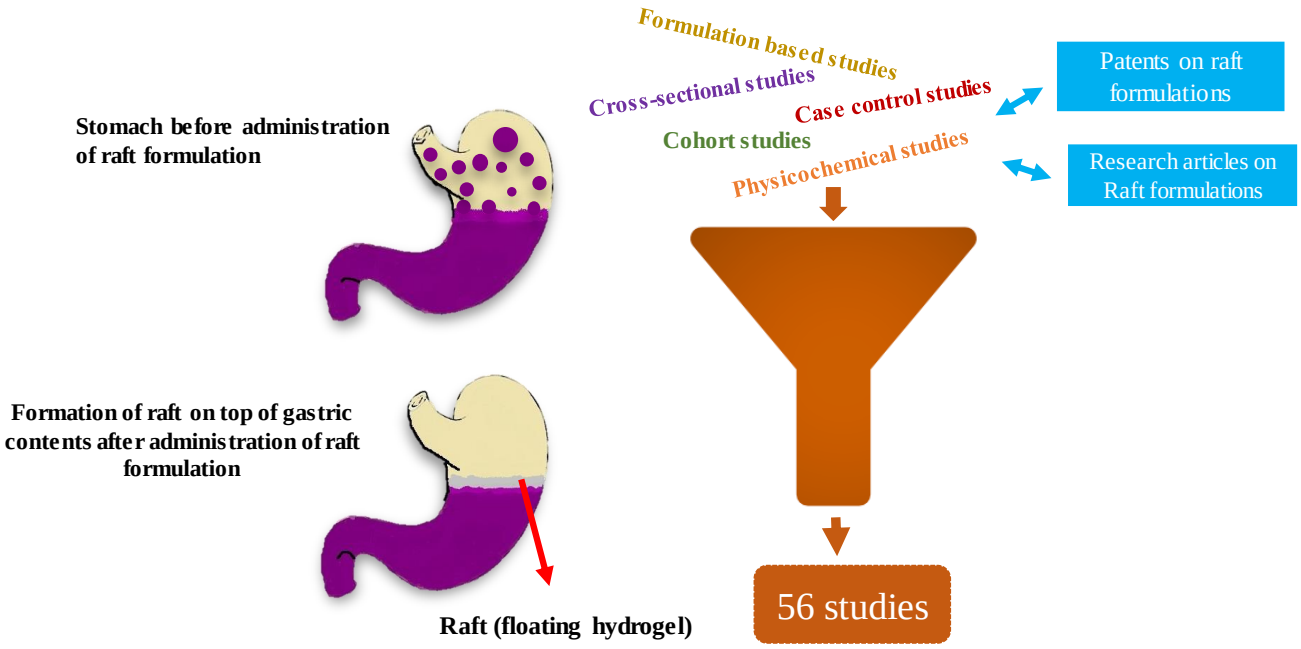
Graphical Abstract:



Highlights:

1- A systematic review of the use of polymers as raft-forming agents was conducted.

2- A large number of included studies primarily reflect the use of alginate and pectin for fabricating anti-reflux raft formulations.

3- Fewer studies have reported the use of pectin, xanthan gum and raw psyllium fibres (husk).

4- It highlighted the importance of using different active and inactive materials, controlling different formulation factors and characterisation of raft forming formulations.

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Master by Research Student

Ms. Maria Yousaf is currently pursuing her MRes degree in Pharmaceutical Sciences at University of Huddersfield, Huddersfield, United Kingdom. She received her Pharm.D degree from University College of Pharmacy, Punjab University, Lahore, Pakistan. Her research interests include development of novel formulations using natural polymers for the treatment of gastric disorders.

Mr. Jorabar Singh Nirwan BSc, MSc

PhD Research Student

Mr Jorabar Singh Nirwan is currently pursuing his PhD in Pharmaceutical Sciences at the University of Huddersfield, Huddersfield, United Kingdom. He also received his BSc in Pharmaceutical Sciences and MSc in Pharmaceutical and Analytical Science at the University of Huddersfield. His research interests include the development and characterisation of novel pharmaceutical formulations for the treatment of gastroesophageal reflux disease (GERD).

Peter Timmins PhD, BPharm, FRPharms

Visiting professor in Pharmaceutics and Biopharmaceutics.

Professor Timmins obtained his degree in pharmacy and his PhD from the University of Bradford and, after working for a brief period as a quality control pharmacist at a UK NHS hospital, joined pharmaceutical industry. He was promoted to positions of increasing responsibility and recently retired from the role of Executive Director in Drug Product Science and Technology, part of Pharmaceutical Development, at Bristol-Myers Squibb Research and Development (BMS). His group at BMS was responsible for creating, or adapting, and applying drug delivery solutions for drug candidates entering development that were significantly challenged by solubility in assuring good oral bioavailability and those candidates that need modified release technology. The team was spread across geographies, with staff in New Brunswick, New Jersey (USA) and Moreton (UK). He was also the head of the Moreton R&D site. During his industry career was an active researcher in advancing oral drug delivery technology, collaborating with universities and commercial organisations, including other pharmaceutical companies.

Retiring from his industry role has allowed him to refocus on his academic activities, contributing to the research work in the drug discovery/drug product development interface. He is active in pharmaceutical materials science, aiming to optimise the physical properties of active pharmaceutical ingredients and excipients to enable effective drug product design. He has also maintained his long-established research in drug delivery, including oral controlled release and amorphous solid dispersions and the characterisation of polymers used for that purpose. He is author or a co-author of over 100 peer reviewed publications, several books or book chapters and an inventor or co-inventor on 30 patents.

Alan M. Smith PhD

Professor of Biopolymer Science

Alan is a Professor in Biopolymer Materials. He graduated from Salford University (Biochemical Science) in 1997 before gaining his PhD from Cranfield University developing polysaccharide substitutes for gelatin in the production of pharmaceutical capsules under the supervision of Prof. Ed

Morris. Following his PhD Prof Smith worked for 2 years as a formulation scientist within the pharmaceutical industry before taking up a position as a polysaccharide chemist at Industrial Research Limited, Wellington, New Zealand. On his return to the UK Prof. Smith has worked as a research fellow at the University of Birmingham (School of Dentistry) and Aston University (School of Pharmacy) developing 3D cell scaffolds and polysaccharide based drug delivery systems. In 2008 he joined the tissue regeneration and interface laboratory within Chemical Engineering at the University of Birmingham where he continued to develop his research on biopolymers for tissue engineering and drug delivery applications before being appointed as a Senior Lecturer in Pharmaceutics at the University of Huddersfield in March 2011. He was promoted to Reader and Professor of biopolymers science in 2016 and 2018, respectively.

Barbara R. Conway PhD, BPharm, FRPharms, FHEA

Professor of Pharmaceutics and Head of Pharmacy

Barbara is Head of Pharmacy at the University of Huddersfield. She was appointed as Professor of Pharmaceutics at the University of Huddersfield in 2010. Following her first degree in Pharmacy at Queen's University, Belfast, she registered as a pharmacist in 1990 and practised full-time in community pharmacy until joining Aston University in Birmingham in 1992 to undertake a Ph.D. Her PhD research project at Aston was in the pharmaceutics and drug delivery field, focusing on microencapsulation for delivery of biopharmaceuticals. Following completion of her PhD studies in 1995, she was employed in various posts at Aston University, including lecturer and senior lecturer and was Director of the M.Pharm programme prior to moving to the University of Huddersfield in 2010 as Professor of Pharmaceutics. During this time, she also became a Fellow of the Higher Education Academy and supervised projects on the application of e-learning technologies in Pharmacy. She was also a Medici Fellow, specialising in driving forward innovation within the university sector and hold several patents in the pharmaceutical area. She has supervised over 40 Ph.D. students and on-going research programmes focus on strategies to improve skin antisepsis and delivery of antimicrobials, solubility enhancement for poorly soluble drugs, the mechanical properties of pharmaceuticals and excipients and nanodissolution. She has a number of successful collaborations with other universities, NHS and pharmaceutical industry leading to publications and development of new products.

Muhammad Usman Ghori PhD, Pharm.D, SRPharmS, PGCHE, FHEA

Senior Research Fellow and Admission Tutor

Dr Ghori was graduated with a Pharm.D (Doctor of Pharmacy) degree from B. Z. University (Pakistan) in 2009 and became a registered pharmacist (RPh) with the Punjab Pharmacy Council, Pakistan. He pursued his career as a Community Pharmacist in Pharmagen Health Care Ltd and where he accede to a managerial role in the short span of time. Dr Ghori joined the University of Huddersfield for PhD in 2010, during his PhD, he presented his findings at many national and international conferences and published his findings in high impact journals. He has successfully established the student chapter of the American Association of Pharmaceutical Sciences (AAPS) at the University of Huddersfield and served as its founding Chair (2014-15). He was also the proud recipient of the prestigious vice-chancellor research student of the year award 2015. He was awarded his doctorate in January 2015 and subsequently appointed as a Post-doctoral Research Assistant in School of Applied Sciences at the University of Huddersfield, and he has successfully developed a patented AFM based nanoscale chemical imaging technique, CIDA (chemical imaging by dissolution analysis), and won the prestigious platinum award 2016 from Bruker Nano-surface, UK. He was also named among the outstanding performing staff for the year 2017-18 by the University of Huddersfield, UK. Currently, he is working as a senior research fellow and admission tutor (Pharmacy) at the University of Huddersfield. His research focused on the design, development and characterisation of new materials, instruments and technologies including 3D and 4D printing, nanoscale chemical, electrical and mechanical imaging-based techniques for drug delivery and biomedical applications.

Abstract

Gastroesophageal reflux disease (GORD) is a common condition induced by unwarranted reflux of gastric and duodenal contents into the oesophagus, and insufficient clearance of refluxate from it. Pharmaceutical formulations possessing raft-forming capability offer an excellent alternative to conventional treatment options to treat uncomplicated GORD. These formulations typically contain a polymer, which performs distinctively upon contact with gastric acid and develops a foam-like structure that can float on gastric contents. This review aims to feature research articles and patents that cover this topic. After undergoing a standardised literature search following PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines, we have included 38 research articles and 18 patents describing the role of raft-forming polymers in the treatment of GORD. This is a comprehensive review of formulation/testing of raft-forming polymers. As expected, the majority of the studies focused on alginate; however, fewer studies have reported the use of pectin, xanthan gum and raw psyllium fibres (husk). Moreover, it can be concluded from this comprehensive systematic review that a detailed characterisation of raft forming formulations, type and concentration of used active and inactive materials and different formulations factors are essential for the development of successful anti-reflux raft forming formulations.

Keywords:

Raft-forming agents; Gastroesophageal reflux disease; Raft formulations; Systematic review; Reflux.

1- Introduction

Gastroesophageal reflux disease (GORD) is one of the most prevalent gastric disorders and is defined as a condition in which the gastric and duodenal contents reflux back into the oesophagus causing troublesome symptoms and complications such as heartburn and acid regurgitation.[1,2] The prevalence of this condition is widespread and its associated symptoms affect individuals globally. In Western countries, the prevalence of GORD and its associated symptoms is 10-20%.[3,4] However, in Asia, GORD prevalence has been found to be as low as 2.3%, whereas a study conducted in India estimated the prevalence of GORD to be 16 -18%, which is analogous to Western countries.[5,6] Limited studies have been conducted on the prevalence of GORD in Africa, although a Nigerian study estimated the prevalence of GORD to be 23%.[7,8]

GORD has proven to have a substantial burden on public health strategies as its treatment is costly and symptoms can affect the quality of life of patients. [9-11] Based on endoscopic findings, GORD can be categorised into two main classes: non-erosive reflux disease (NERD) and erosive reflux disease (ERD). The former class refers to reflux without the presence of oesophageal mucosal damage, and the latter class refers to reflux with the presence of oesophageal mucosal damage (erosive oesophagitis), and can potentially lead to the development of Barrett's oesophagus.[12,13] The pathophysiology of GORD is multifactorial, although multiple studies have concluded that reflux occurs almost entirely during episodes of transient lower oesophageal sphincter relaxation (TLOSR) [14,15]. Typically, reflux of gastric contents is prevented by the lower oesophageal sphincter (LOS) which acts as a one-way system by allowing ingested liquids and solids into the stomach while preventing the reflux of gastric contents into the oesophagus. However, episodes of transient relaxation of the LES also occur which serve the purpose of allowing trapped air located in the proximal stomach to escape.[16] The frequency of these episodes is similar in asymptomatic individuals and

individuals with GORD, although it has been found that TLOSRs are twice as likely to be associated with episodes of acid reflux in those with GORD than those without the condition.[17]

Factors that are associated with an increased risk of GORD link mainly to genetics, lifestyle and environment. [18] The prevalence of GORD is higher in white individuals in comparison to the black community. [19] Additionally, numerous studies have shown that there is a positive correlation between age and prevalence of GORD. [20-22] GORD prevalence in obese individuals is also greater compared with those with a normal body mass index (BMI). [3] Moreover, smoking and the consumption of alcohol, coffee and carbonated drinks are considered as risk factors for GORD. [8,23] Multiple studies have also concluded that a combination of hormonal changes and physical alterations increases the vulnerability of pregnant women to GORD especially in the third trimester. [24-26]

The management of GORD includes both non-pharmacological and pharmacological approaches. Non-pharmacological treatment options include lifestyle modifications including changes in diet, sleeping posture and weight reduction. [27] Pharmacological interventions for the treatment of GORD can be divided into two sub-types: non-raft formulations and raft formulations. The most commonly adopted therapy for the treatment of GORD involves the use of antacids, histamine-2-receptor antagonists (H_2RAs), proton pump inhibitors (PPIs), sucralfate, prokinetic drugs and alginate-based raft formulations.[28] Antacids are formulated using different acid-neutralising agents (aluminium and magnesium hydroxide, calcium carbonate, sodium citrate and sodium bicarbonate). These agents are alkaline and neutralise the gastric acid, which results in symptomatic relief.[29] However, H_2RAs and PPIs both interfere with gastric acid production.[30,31] Although PPI therapy is commonly available and results in a reduction of disease symptoms, it has shown to be associated with side effects such as hypocalcaemia, hypomagnesemia, *Clostridium difficile* infections and pneumonia.[32] Gastric acid, which is secreted by the parietal cells present in the stomach, plays a vital role in the

digestion of proteins by activating pepsinogen, facilitating the absorption of nutrients such as folic acid, ascorbic acid, β-carotene and various minerals. It also prevents fungal or bacterial infections in the small intestine by providing an acidic hostile environment in which many ingested pathogens are unable to survive. Therefore, the presence of gastric acid is essential for normal physiological functions of the body. This insight calls for appropriate therapeutic action, which deals with unnecessary acid reflux without interfering with the natural defence and digestive system of the body. The most rational approach to manage GORD is to minimise the exposure of the oesophagus to acid reflux. Therapeutic agents, like H_2RAs and PPIs, suppress the acid production and antacids neutralise gastric acid; hence, interfering with the normal function of gastric acid. In such cases, raft-forming anti-reflux formulations can potentially be an ideal therapeutic choice, exhibiting a unique non-systemic mechanism for protection of the oesophageal mucosa. [33-35] Raft-forming systems contain at least one or more gel or raft-forming agents along with alkaline bicarbonates and carbonates, sometimes in combination with an acid neutraliser. [36-38] Different polymers, mainly from natural origin, can develop floating rafts. [39,40] Hence, this article presents results from a systematic literature search adopting the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines to review the range and polysaccharide polymers reported and evaluate their application potential.

2- Methodology

2.1- Search plot, inclusion and exclusion criteria

This systematic review was performed in accordance with the PRISMA 2009 guidelines and the process of inclusion and exclusion is illustrated in Figure 1. [41] For inclusion of as many studies as possible on raft-forming agents for GORD treatment, a wide-ranging search plot for PubMed, MEDLINE, EMBASE, Scopus, Google Scholar, Google Patents and Espacenet was established. Search terms were ‘raft-forming agents’, ‘raft-forming polymers’, ‘raft-forming

biopolymer', 'anti-reflux formulations', 'gastroesophageal reflux disease', 'GORD', and 'GERD'. The primary investigators (MY, JSN and MUG) screened the titles, abstracts and full texts for articles and patents reporting on (a) raft-forming agents, (b) anti-reflux formulations, (c) gastroesophageal reflux disease (GORD), and (d) characterisation methods/techniques of raft-forming anti-reflux formulations. The publication period was from 1st January 1947 to 31st July 2018, and no language restrictions were applied.

2.2- Data extraction

All the included studies were catalogued, and data were tabulated in Microsoft Excel® 2013. Extracted data from selected studies comprised the agent used for raft formation, a summary of aims, and conclusion in the case of research articles. The data extracted from patents included the agent used for raft formation, and a summary of claims and the invention.

2.3- Quality assessment

The quality of the included studies was assessed using the quality assessment criteria expressed in Table 1. This assessment aimed to evaluate the quality of study design and bias. The primary investigators (MY, JSN and MUG) independently assessed every included study and rated each study according to the predetermined criteria, Table 1. The final score was assigned to the studies and patents after a detailed discussion. The results of this quality assessment for research articles and patents are presented in Table 2 and Table 3, respectively.

3. Results and discussions

The search plot resulted in 11688 records, of which, 11107 were articles and 581 were patents. After the exclusion of 7326 duplicates (6895 articles and 431 patents), 4212 articles and 150 patents were screened by title and abstract, which resulted in the removal of a further 4076 articles and 102 patents. Consequently, 184 investigations (136 articles and 48 patents) were subjected to full-text screening which resulted in the exclusion of 126 (98 articles and 28

patents) and inclusion of 56 records (38 research articles and 18 patents). The main reasons for exclusion were the use of rafts for the treatment of disorders other than GORD and as a drug delivery system. Figure 2 describes the distribution of the number of research articles and patents focused on each raft-forming agent. Characteristics of the included research articles and patents are summarised in Table 4 and Table 5, respectively. Moreover, selected studies are grouped by polymer used and discussed separately in the succeeding sections.

3.1. Alginates

Alginates are natural polysaccharide polymers isolated from brown seaweed (Phacophycae) and often characterised as a dietary fiber. [42] The structure of alginate consists of L-guluronic acid and D-mannuronic acid residues interlinked by 1:4 glycosidic linkages, as displayed in Figure 3a. [43] Many investigations have been carried out to determine the raft-forming properties of alginate and its salts. These studies revealed that, in the acidic environment of the stomach, alginate salts or alginic acid precipitate to form a low-density viscous gel. Additionally, alginates can form rafts both *in-vivo* and *in-vitro*, although, *in-vivo*, alginates form a gel within seconds after exposure to gastric acid, whereas, *in-vitro*, they begin to form a gel after a few minutes of administration. [36,44] One of the most well-known examples of alginate-based raft formulations is Gaviscon® liquid, which contains sodium alginate, calcium carbonate, and sodium bicarbonate, and develops a robust floating raft in the acidic environment of the stomach.[45] Alginates are often combined with other therapeutic classes such as antacids, H_2RAs and PPIs to increase the efficacy of raft formulations. [46,47]

A study conducted by Malmud et al. [44] outlined the mechanism of action by which alginates reduced gastroesophageal reflux (GOR) index. Gastroesophageal scintigraphy was employed to measure the GOR index quantitatively. This technique involved oral administration of technetium-99m (Tc-99m) sulphur colloid solution, which showed that AAC reduced GOR

index from 9.9% (± 1.3%) to 6.5% (± 0.8%) ($p < 0.05$). No change in the lower oesophageal sphincter pressure was observed. Additionally, a dual-nuclide scintigraphy technique was used in which alginic acid was labelled with strontium-87m (Sr-87m-AAC) to investigate the AAC position in the stomach. Results found that the major portion of AAC was present in the upper half of the stomach in the form of a viscid floating raft which resulted in the improvement of GOR. [44]

The raft forming ability of alginates was also demonstrated in a study conducted by Washington et al. (1985). The authors applied the technique of pH telemetry for the measurement of *in-vivo* pH-time profiles of two antacid formulations, Asilone® Suspension and Gaviscon® liquid. Additionally, an *in-vitro* test (the Rossett and Rice test) was used to evaluate their acid neutralisation capacity, and an *in-vitro in-vivo* correlation (IVIVC) was attempted. In both cases, Gaviscon® liquid successfully formed a raft. However, initial results showed a poor IVIVC, but modification of *in-vitro* test procedures, including raft breaking strength assessment and pH time profiles, improved this correlation. [48] In the following year, another study conducted by Washington et al. investigated the effect of incorporating aluminium hydroxide into alginate-based raft formulations. Neutralisation profiles of the stomach were obtained, and a microcomputer-controlled apparatus determined the raft breaking strength of these formulations. These tests showed that aluminium hydroxide remained trapped in the alginate and could not neutralise the gastric acid contents present below the alginate layer. Thus, it was concluded that the strength of the alginate raft was reduced with the inclusion of aluminium hydroxide and this weakened the raft barrier. [46] In a separate study, the same authors also tested the raft strength and neutralisation profiles of alginate rafts produced by four formulations of liquid Gaviscon®. All four formulations displayed different raft breaking strengths and pH-time profiles even though the concentration of alginate in each formulation was the same (5% w/v). Therefore, the authors concluded that different

formulations with the same trade name might differ in functionality based on the other excipients used in the formulation. The addition of an antacid (aluminium hydroxide) into the liquid Gaviscon® formulations increased its capacity to neutralise gastric acid, but the strength of the raft was compromised. It was theorised that this may be due to the antacid competing for acid with the carbonate component, hence the formation of carbon dioxide bubbles required to elevate the raft is slower. This resulted in the formation of a less viscous raft, resulting in the provision of a weak reflux barrier at the opening of the oesophagus. [49]

Later, Castell (1992) tested a hypothesis stating that alginic acid primarily decreased reflux when individuals were in the upright position. This evaluation included a comparison of alginic acid plus antacid with antacid alone as a control. Ten individual volunteers were randomly administered either alginic acid-antacid or only antacid immediately after a meal. The study showed that the alginic acid-antacid formulation was more effective at reducing postprandial reflux in the upright position compared with antacid alone. However, this effect was not seen in the supine position, supporting the original hypothesis of the study. [50] In the same year, the prokinetic agent cisapride was compared with Gaviscon® plus Carobel® (a thickening agent made from carob seed flour) in the treatment of GOR. In a randomised group study, fifty infants were given either oral cisapride or Gaviscon® plus Carobel®. Results were obtained using 24-hour pH monitoring and a diary score. According to the parents of the infants, 53% of infants in the cisapride group experienced improvement of GOR symptoms. However, a significantly greater improvement, 79%, was reported in the group receiving Gaviscon® plus Carobel®. Diary scores also showed an improvement in both groups with marked improvement in the Gaviscon plus Carobel group. It was concluded that conventional therapy of GOR in infants with Gaviscon plus Carobel was a more effective treatment option. [51]

Hill & Wade, 1993 using creep viscometry for raft strength estimation, evaluated the raft forming properties of alginates. Their study characterised the raft-forming properties of

chewable commercial tablets comprising alginic acid and antacids (aluminium hydroxide and magnesium trisilicate). The outcomes demonstrated that increasing alginic acid levels in the formulation mainly increased the viscosity of the raft. On the other hand, increasing the concentration of antacids reduced the raft strength, with aluminium hydroxide having a significant impact. [52]

A study by Washington & Denton, compared liquid Gaviscon® with Algitec® (a sodium alginate and cimetidine combination). Both formulations were given to twelve healthy volunteers to evaluate the gastric acid reflux suppression. A Tc-99m labelled meal which could trigger reflux, was given to these volunteers and thirty minutes after receiving the meal, these subjects were either treated with liquid Gaviscon®, Algitec® or left untreated. Reflux of acid and food was measured using a pH electrode, and gamma detector positioned 5 cm above the oesophageal sphincter junction. Both of the formulations showed significant suppression in comparison to the control group. However, intake of the formulation containing alginate without the addition of an H_2RA resulted in a greater reduction in reflux compared with the formulation with an H_2RA. [53]

In 1997, Johnson et al. investigated the impact of molecular weight of alginate on its raft strength and dimensions using texture analysis. Additionally, two gas-forming agents (sodium and potassium bicarbonate) and two divalent cationic salts (calcium carbonate and zinc carbonate) were included. The results showed that the volume of rafts increased when divalent cations and low molecular weight alginate salts were used, and it was concluded that alginates with a higher gulucuronic acid content and lower molecular weight develop rafts of considerably higher strength. [45] A second report by Johnson et al. employed an image analysis technique to assess the dimensions of bubbles formed in various alginate-based raft formulations. Raft-forming formulations were prepared containing three sodium alginate samples, namely LFR 5/60, LF 120M and LF 10/40RB, representing a range of uronic acid

content (67.2%, 50.9%, and 42.4%, respectively). These formulations contained sodium and potassium bicarbonate as gas evolving agents, and calcium and zinc carbonates as divalent cations. The perimeter, area, mean diameter and sphericity of bubbles were evaluated. The results demonstrated that the LFR 5/60-based anti-reflux formulations developed the largest bubbles; however, the viscosity was comparatively low. It was concluded that lower molecular weight alginates produce bubbles with larger dimensions. [54]

A hybrid study compared the gastric residence time and distribution of Topaal Whip® (a novel anti-reflux agent containing 400 mg alginic acid, 60 mg aluminium hydroxide, 80 mg magnesium carbonate and 260 mg silicon dioxide per therapeutic unit of 3 g) and liquid Gaviscon®. [55] Both formulations were labelled with indium-113m, and gamma scintigraphy was performed to determine gastric residence measurement of the developed rafts. The authors deduced that Topaal Whip had a distinct advantage over other anti-reflux formulations as the pre-injection of the gas (carbon dioxide, CO_2) to the formulation removed the need to rely on the amount and concentration of gastric acid to form a raft. Furthermore, it was also concluded that Topaal Whip formed an effective raft over gastric contents and the residence time was longer than liquid Gaviscon®. [55] In another study on Gaviscon®, Zentilin et al. assessed acid and non-acid reflux episodes in subjects after the intake of Gaviscon® in fed (refluxogenic heavy meal) conditions using multichannel electrical impedance and pH-metry. In both upright and supine positions, these techniques showed that alginate-based formulations were successful in suppressing the number of acid reflux events. [56] During the same year, Dettmar et al. investigated the effects of omeprazole pre-treatment on the formation of alginate rafts and their gastric residence time. A crossover study was conducted in twelve healthy individuals who received two alginate tablets labelled with indium-111, in the presence or absence of omeprazole pre-treatment. After alginate tablet administration, gamma scintigraphy was performed in the presence of a Tc-99m labelled meal for three hours. The study concluded that

pre-treatment with omeprazole had no significant effects on the raft-forming ability and raft persistence in the stomach of alginate tablets. [47]

The efficacy of different alginate-based anti-reflux products was evaluated by measuring multiple properties including cohesion, buoyancy, voluminous, resistance and durability of action of these anti-reflux formulations (Algicon®, Gastrocote®, Gaviscon Advance®, Gaviscon Liquid®, Gaviscon Liquid Antacid®, Gaviscon Extra Strength®, Mylanta Heartburn Relief®, Peptac Liquid®, and Rennie Duo®). [57] This study demonstrated the *in-vitro* effectiveness of developed rafts using the theoretical acid neutralising capacity (ANC) of each product. The formulations with high ANC and no calcium ion source effectively had lower raft strength, volume and weight. [57] Giannini et al. performed an open-labelled, prospective, randomised, parallel group clinical trial. The patients, who were experiencing GORD symptoms at least three days a week before commencement, received a single dose of sodium alginate (Gaviscon® Advance) and an antacid (magaldrate anhydrous oral suspension (Riopan® gel)), at the onset of symptoms during a 3-day run-in period. The study concluded that the alginate-based formulation was efficient at relieving the reflux symptoms and displayed a propensity towards a more extended duration of action and effectiveness compared with magaldrate. [58] Similarly, Strugala et al. examined the effectiveness of an alginate-based formulation (Gaviscon® Advance) in protecting the oesophagus from pepsin and bile acids using an *in-vitro* Franz cell model. The results suggested that the formulation could remove pepsin and bile acids from the refluxate, as well as affect the enzymatic activity of pepsin, thus preventing damage to the oesophagus. [59] Although these studies display the effectiveness of Gaviscon® in relieving GORD symptoms, there are multiple different formulations of Gaviscon®. Hence, Hampson et al. investigated the *in-vitro* efficacy of two raft-forming formulations: Gaviscon® Liquid (GL) and Gaviscon® Double Action Liquid (GDAL). A texture analyser was used for the determination of raft strength and resilience. *In-vivo* efficacy

of the developed rafts was measured by comparing the gastric retention of alginate rafts using gamma scintigraphy with the two liquid dosage forms radiolabelled with indium-111 and a test meal radiolabelled with technetium-99m (Tc-99m). The results indicated that the GDAL formulation had greater raft strength compared with GL in both *in-vivo* and *in-vitro* environments. [60]

Although GORD has been found to be highly prevalent in infants and children, a limited number of studies have been conducted to assess the efficacy of raft-forming agents in the treatment of the condition in infants. [61] Atasay et al., (2010) evaluated the efficacy of sodium alginate in the treatment of GORD in pre-term infants. In a randomised controlled trial, 1 ml/kg Gaviscon® liquid was administered four times a day after every two days to preterm infants. The reflux events were recorded using 24-hour pH monitoring. The results indicated an improvement in 83% of GORD suffering infants. This study demonstrated that sodium alginate is safe and effective for GORD treatment in preterm infants.[62] Similarly, Corvaglia et al. conducted a clinical trial study to determine the effect of sodium alginate in preterm new-borns suffering from GOR using pH and impedance monitoring techniques and observed a reduction in the number of acid reflux episodes.[63] In a second clinical trial, Corvaglia et al. studied the potential of sodium alginate to reduce the intensity of GOR-related apnoea of prematurity (AOP) in 28 preterm infants using multichannel impedance, pH monitoring, and polysomnography. The results of this investigation revealed a marked reduction in acid reflux; however, the GOR related AOP remained unaffected by administration of sodium alginate. [64]

Kwiatek et al. (2011), evaluated the ability of the alginate reflux formulation GDAL to neutralise gastric acid and acid pocket displacement. pH monitoring, manometry and fluoroscopy was conducted in each subject three times in different conditions; (a) fasted, (b) 20 minutes after the consumption of a meal, and (c) 20 minutes later after the consumption of oral dose (20 ml) of GDAL. The results showed that the formulation produced an alginate-

antacid raft. This raft was formed in a suitable position and relieved GORD symptoms in 8/10 subjects. [65] Pouchain et al. compared an alginate-based formulation (Gaviscon®) with omeprazole in clinical settings. A 14-day multicentre randomised double-blind, double-dummy non-inferiority trial of Gaviscon® and omeprazole was carried out in patients experiencing GORD symptoms 2-6 days per week. The results of this study indicated that there was no significant difference in the performance of both these formulations in relieving GORD symptoms. Therefore, it was concluded that Gaviscon® is an effective alternative treatment for moderate GORD in primary care. [66]

The efficacy of an alginate-antacid (Gaviscon® Advance (GA)) and a non-raft-forming antacid in the suppression of gastric reflux were compared in a study using magnetic resonance imaging (MRI) and pH impedance monitoring. The results of this study showed that a mass of GA was formed at the oesophagogastric junction (OGJ), which demonstrated reduction in reflux events more efficiently in GORD patients. This investigation concluded that GA was more capable of reducing reflux events compared with the non-raft-forming formulation. [67] Another study compared the effectiveness and safety of a sodium alginate suspension with omeprazole in patients suffering from non-erosive reflux disease (NERD). In a randomised clinical trial, a sodium alginate suspension was administered three times a day, whereas omeprazole was given once daily. The results were obtained by means of a patient diary or a questionnaire completed before and after the trial. The results of the trial showed no significant statistical difference between sodium alginate suspension and omeprazole. Therefore, it was concluded that sodium alginate suspension is not inferior to omeprazole in the treatment of NERD in patients. [68]

A study by Ruigh et al. compared the efficacy of Gaviscon® Double Action (GDA) with Antacid Liquid Supreme®, an antacid preparation containing magnesium hydroxide, in the suppression of postprandial acid reflux events in GORD patients. Fourteen patients were

involved in a randomised clinical trial to assess liquid movement in the oesophagus and its motility and using impedance–pH monitoring and manometry tests, respectively. The parameters measured included acid exposure to the oesophagus, number of reflux events, intensity of reflux, reflux mechanism and symptoms. Both formulations resulted in a similarity number and spatial distribution of reflux events but GDA was more effective than antacid in minimising the exposure the oesophagus to acid. [69] A further study, the role of GDA in the reduction of heartburn, acid regurgitation, and dyspepsia in patients experiencing mild to moderate GORD was assessed. Patients involved in this study received GDA or a placebo drug in a randomised manner for seven days. The endpoint of this trial compared the change in the condition of patients who received either GDA or placebo, using the Reflux Disease Questionnaire (RDQ). Scores from these questionnaires showed that GDA was statistically superior in suppressing GORD symptoms and dyspepsia; however, the occurrence of adverse events (AEs) in both formulations was the same. This investigation concluded that GDA was superior to the placebo drug in treating symptoms of GORD in patients with mild to moderate GORD. [33]

The effectiveness of an alginate-based formulation (GA) in patients experiencing reflux symptoms who were also taking a once-daily dose of a PPI was evaluated. 133 patients were involved in this multicentre, randomised, placebo-controlled clinical trial. Outcomes were measured by comparing the scores received in the Heartburn Reflux Dyspepsia Questionnaire (HRDQ). GA and a placebo drug were given to patients in addition to PPI therapy. The results showed that the change in HRDQ scores in patients receiving GA was significantly higher than those administered the placebo. The number of reflux events at night also decreased remarkably with GA treatment. This study concluded that inclusion of GA in the treatment regime of patients receiving PPI therapy had further reduced the burden of reflux symptoms.[70] Alecci et al. also assessed the effectiveness and safety profile of a formulation containing sodium

alginate and sodium bicarbonate named Mucosave® on GORD symptoms. 118 patients experiencing mild to moderate GORD were involved in a randomised trial. These patients were treated with Mucosave® and a placebo drug for two months. These individuals completed questionnaires before and after this two-month trial and statistical results of the scores revealed that Mucosave® significantly improved GORD symptoms in patients compared with the placebo drug. It was concluded that Mucosave® is safe and effective for the treatment of mild to moderate symptoms of GORD. [71]

A clinical trial by Yuan et al. involved the examination of GDA tablets and its efficiency on oesophageal pH after taking a meal in 44 GORD patients. These patients were randomly administered GDA or placebo drug after ingesting a reflux inducing meal, and the changes in pH were monitored. The percentage of the extent of which the pH increased above 4.0 was measured. Data from all the patients were accumulated, and the results showed significant benefits of GDA statistically. It was concluded that GDA is safe and effective for the treatment of GORD. [72]

Gaviscon® Double Action Mint Liquid, alginate-antacid) was compared with a once-daily dose of PPI treatment for suppression of reflux symptoms was studied. Two randomised trials were conducted which involved patients taking a standard dose of PPI. Gaviscon® or a placebo drug (composed of water, maltitol, xanthan gum, methyl/propyl parabens, titanium dioxide, peppermint and sodium hydroxide to match the appearance, smell, taste, viscosity and pH of Gaviscon® Double Action Mint Liquid) was added to the treatment regime and the outcomes were measured in these individuals. The results showed a significant level of suppression of reflux events in patients receiving the Gaviscon® formulation compared with the placebo. The study concluded that the placebo produced no response in patients taking PPI treatment whereas Gaviscon® reduced reflux episodes when given in combination with PPIs. [73] In a recent study by Hanif et al., the raft forming ability of a formulation containing alginates and pectin

was determined, Box Behnken design (BBD) was used to determine the response surface design. The dosage form developed for this formulation was a tablet. Characterisation of granules used to form these tablets was conducted by determining their angle of repose, bulk density, and tap density. Additionally, other physical tests were performed such as tablet thickness test, friability test, and tablet hardness test. The raft strength, volume, weight, resilience, thickness, and acid neutralizing capacity were also assessed. Floating lag time and a total floating duration of rafts were evaluated using a modified USP type II dissolution apparatus. Results showed that the formulation had a significant potential to be considered as a raft forming formulation for the treatment of GORD. [74]

The chemical characteristics of alginate rafts for good raft performance were measured to explain how the physicochemical properties of the material used in formulations have an impact on its raft-forming capability. The formulations investigated were: GDA, Gaviscon® Original, Peptac® Liquid, Algycon® tablets, Maalox® RefluRapid liquid suspension, Mylan® Liquid Suspension, and Rennie Duo® liquid suspension. This study included an analysis of alginate content by HPLC, determination of the extent of neutralisation, and the acid neutralisation profile within the rafts. Also, the effect of raft structure on acid neutralisation was also determined. Results of these analyses concluded that GDA was superior to all other competitor formulations. Moreover, GDA resulted in high porosity allowing neutralisation of gastric acid to last for longer durations. [75]

In an early invention, Withington demonstrated that a pharmaceutical liquid formulation can suppress gastric reflux. The liquid composition consisted of an aqueous medium containing 4.0-6.0% w/v of low viscosity grade sodium alginate, 2.0-3.5% w/v sodium bicarbonate, 1.2-2.0% w/v calcium carbonate and 0.6-1.2% w/v sodium salt of an acrylic polymer cross-linked with 1% allyl-sucrose. Measurement of viscosity showed that the viscosity was within the range of 3-60 centipoise. The claims included the development of a composition for the

treatment of GORD, which comprised a low viscosity grade sodium alginate, 0.16-2.60 parts by weight of sodium bicarbonate and 0.10-1.04 parts by weight of calcium carbonate. These ingredients were present according to the weight of sodium alginate. [76] In another patent, issued in 1988, Luber et al. invented a method for the preparation of a viscosity-stable antacid formulation consisting of alginic acid and antacid. The formulated product was a stable preparation, whose viscosity was stable even at high temperatures. The claims of this invention also included setting up a method for the preparation of an aqueous antacid composition that was stable even with variations in viscosities. It comprised an alginic acid salt and antacid, which affected the viscosity of this composition. Different temperatures and times were also applied to the recovery of the stable product in a form that could help in the formation of a viscosity stable antacid preparation. [77]

Davin developed a pharmaceutical suspension for the treatment of GORD, in which alginic acid was used as a raft-forming agent to serve as a physical barrier against regurgitation. Other ingredients used to prepare this suspension were aluminium hydroxide, magnesium carbonate and hydrated silica, and either xanthan gum, magnesium alginate or glycerol was used as a thickening agent. [78] A formulation comprised of ranitidine (1.25-10%), alginic acid (5-35%) and carbonate or bicarbonate (2-15%) had successfully established its treatment for GORD. [79] Similarly, an invention by Sims & Slivka claimed the application of a pharmaceutical preparation using alginates for the relief of indigestion, heartburn and GIT disorders. This formulation consisted of an H_2 antagonist (Famotidine), alginates and simethicone. [80] A patent by Mitra in 1998 included an invention for the treatment of gastrointestinal disorders. This composition included a PPI and an antacid rafting agent (aluminium hydroxide, magnesium carbonate, and alginic acid) in a potent therapeutic amount.[81] Similarly, Douglas et al. also used alginic acid as a raft-forming agent. Claims of this patent included the formation of a defensive

and protective layer on top of the gastric contents which precedes the stomach contents into the oesophagus, thus protecting the mucosa from further irritation. [82]

Field et al. invented an aqueous pourable liquid formulation for the treatment of GORD, reflux oesophagitis, gastritis, dyspepsia or peptic ulcer. This invention described the development of an aqueous pharmaceutical formulation comprised of at least 8% sodium alginate, potassium bicarbonate, carbomer, and calcium carbonate in variable amounts. Other components including sodium hydroxide, ethyl parahydroxybenzoate and any one of sodium butyl parahydroxybenzote or sodium saccharin were also present in the formulation. [83] Alginic acid was also used by Dettmar et al. for a composition to treat conditions caused by or associated with gastric reflux. These alginates were either sodium, potassium or magnesium salts, present along with a source of carbon dioxide, and a divalent or trivalent cation. [39] Eccleston & Peterson also used alginic acid for the development of a formulation capable of forming a gastric raft to treat GORD. Components of this preparation comprised alginic acid, pectin and a component that produced gas after encountering gastric acid. At low pH, a strong gel was formed by the interaction of alginates, pectin and a gas generating agent selected from either sodium or potassium salt. An active ingredient, such as an antacid, was also added to trigger the neutralisation of gastric acid. [84]

Ghisalberti et al., effectively invented a pharmaceutical formulation to treat GORD symptoms and dyspepsia in humans and other mammals. The composition comprised a combination of low and high molecular weight alginates and D-limonene (the most common terpene in nature found in several citrus oils and considered a natural remedy for acid reflux) in a micro dispersed form. It was also claimed that improvement of this combination could be achieved with the addition of an antacid. [85]

The development of a novel pharmaceutical fluid for the treatment of GORD was achieved by Hoon et al. This composition had the ability to form a floating gel with high physical strength. Alginic acid was used an active ingredient for the formation of raft to treat GORD. This liquid composition thus consisted of alginic acid, alkali metal bicarbonate or carbonate and a gel strength-enhancing agent. The gel strength-enhancing agent for this formulation was selected from either xanthan gum, guar gum, gum arabic or pectin. [86] In 2013, Kim et al. invented a pharmaceutical composition for the treatment of GORD. This pharmaceutical product was developed to provide a low-viscosity composition for oral administration for the treatment of GORD. Furthermore, the composition was designed to be easily administered, have high storage stability, and not require large amounts of synthetic preservatives. This invention detailed the formation of a stable gel, which could float on top of the stomach and thus, provide effective treatment for GORD. The claims for this study included a composition consisting of alginic acid or alginate and a gel strength enhancer. The polysaccharides used for the composition were either xanthan gum, guar gum, gum arabic, maltodextrin or pectin. The gel strength enhancer used was either an enteric polymer or a polysaccharide. The potential enteric polymers were purified shellac, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose succinate, methacrylate polymer, acrylate copolymer or acrylic acid. [87] Vasilevich et al. invented an anti-reflux raft formulation for the treatment of GORD. For raft formation, a raft-forming agent and antacid, sodium alginate, calcium carbonate, and hydroxyapatite were included in the formulation. A magnesium containing compound was selected from any one of magnesium hydroxide, magnesium carbonate or magnesium oxide preparations. The invention included the development of a pharmaceutical preparation for treating reflux symptoms and contained different mass ratios of 26.9-53.0% of sodium alginate, 7.4-18.5% of potassium bicarbonate, 20.4-40.3% of calcium carbonate, 3.1-23.5% of compounds containing magnesium and 2.0-14.2% of hydroxyapatite.[88] Madaro invented an

oral formulation for the treatment of GORD. This composition consisted of alginic acid, carbomer, tamarind extract and calcium carbonate or potassium hydrogen carbonate. The amount of alginic acid included in the most preferable formulation was 50-500 mg and had a viscosity below 2000 mPas when 10% of it is included in water. The prepared composition was able to form an effective barrier on top of stomach contents for the protection of mucosa of stomach and oesophagus. Furthermore, this preparation could be formulated as either a tablet or suspension. [89]

It has been discerned from this systematic review process that the raft characterisation (e.g. raft strength, resilience, volume and bouyancy) plays an important role in the devlopment of successful alginate antireflux formulations. Moreover, these properties depends on different factors, for example, (a) type of alginate (different mannuronic (M) and guluronic acid (G) residues ratio, M/G) (b) different formulation factors (e.g. viscosity and pH) and (c) concentration of active and inactive additives. Additionaly, it can be concluded from this review that the above mentioned factors are imprative to develop fomrulations capable of developing stronger and coherent rafts that has the ability to reduce the stimulated gastric reflux.

3.2. Pectin

Pectin is a complex polysaccharide extracted commercially from citrus peels and apple pomace. [90] The structure of pectin is displayed in Figure 3b and consists of α-1, 4-linked D-galacturonic acid, which is partly methyl esterified. Additionally, the side chain contains various neutral sugars, such as rhamnose, arabinose, and galactose. [91] ‘Smooth segments’ in the structure consist of 6-methylated, and 2- and/or 3- acetylated poly-α-(1->4)-D-galacturonic acid residues. In addition, ‘hairy segments’ are also present known as non-gelling areas of alternating α-(1->2)-L-rhamnosyl-α-(1->4)-D-galacturonosyl sections containing branch-

points with neutral side chains (1-20 residues) of mainly α-L-arabinofuranose and α-D-galactopyranose (rhamnogalacturonan I).[91] Based on the degree of esterification, pectin can be classified into two main groups: the first group is low-methoxy pectin which requires calcium to form a gel. The second group is high-ester pectin which is capable of forming gels in aqueous systems with a high content of soluble solids and low pH.[92] Both types can be used as raft-forming agents for anti-reflux formulations.[40]

Several articles have reported and successfully used pectin as a raft-forming anti-reflux agent. In 1988, Washington et al. conducted clinical trials in which a radiolabelled meal was administered to six healthy individuals. The purpose of this trial was to analyse the gastric distribution and gastric residence time of a pectin-based raft formulation, named FF5005 (mixture of pectin and casein), using gamma scintigraphy. It was revealed that the formulation showed *in-vivo* behavior similar to that of alginate containing anti-reflux formulations. [93] Havelund & Aalykke in 1997 investigated a pectin-based raft-forming formulation, Aflurax®, for its ability to reduce oesophageal acid exposure and its efficacy in maintaining GORD treatment outcomes. Acid exposure during erosive oesophagitis was determined in 14 patients. Additionally, 88 patients were treated with omeprazole to heal erosive oesophagitis. Further, two tablets of Aflurax® or placebo were administered four times daily to maintain the efficiency, and the pH was monitored every 12 hours. Aflurax® significantly delayed recurrence of moderate to severe heartburn and erosive oesophagitis. However, acid exposure was not significantly reduced in pH-metry studies. [94] Another clinical trial study investigated the effect of a Aflurax® on heartburn in patients experiencing reflux symptoms after having a heavy meal. [95] Two tablets of Aflurax® or placebo drugs were given to patients four times a day and revealed the potential of Aflurax® for use in the treatment of GORD. [95] Another study also assessed the raft forming characteristics of Aflurax®, in comparison to a placebo containing the same active drug but without pectin. [96] In a randomised trial using a modified

Rossett and Rice test, the pH of the raft remained intact above pH 3 for 130 minutes, but there was no change in the pH of the acid phase. The results also concluded that the raft formed by Aflurax® had significant anti-reflux properties by reducing the amount of food and concentration of acid in the oesophagus. [96] However, a study using esomeprazole (20mg) had shown superior results in comparison to pectin based anti-reflux formulations. [97]

Three patents utilised pectin as a raft-forming agent for anti-reflux raft formulations. A prominent feature of the formulation invented by Foldager was that it could float on top of stomach contents. Claims for this invention described a composition containing 1-50% by weight of low methoxylated pectin, 1-30% by weight of neutralising agents such as magnesium subcarbonate or potassium bicarbonate, a buffering agent, and caseinates from a group of sodium, potassium or ammonium caseinates. This formulation was invented for the treatment of GORD or the alleviation of upper GIT disorders. [98]

An anti-reflux formulation that consisted of low methoxylated pectin as a raft-forming agent and an antacid was formulated with the inclusion of carbonate, bicarbonate or subcarbonate as gas-forming agents. The antacid or acid neutralising agent could be an alkali metal or alkaline earth metal salt of sodium, potassium, magnesium, calcium, aluminium or ammonium. This product also contained a buffer substance, preferably casein or milk powder, which had the ability to become entrapped in the gel structure formed by pectin, thereby providing a prolonged period of acid buffering effect. [99]

Another invention on pectin-raft was formulated and was capable of treating GORD.[84] Components of this raft-forming preparation were alginic acid, pectin and a material capable of producing gas after coming into contact with gastric acid. The invented combination product claims the formation of strong gels at low pHs. The gel is formed by the interaction of alginates, pectin and a gas generating agent selected from either sodium or potassium salt. An active

ingredient, such as an antacid, was added in order to trigger the neutralisation of gastric acid. The formulation was stated as being suitable for oral administration in the form of tablets, capsules or powder sachets. [84]

3.3. Xanthan Gum

Xanthan gum is produced by the pathogenic bacterium, *Xanthomonas campestris* by aerobic fermentation and is widely used as a stabiliser for an extensive variety of suspensions, emulsions, and foams. [100,101] Xanthan is made up of cytoplasmic sugar nucleotides, acetyl CoA, and phosphoenolpyruvate. [102] The structure of xanthan gum is displayed in Figure 3c and consists of repeated pentasaccharide units formed by two glucose units, two mannose, and one glucuronic acid unit, in the molar ratio 2.8:2.0:2.0. [103] The bio-adhesive and protective properties of xanthan gum in the oesophageal mucosa have proven to be beneficial for GORD treatment. [39]

One patent claiming raft-forming characteristics of xanthan gum has been included in this review. A composition containing antacid, which could form a gel-like floating layer in aqueous acid was described. This antacid composition consisted of a suitable amount of xanthan gum to form a stable raft while allowing the suspension to remain pourable (approximately 0.01 wt.% to 4 wt.%), as well as hexitol-stabilised aluminium hydroxide in a sufficient amount to neutralise stomach acid (approximately 0.05 wt.% to 6.0 wt.%). A gas-forming agent was also present which generated non-toxic gas when it was exposed to aqueous acid, causing the gelatinous mass to float. [104]

3.4. Isapghula husk/ fibers

Isapghula *(Plantago ovata)* husk is a natural fibrous polysaccharide well-known for its laxative properties. Dispersion of isapgol husk in water forms a swollen gel-like mass in an acidic environment.[105] There is only a single study conducted to date on the use of raw isapghula

husk/fibers as a raft-forming agent. A raft-forming antacid suspension, prepared with the use of isapgol was described, and its neutralisation profile was evaluated. Isapghula was used as a raft-forming agent together with sodium bicarbonate, and aluminium hydroxide and formulations were tested for their acid neutralisation properties and raft strength. The authors concluded that raw isapgol husk had the potential to be used for the formation of a raft-forming antacid suspension, although extensive clinical trials need to be conducted. [106]

4- Conclusions

This comprehensive systematic review has identified four polysaccharide polymers currently being used or with the ability to be used to develop raft-forming formulations for the treatment of GORD, with alginates being by far the most widely studied. A significant number of studies and patents dating back to 1979 have led to alginates being established as the leading raft-forming agent used in raft-forming anti-reflux formulations today. However, considerable variations in the efficacy of alginate-based raft-forming formulations have been reported and may be due to multiple factors including the type of alginate material used, formulation of the alginate-based anti-reflux product, the addition of excipients and active additives-co-medication. Other polymers identified in this review are pectin, xanthan gum and isapghula husk/fibers. Although these demonstrated raft-forming abilities and displayed potential to be used as raft-forming agents in anti-reflux formulations, their current use is considerably limited as they are not widely studied specifically for GORD. Moreover, it can be concluded from this comprehensive systematic review that a thorough assessment of raft-forming formulations (e.g. raft strength, resilience, volume and buoyancy), type and concentration of used active and inactive materials and different formulations factors (e.g. viscosity and pH) are essential for the development of successful anti-reflux raft forming formulations.

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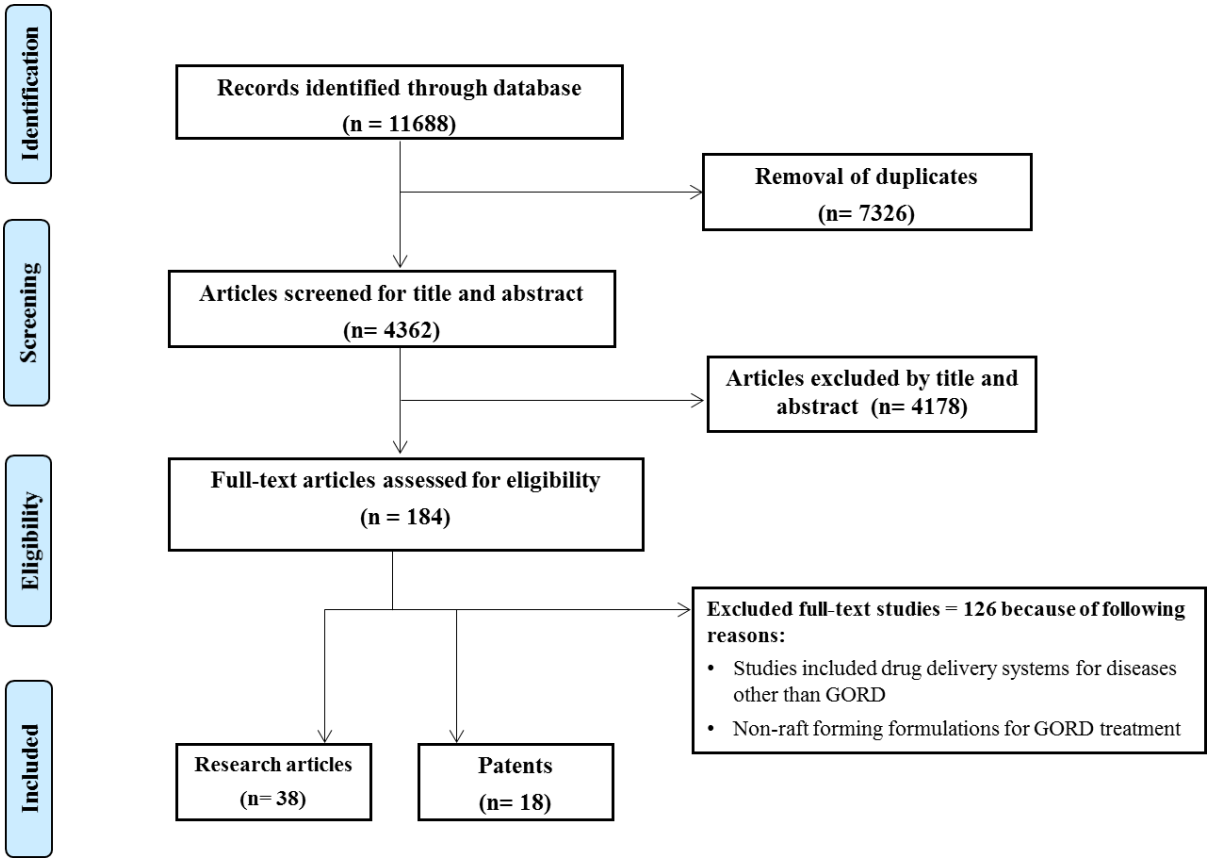

Figure 1, Flow chart illustrating the literature search according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

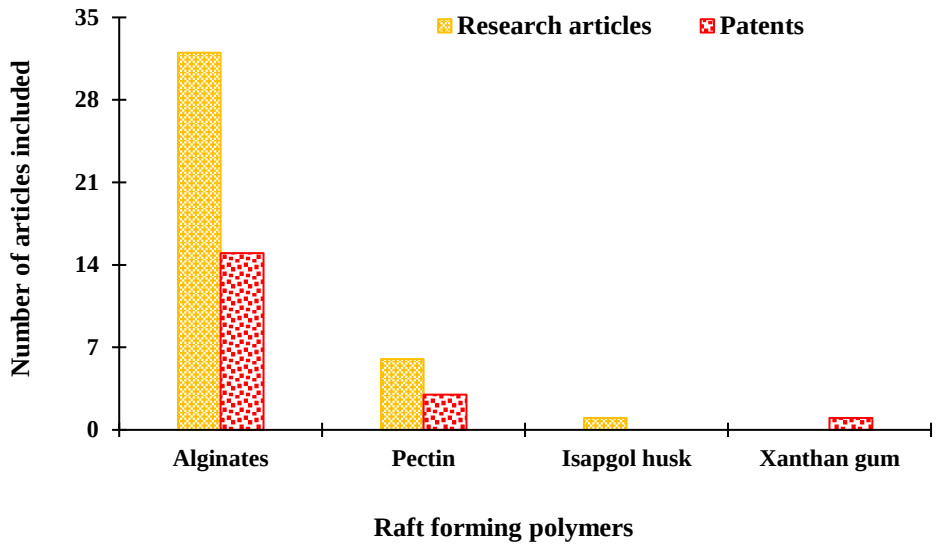

Figure 2, Bar chart indicating the number of articles and patents included in this systematic review

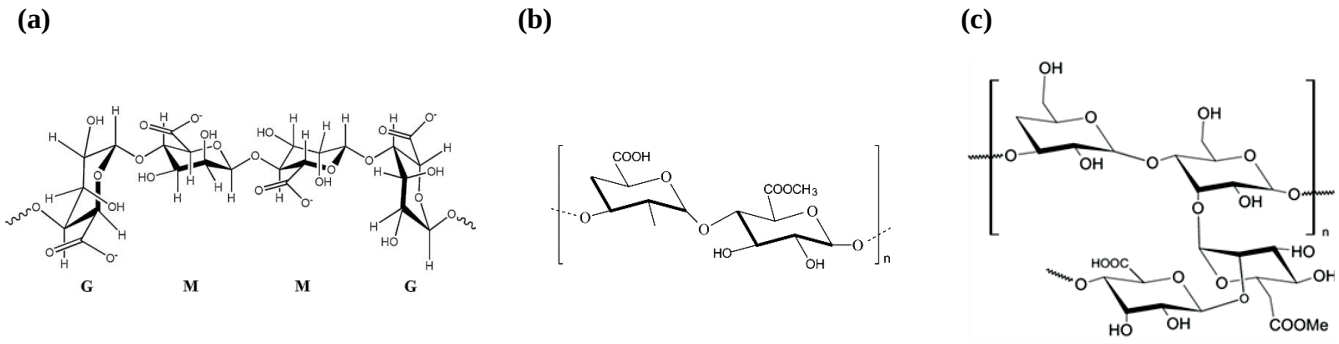

Figure 3, Chemical structure of (a) alginate (*G is guluronic acid unit and M is mannuronic acid unit),* (b) pectin and (c) xanthan gum *(Me = - CH3)*

Table 1, Criteria used for the quality assessment of studies included in this systematic review.

Quality rank	Description
***	The selected studies in the report were considered unbiased and were included with full confidence considering the described method, results, discussion and conclusions.
**	The selected studies in the report were considered unbiased and were included with a reasonable confidence considering the described method, results, discussion and conclusions.
*	The selected studies in the report were considered unbiased and were included with some minor issues considering the described method, results, discussion and conclusions.

Table 2, Summary of quality assessment of articles included in the systematic review.

Reference	Quality	Reference	Quality
44	***	67	***
45	**	66	***
47	***	93	***
50	***	62	***
51	***	53	***
52	***	49	***
54	***	55	***
57	**	69	***
58	***	59	**
60	***	70	***
63	***	106	**
64	***	33	***
65	**	96	***
68	**	48	***
71	***	72	***
73	***	56	***
74	**	46	***
75	***		
94	***		
95	***		

97 ***

Table 3, Summary of quality assessment of articles included in the systematic review

Reference	Quality	Reference	Quality
39	***	86	***
76	***	87	***
77	***	88	***
78	***	89	***
79	***	98	***
80	***	99	***
81	***	104	***
82	***		
83	***		
84	***		
85	***		

Table 4, Summarised characteristics of included research articles

Study design	Raft forming polymer	Aim(s)	Conclusion(s)	Reference
Randomised double-blind trial	Alginate	To determine the effectiveness and safety profile of GDA in the reduction of heartburn and acid regurgitation in patients experiencing mild to moderate GORD.	Data was accumulated after collecting questionnaires from patients who were given GDA or placebo drug before and after a randomised clinical trial. Statistical results concluded that GDA was effective and had a suitable safety profile in treating GORD patients.	33
Physicochemical characterisation	Alginate	Study of the mechanism by which alginic acid compound (AAC) reduced gastroesophageal reflux (GOR) index.	Gamma scintigraphy demonstrated that AAC formed a viscid barrier on top of stomach acid, which helps in the relief of GORD symptoms.	44
Formulation based study	Alginate	Evaluation of the effects of alginate molecular structure on raft strength and its dimensions.	Texture analyser was used to measure raft breaking strength. The results concluded that stronger rafts were formed when the molecular weight of alginate is low and guluronic acid content is high.	45

Formulation based study	Alginate	Inspection of gastric pH changes and the strength of raft formed after inclusion of aluminium hydroxide in an alginate based antacid raft formulation.	The outcomes concluded that efficacy of GORD treatment and raft strength decreased. Aluminium hydroxide remained trapped in the raft.	46
Balanced, cross over study	Alginate	Evaluation of gastric residence time and extent of suppression of acidity by alginate rafts in patients who were pre-treated with omeprazole.	Gamma scintigraphy was carried out in patients who were given alginate tablets, either in the presence or absence of omeprazole pre-treatment. Results obtained after this trial showed pre-treatment with omeprazole had no effect on the raft forming ability of alginate.	47
Physicochemical characterisation study	Alginate	Using pH telemetry, measurement of the *in-vivo* pH-time profile of two antacid formulations, Asilone® suspension and Gaviscon® liquid, was conducted.	The results of this experiment were compared with Rossett and Rice (1954) test. This test gave poor results in *in-vivo*. Although, *in-vitro* test was improved to set its comparison parameter with the *in-vivo* test for both selected anti-reflux formulations.	48

Physicochemical characterisation study	Alginate	Analysis of four different globally accepted formulations of GA for examination of their raft strengths and pH-time profiles.	The Rossett and Rice (1954) test was conducted. It was concluded that all of the formulations had different capacities to neutralise gastric acid and different raft breaking strengths. Although, addition of antacid into GA had reduced the neutralisation capability and raft breaking strength of the formulation.	49
Randomised clinical trial	Alginate	To test the hypothesis that alginic acid relieves reflux symptoms in the upright position more efficiently than in supine position.	Administration of a combination of alginic acid and antacid, given after a heavy meal, relieved symptoms in GORD patients more efficiently in the upright position compared with supine position.	50

Randomised clinical trial	Alginate	In a randomised clinical trial, the efficacy of cisapride and Gaviscon plus Carobel was investigated	The data showed that cisapride was not as effective at treating GORD compared with Gaviscon plus Carobel administration.	51
Physicochemical characterisation study	Alginate	Evaluation of the applicability of the creep viscometry method for categorisation of features such as, raft strength of alginate-antacid tablets.	Curves obtained as a result of creep viscometry displayed raft strength of these formulations. These parameters showed that creep viscometry could be used for evaluation of different properties of rafts or other gel forming formulations.	52
Randomised single-blind cross-over study	Alginate	Comparison of an alginate based conventional anti-reflux formulation (Gaviscon) with a combination of alginate and antacid (Algitec).	Radio-labelled meals were given to patients along with either Gaviscon or Algitec. A pH electrode and gamma detector were fitted into the oesophagus to determine any changes by either drug. Outcomes showed that Gaviscon was significantly more involved in the	53

			reduction of reflux symptoms compared with Algitec.	
Physicochemical characterisation study	Alginate	Image analysis was used to examine dimensions of bubbles formed in alginate rafts along with assessing other features of these alginate rafts.	Perimeters, areas and mean diameters were measured, and results of these studies showed that there is a relation between bubbles formed in alginate rafts and their viscosity.	54
Unblind two way crossover study	Alginate	Comparison of Topaal Whip with Liquid Gaviscon. Evaluation studies included assessing the gastric distribution and gastric residence time of these formulations.	Gamma scintigraphy was used to measure gastric distribution and gastric residence time of these formulations. Results showed that Topaal Whip was very effective as an anti-reflux formulation.	55
Cross-sectional study to study physicochemical characterisation	Alginates	Assessment of acid and non-acid reflux into the oesophagus before and after administration of GA.	It was concluded by the findings that Gaviscon Advance reduces reflux events and decreases the reflux of gastric contents in the oesophagus.	56

Physicochemical characterisation study	Alginates	Estimation of different liquid products in raft formation by evaluation of properties like raft strength, coherence, voluminosity and buoyancy.	The experimental results showed that, products had a higher acid neutralising capacity (ANC) and free of calcium ions acted as weaker rafts. These formulations appeared as precipitates instead of forming gels. Liquids with a high ANC along with calcium ions formed rafts having average strength and volume. Products which had low ANC resulted in formation of strong rafts having medium or large weight. Liquids having low ANC and a calcium ion formed the strongest rafts.	57
Randomised clinical trial	Alginates	Comparison of the effectiveness of sodium alginate with magaldrate anhydrous (antacid) in relieving reflux symptoms in GORD patients.	Results of a randomised clinical trial showed that, sodium alginate had longer duration of action and extent to which it relieved reflux	58

			symptoms when compared to antacid.	
Physicochemical characterisation study	Alginates	Investigation of the impact of GA in protecting the oesophagus from the hazardous effects of pepsin and other bile acids.	*In-vitro* methods along with a calorimetric technique were employed to examine the effects of GA in protecting the oesophagus from gastric acid. Results showed that GA had a significant role in controlling reflux symptoms and protecting oesophagus from damage caused by gastric juices.	59
Physicochemical characterisation study	Alginates	Comparison of the effectiveness of alginate suspension and alginate-antacid suspension, *in-vivo* and *in-vitro*.	Raft strength and resilience of rafts was measured using a texture analyser. Results of these tests showed that the formulation containing alginate-antacid had significant dominance on alginate rafts, both *in-vivo* and *in-vitro*.	60

A pilot crossover Study	Alginate	Assessment of the potency of sodium alginate in relieving GORD in preterm infants.	Clinical trial in preterm infants and evaluation of results via pH-metry showed that a significant percentage of infants reduced GORD symptoms after administration of sodium alginate.	62
Randomised clinical trial	Alginate	Estimation of the effect of sodium alginate in new-borns suffering from GORD.	Sodium alginate decreased acid reflux in new-borns whereas no effect on non-acid reflux was witnessed.	63
Randomised controlled trial	Alginate	Evaluation of the effectiveness of sodium alginate, in reducing the intensity of GORD related apnoea.	Multichannel impedance, polysomnography and pH-metry in selected GORD patients showed that reflux symptoms were reduced with sodium alginate administration.	64

Cross-sectional study	Alginate	To examine the capability of an alginate-antacid formulation named Gaviscon Double Action Liquid (GDAL), in acid neutralisation and acid pocket displacement.	In a randomised clinical trial, patients were given GDAL 20 minutes after their meal. pH monitoring, manometry and fluoroscopy studies were performed. Results of this experiment showed that post prandial administration of GDAL eliminated or displaced the acid pocket in GORD patients.	65
Randomised clinical trial	Alginate	Comparison of short term efficacy of Gaviscon with omeprazole in treatment of GORD symptoms in a clinical setup.	Statistical analysis of the clinical trial data showed that Gaviscon had similar results to omeprazole, achieving relief of heartburn for a duration of 24 hours. Hence, it could be considered as an efficient treatment for GORD symptoms.	66
Randomised controlled double-blind study	Alginate	Evaluation of the efficiency of two formulations in which one is an alginate-based raft formulation (GA) and the other	Magnetic resonance imaging (MRI) and pH monitoring was carried out. Alginate based formulations of GA significantly reduced reflux	67

		is a non-raft-forming anti-reflux formulation in the treatment of GORD.	symptoms by forming a barrier on top of the stomach contents and proved to be better than the non-raft-forming antacid formulation.	
Randomised clinical trial	Alginate	To determine the effectiveness and safety of sodium alginate suspension and omeprazole was compared in non-erosive reflux disease (NERD) patients.	After a randomised trial and statistical evaluation of data, it was concluded that both omeprazole and sodium alginate suspension are equally effective at treating NERD.	68
Double-blinded Randomised clinical trial	Alginate	Comparison of the effectiveness of two formulations in which one was Gaviscon Double Action (GDA) and the other was an antacid, in controlling postprandial acid reflux symptoms in GORD patients.	Manometry and pH monitoring was carried out in patients who received two formulations. It was concluded that GDA was significantly more effective at controlling reflux symptoms that occur after consumption of a heavy meal.	69
Randomised placebo-controlled clinical trial	Alginate	Assessment of addition of an alginate based formulation, named Gaviscon Advance (GA) in the treatment regime of patients who are already taking	Patients were included in a randomised trial and these patients received either a placebo or GA formulation. Results of this data showed that addition of GA in these	70

		PPIs for suppression of reflux symptoms.	patients taking PPI therapy further decreased the frequency of GORD symptoms in these patients.	
Double-blinded randomized-controlled study	Alginate	Testing the safety and efficiency of a pharmaceutical formulation, Mucosave®, on symptoms of gastric reflux. This formulation includes sodium alginate and sodium bicarbonate.	Administration of Mucosave® for two months in GORD patients who completed mquestionnaires to investigate the effect of this formulation. Evaluation of their statistical data showed that Mucosave® significantly benefited GORD patients.	71
Randomised clinical trial	Alginate	To analyse post-prandial effects of Gaviscon tablets on pH of the oesophagus in Chinese GORD patients.	Findings gathered data suggested that Gaviscon Double Action tablets were suitable for the treatment of GORD symptoms.	72
Randomised clinical trials	Alginate	Assessment of the effects of addition of Gaviscon to PPI therapy for the reduction of reflux symptoms.	The outcomes showed that no change in the condition of patients receiving placebo drug was seen. Whereas, Gaviscon significantly	73

			suppressed reflux episodes when given in combination with PPI drug.	
Physicochemical characterisation study	Alginates Pectin	To formulate and investigate the effectiveness of an alginate and pectin based raft formulation by using examining different aspects of this formulation.	Raft strength, raft volume, raft weight, raft resilience, raft thickness and acid neutralising capacity of the raft composition concluded that the developed formulation had a significant capacity to be used as a treatment for GORD.	74
Physicochemical characterisation study	Alginate	To estimate the chemical characteristics of alginate rafts for good raft performance and to study how a formulation leaves an impact on its chemical features.	Alginate contents, extent of acid neutralisation, and acid neutralisation profile was examined with the use of high-performance liquid chromatography (HPLC). Analysis of the effect of raft structure on the acid neutralisation profiles was also done. Obtained results showed that GDA was superior to all other competitor formulations.	75

Physicochemical characterisation study	Pectin	Assessment of gastric distribution and gastric residence time of an anti-reflux formulation containing pectin as a raft-forming agent.	Results of gamma-scintigraphy showed that the pectin based anti-reflux formulation was effective at reducing reflux symptoms. Moreover, properties of this formulation were similar to that of alginate based raft formulation.	93
Double blind randomized placebo-controlled clinical trials	Pectin	Inspection of the capability of a pectin-based raft-forming anti-reflux formulation named Aflurax®, in reducing reflux episodes. In addition, the extent to which this formulation maintains GORD treatment was also quantified.	Results of 12-hr pH monitoring in patients receiving Aflurax® or placebo drug were evaluated. It was concluded that Aflurax® efficiently maintained treatment outcomes in patients experiencing moderate to severe GORD.	94
Double-blind randomized clinical trials	Pectin	Observation of effects of a pectin based anti-reflux raft formulation, Aflurax®, in patients experiencing moderate to severe heartburn after consuming a heavy meal.	After a statistical evaluation of the outcomes of the randomised trial with Aflurax®, reduced symptoms of heartburn in patients who experienced severe GORD	95

			symptoms immediately after having a high fat meal was perceived.	
***In-vivo* and *in-vitro* study**	Pectin	Examination of two formulations used to suppress reflux symptoms. One formulation (Aflurax) contained pectin whereas the other did not.	Rossett and Rice test was performed for these two formulations. Results concluded that, in *in-vitro* conditions, Aflurax had a greater raft strength.	96
Randomised controlled trial	Pectin	Comparison of effects of pectin based raft formulations with esomeprazole in patients experiencing mild to moderate GORD.	Results of these outcome measures concluded that esomeprazole was more effective at relieving reflux symptoms in GORD patients.	97
Physicochemical characterisation	Isapgol	Description of an anti-reflux raft formulation was provided with the use of isapgol husk as a raft forming agent and pH-time profile of these formulations was evaluated.	By using the Rossett and Rice method, *in-vitro* and *in-vivo* examination of the anti-reflux formulation using isapgol husk as raft forming agent was carried out. Results and comparison of these anti-reflux formulation with standard formulation of alginate-antacid showed that isapgol is a	106

		successful candidate to use as a raft forming agent for suppression of reflux symptoms

Table 5, Summarised characteristics of included patents

Patent number	Number of family patents	Raft forming polymer	Summary of claim(s)	Summary of invention(s)	Reference
DE60023873	WO2000067799 GB9910212 ES2251997 CA2371031 CN1173743 JP2002544176 EP1614431 US6610667	Alginate	Claims included formation of a preparation that comprised alginates, xanthan gum and carrageenan gum for the treatment of lesions, irritation of the oesophagus and other troublesome reflux symptoms. An active ingredient could also be incorporated from any of the group of acid neutralising agents, anti-ulcer disease, anti-nausea agents etc. The compositions claimed for such formulation consisted of 0.1-8 parts by weight of alginate, 0.001-3.0 parts by weight of gum selected from a galactomannan.	A pharmaceutical composition containing alginate, xanthan gum and carrageenan in certain proportions for the treatment of irritation in the oesophagus, throat, stomach or other reflux symptoms.	39

US4140760	JPS646172 BE858003 CA1083964 DE2738014 FR2369843 GB1524740 NL188892	Alginate	Pharmaceutical composition for the suppression of gastric reflux was claimed. This liquid product consisted of sodium alginate of low viscosity grade, 0.16-2.6 parts by weight of sodium bicarbonate, 1.2-2.0 % w/v of calcium carbonate and 0.10-1.04 parts by weight of the calcium carbonate. The claimed ratios of sodium bicarbonate and calcium carbonate were taken per part by weight of sodium alginate.	A pharmaceutical liquid formulation was invented which could be used for the treatment of GORD. The main ingredients present in this formulation were sodium alginate, sodium bicarbonate and calcium carbonate in fixed ratios.	76
US4744986	EP0297109 JPH07103039 CA1283360 DE3751478 WO1987005217	Alginate	Formation of an aqueous antacid preparation was stable at various viscosity conditions. This product consisted of alginic acid and an antacid, mainly aluminium salt and prepared under a variety of temperatures and time durations.	Invention consisted of the development of a formulation that was viscosity stable and comprised of alginic acid and an antacid. The preparation was stable even at different temperature variations.	77

EP0506563	DE69201077 EP0506563 FR2674437 ES2067302 DK0506563	Alginate	Composition of a formulation for GORD contained alginic acid, aluminium hydroxide, magnesium carbonate, hydrated silica and xanthan gum, and magnesium alginate or glycerol as thickening agents.	The formulation of a pharmaceutical suspension consisted of 2-7% (w/v) alginic acid, 1.5-7% (w/v) sodium bicarbonate and any one of xanthan gum, magnesium alginate and glycerol for promotion of viscosity of the formulation. This suspension had the ability to treat GORD.	78
US5456918	JPH0482832 BE1002406 CA1327748 DE3931215 FR2636532 GB2222772 NL8902338	Alginate	Composition of a formulation was claimed which had a significant role in the treatment of GORD. This preparation consisted of 1.25%-10% w/w of ranitidine, 5%-35% w/w alginate component and 2%-15% w/w of sodium bicarbonate or potassium bicarbonate. An antacid was also selected from any one of, aluminium hydroxide, magnesium trisilicate, to be added in this formulation .	The invention consisted of ranitidine, alginic acid and carbonate or bicarbonate. The composition was in the form of a capsule or tablet. It was suitable for the treatment of GIT disorders and reflux oesophagitis.	79

WO1995001780		Alginate	Design of a pharmaceutical composition was claimed for the treatment and relief of indigestion, heartburn and other GIT disorders. It consisted of 5-40 mgs H_2 antagonist (Famotidine), 200-500 mgs alginates and 20-40 mgs simethicone optionally.	Components with formulation of H_2-antagonist, alginates and simethicone successfully treated and gave relief to indigestion, heartburn and other GIT related disorders.	80
WO1998023272	JP2001509791	Alginate	Making of a PPI and antacid raft-forming agent resulted in the treatment of gastrointestinal disorders. This formulation consisted of alginic acid, aluminium hydroxide and magnesium carbonate	A formulation with PPI, alginic acid and an antacid resulted in the treatment of gastrointestinal disorders.	81
KR20010020438	WO1998048814 CA2288743 CN1286468 JP2001522368 EP1842544	Alginate	Formation of a protective barrier on top of gastric muscosa was claimed. This film had the ability to form a floating raft. Formation of this raft was facilitated in the	A composition was invented that contained alginates or alginic acid. This composition was applicable for the formation of a protective film on the gastric mucosa. Presence of an average	82

	US6395307		presence of mannuronic and guluronic acid, which formed a raft after coming in to contact with gastric acid. This film consisted of 10-90% carbonate and alginates or 90-10% alginic acid. It also comprised of 1-10%, 2-10%, 2.5-8% or ideally 4-6% alkali metal bicarbonate, polyvalent metal ion, preferably calcium or aluminium.	ratio of mannuronic acid residues and guluronic acid residues was evident in this formulation. This product also comprised of a known concentration of sodium carbonate and alkali metal bicarbonate.	
US5681827	EP0813407 JPH11501044 CN1123337 DE69621785 ES2174054 WO1996027368 EP0813407	Alginate	Formation of a pharmaceutical preparation suggested the treatment of reflux oesophagitis, gastritis, dyspepsia and peptic ulcer. This preparation consisted of sodium alginate, potassium bicarbonate, carbomer and calcium carbonate, in different compositions. It also comprised of any one of sodium hydroxide, ethyl parahydroxybenzoate, sodium butyl	An aqueous pharmaceutical composition was disclosed that consisted of 8% sodium alginate, potassium bicarbonate and carbomer for the treatment of gastrointestinal distress and reflux oesophagitis.	83

			parahydroxybenzote or sodium saccharin.		
WO2003037300	US20050063980 EP1441694 JP2005507409	Alginate Pectin	Formation of gels caused by the interaction of alginate and pectin, gas producing material preferably sodium or potassium bicarbonate in the presence of an antacid for effective neutralisation of gastric acid was claimed. Composition of this formulation comprised of 50-500mg and 2-20 % wt. alginic acid, 5-500mg and 2-20 wt % pectin, 50-500 mg or 2-20 wt. % bicarbonate of alkali along with antacid.	The formation of a gastric raft composition for the treatment of GORD consisted of alginic acid, pectin and a gas producing material capable of producing a non-toxic gas after coming in to contact with aqueous acid	84
WO2010092468		Alginate	Use of combination of alginates and micro dispersed d-limonene in the treatment of GORD. Composition claimed includes 250-500 mg or 300-400mg high and low molecular weight	Formation of pharmaceutical compositions to treat and relieve GORD symptoms and dyspepsia in mammals including humans. The composition consisted of a combination of low and high molecular weight	85

			alginates, 100-500mg or 200-300mg d-limonene, 150-1500mg or 250-1000mg antacids, alkali metal carbonate or bicarbonate or aluminium hydroxide.	alginates and d-limonene in micro dispersed form. The combination could be further improved with addition of an antacid.	
WO2012128520	KR20120108218	Alginate	Claims included preparation of a formulation containing alginic acid as an active ingredient for treatment of GORD. Gel strength enhancing agent for the formulation was selected from either xanthan gum, guar gum, gum arabic or pectin. This liquid composition thus consisted of alginic acid, alkali metal bicarbonate and a gel strength enhancing agent.	A pharmaceutical novel liquid was developed with the ability to form a floating gel with a high structural strength that could be administered orally.	86
WO2013187720	KR101417287	Alginate	A composition with alginic acid or alginate and a gel strength enhancer was prepared. Gel strength enhancer was either an enteric polymer or	Formation of a pharmaceutical composition for the treatment of GORD was invented with a novel liquid composition that improved the ease of administration, simplified the	87

			polysaccharide. Enteric polymer could be purified shellac, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose succinate, methacrylate polymer, acrylate copolymer, acrylic acid etc. Polysaccharide used for the composition was either xanthan gum, guar gum, gum arabic, maltodextrin or pectin	manufacturing process, enabled sterilization and formed a floating gel of structurally superior strength enabling treatment of GORD.	
EP2806880	WO2013111077	Alginate	Claims included the invention of a pharmaceutical composition for anti-reflux antacids containing sodium alginate and calcium carbonate, which additionally comprised of potassium bicarbonate, compounds having magnesium and hypoxyapatite in the fixed ratio of their percentage mass.	Development of pharmaceutical composition for performing functions similar to anti-reflux antacid drugs. This formulation consisted of sodium alginate, calcium carbonate and hydroxyapatite.	88

EP3184115		Alginate	Claims included formation of an oral composition for the treatment of GORD. This formulation comprised tamarind extract, alginic acid, carbomer, carbonate or hydrogen carbonate. Composition consisted of 25-900 mg per dosage unit of alginic acid but 50-500 mg concentration was most preferable.	Pharmaceutical composition was invented to treat conditions such as, rapid relief of GORD, inflamed tissues and for the prevention of the formation of insoluble deposits which caused obstruction of the oesophagus.	89
US5068109	EP0286085 JP2710375 CA1319106 DE3872560 DK179687 ES2033977 WO1988007862	Pectin	Formation of an antacid composition comprising 1-50% by weight of low methoxylated pectin was claimed. This preparation also included 1-30% by weight of neutralising agent such as magnesium subcarbonate or potassium bicarbonate, and a buffering agent.	The inclusion of pectin in the composed antacid displayed floating properties and reduced the symptoms of GORD or for alleviation of upper GIT disorders.	98

DK169122		Pectin	Formation of an antacid preparation having an acid neutralising agent that has the ability to become entrapped in the gel formed by pectin was claimed.	Invention included development of an antacid preparation containing pectin and acid neutralising agent such as antacid. Antacid had the capability of becoming trapped in the gel structure of pectin at acidic pH. This formulation formed a gel or foam on contact with an acid and a gas-forming agent such as, carbonate, bicarbonate or subcarbonate.	99
US5360793	EP0626168 JPH06340534 CA2123534 DE69423812 ES2145092	Xanthan Gum	This patent claimed the development of a composition for the treatment of gastric reflux. The formulation comprised of 0.5-6.0; wt % aluminium hydroxide, 0.1-1.8 wt% xanthan gum, 0.1-1.8 wt% carbonate ions, 5-50 wt%	Invention comprised formulation containing antacid, which had the ability to form a gel-like floating layer after coming in to contact with aqueous acid. This antacid composition included xanthan gum as an active ingredient, aluminium hydroxide as an antacid and a gas forming agent that	104

	bulking agent, water, preservatives and colorant.	generated non-toxic gas when it came in to contact with aqueous acid