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RESEARCH ARTICLE



## A comparative study on the raft chemical properties of various alginate antacid raft-forming products

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### ABSTRACT

**Objective:** Research to measure the chemical characterization of alginate rafts for good raft performance and ascertain how formulation can affect chemical parameters.

**Significance:** A selection of alginate formulations was investigated all claiming to be proficient raft formers with significance between products established and ranked.

**Methods:** Procedures were selected which demonstrated the chemical characterization allowing rafts to effectively impede the reflux into the esophagus or in severe cases to be refluxed preferentially into the esophagus and exert a demulcent effect, with focus of current research on methods which complement previous studies centered on physical properties. The alginate content was analyzed by a newly developed HPLC method. Methods were used to determine the neutralization profile and the acid neutralization within the raft determined along with how raft structure affects neutralization.

**Results:** Alginate content of Gaviscon Double Action (GDA) within the raft was significantly superior ( $p < .0001$ ) to all competitor products. The two products with the highest raft acid neutralization capacity were GDA and Rennie Duo, the latter product not being a raft former. Raft structure was key and GDA had the right level of porosity to allow for longer duration of neutralization.

**Conclusion:** Alginate formulations require three chemical reactions to take place simultaneously: transformation to alginic acid, sodium carbonate reacting to form carbon dioxide, calcium releasing free calcium ions to bind with alginic acid providing strength to raft formation. GDA was significantly superior ( $p < .0001$ ) to all other comparators.

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Alginate; antacid; formulation; chemical characterization; raft structure; acid pocket; neutralization

### Introduction

Gastroesophageal reflux disease (GERD) is a common disease affecting up to 40% of the population in the Western countries [1]. Various medication options are available for consumers to treat reflux, and one of the options is alginate reflux suppressants which have been used in the treatment of GERD for more than 40 years [2].

Alginate-based formulations offer rapid symptom relief, making them the best option for on-demand treatment [3]. Alginate-based products fall into two main categories, those containing alginate as the principle active agents and those that in combination with the alginate also contain a significant amount of antacid. In terms of the alginate component, this can be present as any salt of alginate, typically sodium alginate and magnesium alginate as well as alginic acid [4].

Previously reported *in vitro* raft characterization papers [4,5] have been based on the measurement of the physical properties of the raft such as raft strength, raft resilience, and raft volume. However, what has been missing from the literature are publications describing the chemical characterization of these buoyant and voluminous rafts which allow the raft to effectively impede the reflux into the esophagus or in severe cases to be refluxed preferentially into the esophagus and exert a demulcent effect. This paper presents a new direction to the *in vitro* characterization of the alginate raft. The chemical characterization of the rafts in combination with the physical characterization contributes to a

better understanding of how differently formulated products can affect key chemical properties of the rafts that are relevant to the mode of action of these products.

The aim of this research was to measure relevant chemical characteristics of the alginate rafts that are useful as additional indicators for good *in vivo* raft performance, and highlight how the formulation can affect these parameters. New *in vitro* methods were developed to facilitate the chemical characterization.

The methods developed utilize physiological conditions in terms of gastric and acid pocket pH [6,7], and acid pocket size [8,9]. The term postprandial acid pocket was first described by Fletcher et al. in 2001 [8] and since these early studies, the acid pocket has been well established and investigated by many groups [10]. Fletcher et al. demonstrated through pull-through pH studies that a pocket of acid at the gastroesophageal junction that escaped the buffering effect of meals remained highly acidic (median pH 1.6) [8].

The choice of the products included in this research was based on the selection of alginate raft-forming products. This included similar formulations in terms of the content of the active ingredients, formulations with different alginate/antacid ratio where the antacid component is significantly greater, and finally an alginic acid-based product. All products selected are claimed as proficient raft formers by their manufacturers.

The chemical parameters studied as part of the current research are as follows: (i) alginate content within the raft, as a

measure of drug release characteristics and availability of the active in the site where it is needed, the raft; and (ii) neutralization profile of the raft as a measure of the capacity for the raft to act as a reservoir of antacid and provide sustained protection against acid. As complementary data, the following parameter has also been studied: (iii) raft structure effect on the neutralization capacity of the raft as a measure of the availability of the antacid trapped within the raft to be utilized.

The results generated from this work show that Gaviscon Double Action (GDA) liquid offers a superior *in vitro* performance than the other products tested in terms of drug utilization and acid neutralization capacity (ANC).

## Materials and methods

### Materials

Alginate antacid products investigated were as follows: GDA and Gaviscon Original (GO) (RB, Slough, UK), both liquid format, Peptac liquid (Pinewood Laboratories Limited, Clonmel, Ireland), Algycon tablets (American Taiwan Biopharma, Bangkok, Thailand), Maalox RefluRAPID (Sanofi-Aventis, Gentilly, France) liquid suspension, Mylan liquid suspension (Mylan, Pennsylvania, USA), and Rennie Duo (Bayer, Leverkusen, Germany) liquid suspension. GDO, GO, Peptac, Maalox, and Mylan had maximum dose of 20 ml, Rennie had maximum dose of 10 ml, and for Algycon, maximum dose was three tablets resulting in active doses as presented in Table 1.

### Methods

#### Alginate content within the raft tested at pH 1.0

Rafts were formed by adding the manufacturer's maximum recommended dose, which in the case of GDA, GO, Peptac, Maalox, and Mylan was 20 ml, Rennie was 10 ml, and Algycon was three tablets (which were ground with 10 ml of deionized water), to a plastic beaker containing 70 ml of media (previously equilibrated to 37 °C). The media contained 1 mg/ml pepsin, 2 mg/ml sodium chloride, and 0.1 M hydrochloride acid (HCl) (pH 1.0) to form rafts close to *in vivo* conditions. Each raft was maintained at 37 °C for 30 min using a water bath. After 30 min of raft development, each raft was washed with deionized water three times and all floating raft pieces were removed into a centrifuge tube. Deionized water at 4 °C was added to each tube to a final fill of 40–45 ml and shaken using a linear shaker at 250 rpm for 1 min. The tubes were then centrifuged at 4000 rpm for 3 min and the supernatant was

**Table 1.** The products and their active ingredients evaluated in the present study.

Product	Active ingredients listed	(mg/maximum dose)
Gaviscon Double Action	Sodium alginate	1000
	Calcium carbonate	650
	Sodium bicarbonate	426
Gaviscon Original	Sodium alginate	1000
	Sodium bicarbonate	534
	Calcium carbonate	320
Peptac	Sodium alginate	1000
	Sodium bicarbonate	534
	Calcium carbonate	320
Algycon	Alginic acid	600
	Al(OH) <sub>3</sub>	90
	Magnesium carbonate	120
Maalox RefluRAPID	Sodium alginate	500
	Calcium carbonate	164
Mylan liquid suspension	Sodium alginate	1000
	Sodium bicarbonate	534
Rennie Duo	Calcium carbonate	1200
	Sodium alginate	300
	Magnesium carbonate	140

removed. This process was repeated twice. Ethanol at 4 °C was added to the tubes and centrifuged at 4000 rpm for 3 min, repeating twice. The raft was placed into a 40 °C oven to dry to a constant weight (2 days minimum) and the dried raft mass (g) was calculated.

Sodium alginate content within the raft was analyzed by HPLC. A series of standards using the laboratory working standard sodium alginate were prepared at concentrations of 0.2 mg/ml, 0.5 mg/ml, 0.8 mg/ml, 1.0 mg/ml, and 1.5 mg/ml. Each standard was made with pH 8.0 phosphate buffer and centrifuged at 4000 rpm for 15 min. Each whole dried raft was ground into a fine powder and prepared with 5 ml of pH 8.0 phosphate buffer in a volumetric flask and sonicated for 30 min at 37 °C. The raft solution was made up to volume with pH 8.0 phosphate buffer and centrifuged at 4000 rpm for 5 min. Each raft solution was filtered using a 0.2- $\mu$ m syringe filter discarding the first 2 ml of filtrate. Each sample was analyzed by HPLC with a mobile phase of pH 6.5 phosphate buffer. The sodium alginate concentration (X mg/ml) in each sample was determined via the linear equation ( $r^2 \geq 0.99$ ) from the five-point standard graph. The total sodium alginate within the raft was determined using the given calculation:

$$\text{Total Na alginate within the raft (mg)} = X \text{ (mg/ml)} \times \frac{V \text{ (ml)} \times \text{Total raft weight (mg)}}{\text{Sample weight (mg)}}$$

where V (ml) is the volume of the volumetric flask which the raft was dissolved in.

#### ANC within the raft

Flasks containing deionized water and reagent 1 (1.0 M HCl) were incubated at 37 °C for 20 min in a water bath. Reagent 2 (0.5 M NaOH) was contained in a 500 ml amber glass dispensing vessel and heated to 37 °C for 20 min. Rafts were formed in 250-ml glass beakers by adding the manufacturer's maximum recommended dose sample to 70 ml of 0.1 M HCl (pH 1.0) previously equilibrated at 37 °C. After 30 min of maturation, each raft was washed with deionized water and the raft was removed into a centrifuge tube and centrifuged with 4 °C deionized water at 4000 rpm for 3 min. The supernatant was removed and the process was repeated twice. Ethanol at 4 °C was added and centrifuged at 4000 rpm for 3 min, repeating twice. The rafts were dried to constant weight (total mass of isolated raft (mg)) in a 40 °C oven for a minimum of two days.

Each raft was ground and the mass (mg) of the sample was recorded. The sample was transferred into a 250-ml conical flask and 70 ml of deionized water was added. The flask was shaken using an orbital shaker at 37 °C for 1 min at 250 rpm. 30 ml of reagent 1 was added to the flask and returned to the heated shaker for 15 min at 250 rpm. The dispensing vessel containing reagent 2 was connected to an autotitrator. The contents of the conical flask were transferred into a 250-ml beaker to begin the titration analysis. Changes in the pH in response to the addition of reagent 2 were recorded using an Orion 960/940 automatic titration pH meter. Timed readings were 2 s with a constant increment of 0.750 ml until the end point (pH 3.5). The ANC of the alginate raft was calculated using the formulation indicated:

$$\text{ANC} = V \text{ (ml)} - T \text{ (ml)} \times 0.5 \times \frac{\text{Total mass of raft (mg)}}{\text{Sample weight (mg)}}$$

where ANC is the acid neutralizing capacity of the whole raft, V (ml) is the volume of HCl added to the sample, and T (ml) is the volume of titer consumed by the sample.

### Neutralization profile

Rafts were formed in 250-ml glass beakers by adding the manufacturer's maximum recommended dose to 70 ml of 0.1 M (pH 1.0) HCl, previously equilibrated at 37 °C. The rafts were maintained at this temperature for 30 min to allow maturation. The developed raft was transferred into a Buchner funnel discarding any media. A mild filtration was applied to the raft to remove any excess HCl and it was collected to record the pH using a calibrated pH meter. 3 ml of 0.04 M (pH 1.4) HCl solution was applied to the raft and allowed to settle for 5 min before filtering for 3 min. The filtrate was collected and the pH was recorded. This was repeated consecutively until the pH of the filtrate was no longer neutralized (pH <4) by the raft. The pH 4.0 cutoff was used because it is accepted in clinical practice as the transition point from acid to nonacid reflux to denote the clinical relevance from acid gastric conditions to weak acid at pH >4.0.

### Raft structure effect on neutralization profile of alginate rafts

Rafts were formed in 250-ml glass beakers by adding the manufacturer's maximum recommended dose to 70 ml of 0.1 M (pH 1.0) HCl, previously equilibrated at 37 °C. Once the rafts had matured for 30 min, they were carefully removed and placed into a Buchner funnel, discarding any media. A mild filtration was applied to the raft and the excess HCl was collected to record the pH using a calibrated pH meter. 3 ml of 0.04 M HCl solution was added to the raft and allowed to settle for 5 min before applying filtration. The filtrate was collected and the pH was recorded. This was repeated consecutively until two consecutive filtrations were no longer neutralized (pH <4) by the raft. The raft was then removed, placed into a 100-ml beaker, and broken using a spatula. 3 ml of 0.04 M HCl was added and allowed to settle before transferring the raft back to the Buchner funnel and filtering again. The pH of the filtrate was measured. This methodology was developed specifically to study the effect of the raft structure on the neutralization profile of the rafts, hence as part of the methodology the rafts were broken to study the potential for antacid being trapped within the structure and not allowed to react with the acid as it filtered through.

### Characterization techniques

Two additional characterization techniques were introduced to complement the methods already selected demonstrating the chemical characteristics of the alginate-based formulations.

**Differential scanning calorimetry (DSC).** DSC measurements were performed in a Mettler Toledo DSC 30 with Star Software (Greifensee, Switzerland) version 12. A sample mass of ~7 mg was used, in a covered aluminum sample holder with a central pin hole at a heating rate of 5 °C/min, from 25 to 350 °C. The thermograms were processed using the Star Software version 12 and the maximum temperature for each event calculated.

**Fourier transform infrared spectroscopy (FT-IR).** The FT-IR spectra of the sodium alginate and calcium carbonate references and the seven isolated rafts from Algycon, GDA, GO, Maalox, Mylan, Peptac, and Rennie Duo, respectively, over the wavenumber range 4000–650 cm<sup>-1</sup> were recorded after 16 scans using Agilent Cary 630 FT-IR spectrometer (Santa Clara, CA). A small amount of the grinded raft was placed on the optical window and pressed by

the sample press arm. A background spectrum was collected after eight scans prior to each raft analysis.

### Statistical methods

Statistical analyses were performed using GraphPad Prism 4 (GraphPad Software, La Jolla, CA). The alginate content values were analyzed comparing the ratio of GDA to each comparator. For the neutralization profiles, a two-tailed *t*-test was used to analyze the mean neutralization time of GDA against each competitor. ANC data were analyzed using a two-tailed *t*-test. *p*-Values of <.05 have been considered statistically significant.

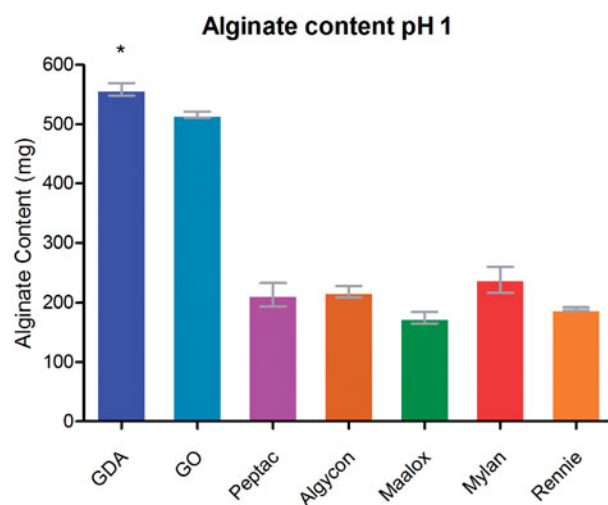
## Results

### Alginate content within the raft tested at pH 1.0

The alginate content within the raft was calculated for each product (Figure 1). The ratio for the geometric mean was calculated as GDA/comparator to determine differences between products. Rafts were formed using the maximum recommended dose by the manufacturer and the results show the alginate content within the raft for GDA was significantly superior (*p* <.05) to all comparator products and GO being significantly superior (*p* <.05) to all other products except GDA (Figure 1).

### ANC within the raft

Products have an initial ANC based on their antacid content, some of it is utilized to neutralize the acid pocket as soon as the product is ingested; however, there is a significant residual amount that ends up trapped within the raft, as it was observed during the raft formation process. The ANC of the rafts was measured to understand the ability of the raft to retain antacid and provide a reservoir of antacid with a benefit. For this measurement, the alginate rafts were formed using the manufacturer's maximum recommended dose. The raft ANC of the seven products evaluated in the current study is shown in Figure 2. The product with the highest raft ANC was Rennie Duo (12.8) followed by GDA (7.9) which were both significantly (*p* <.05) different to the other products evaluated. However, although Rennie Duo demonstrated a high ANC due to the presence of high antacid content, this was the detriment of the product's ability to form a raft.



\* Significantly superior *p* < 0.05 to all other products evaluated.

Figure 1. Alginate content (mg) within the raft.

### Neutralization profile

Once the raft ANC was determined for each product, the ability of the raft to neutralize (pH >4) acid passing through was assessed over consecutive reflux events to study the potential benefit of the antacid trapped within. With each event taking ~8 min (5 min to settle, 3 min to filter through raft), the duration for which each product can neutralize acid was measured (Figure 3). This is considered as a complementary mode of action to the raft lasting 4 h.

The duration of neutralization for each product was determined and the results showed that the two products with the longest duration on neutralization were GDA and GO, with a duration of

neutralization of 93 min seen with GDA, which was in direct contrast to a duration of 27 min observed for Rennie Duo, even though Rennie Duo has a greater concentration of antacid present within its formulation and within the raft. Algycon failed to neutralize any acid, and the other products evaluated demonstrated low duration of neutralization.

### Raft structure effect on neutralization profile of alginate rafts

The lack of correlation between ANC within the raft and the duration of neutralization led to the hypothesis that the structure of the rafts was playing an important role in the duration of neutralization. During the filtration step, it was observed how for some products the acid was filtering through the sides of the raft, while for others the acid was filtering through the whole raft, and with Rennie Duo, the filtration was very fast. Hence, to substantiate the hypothesis, an experiment was designed as explained in the section 'Neutralization profile'. This experiment has helped to differentiate those products presenting with an absorbent raft structure (GDA and GO) demonstrating a longer duration of neutralization of 93 and 61 min, respectively, compared to those products with nonabsorbent rafts (Peptac, Maalox, and Mylan), and nonabsorbent rafts mean the antacid is shielded away from the acid in contact with the raft and not being available to neutralize. Rennie Duo has a porous raft structure and although it had the highest ANC, it had a lower duration of neutralization (27 min) when compared to GDA and GO, and rafts with a very porous structure mean the acid passes through the raft too fast to allow the antacid to react with it. Algycon had no raft structure and a low ANC with zero duration of neutralization. See data presented in Table 2.

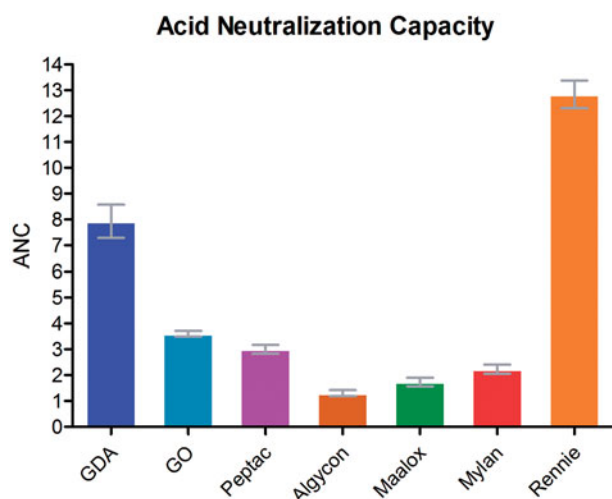


Figure 2. Raft ANC for each product.

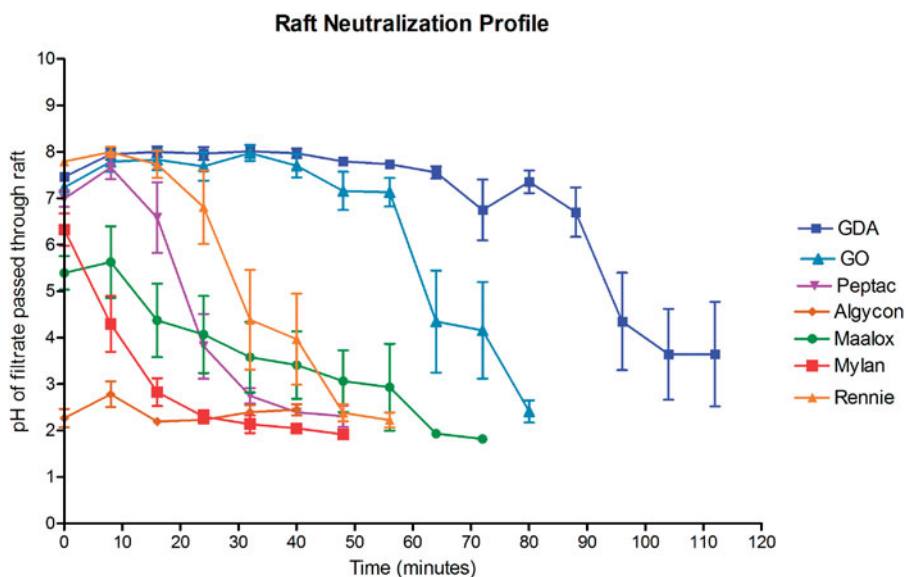


Figure 3. Raft neutralization profiles of each product.

Table 2. Presentation of the acid neutralization capacity, the duration of neutralization and the observed raft structure for each product evaluated.

Product	Acid neutralizing capacity ( $n = 3$ )	Duration of neutralization (min) ( $n = 6$ )	Raft structure
GDA	7.9	93	Absorbent
GO	3.6	61	Absorbent
Peptac	3.3	16	Nonabsorbent
Algycon	1.3	0	No structure
Maalox	1.7	21	Nonabsorbent
Mylan	2.2	5	Nonabsorbent
Rennie Duo	12.8	27	Porous structure



All the products were able to re-neutralize a pH 1.4 solution after the raft was broken, indicating that the structure of the rafts has an effect on the ability of the raft to allow the utilization of the antacid trapped within it. Neutralization occurs when in contact with acid or in severe cases when a reflux event passes acid through the raft. The structure of the raft must have the right level of porosity to allow the acid to be in contact with the antacid for a sufficient period of time for the neutralization reaction to take place. The results show that GDA has the right level of porosity to allow for longer duration of neutralization. This was in contrast to the observations made with Rennie Duo, where as soon as the acid was added, it started filtering through very quickly even without applying a vacuum.

### Ranking of the products

All the data generated during the current study allowed the ranking of the products studied and presented in Table 3. Each ranking position (for each tested parameter) has been marked with points, with the top position getting seven points and reducing by one point as the position lowers by one in the ranking. For each product, the total score has been calculated by adding the total number presented in Table 4. In ranking terms across all the methods, the products were evaluated in GDA and GO and were superior to the other five products tested.

### Differential scanning calorimetry

The thermal characterization of the isolated rafts was evaluated by DSC and the maximum temperatures for each event are displayed in Figure 4. DSC is an important tool for the determination of glass transition and melting/degradation behaviors of polymers. The DSC of the isolated rafts did not exhibit any glass transition which was probably associated with its rigid crystalline structure and occurrence of strong inter- and intramolecular hydrogen bonding driven by the presence of the alginate in the structure.

Table 3. Product classification showing the ranking of the products evaluated.

Method (intervention)	Product position (*)	Statistical significance (GDA versus comparator)	Key findings
Alginate content within the raft	GDA		GDA demonstrates superior alginate content within the raft compared to comparator products
	GO	$p = .0044$	
	Mylan	$p < .0001$	
	Algycon	$p < .0001$	
	Peptac	$p < .0001$	
	Rennie Duo	$p < .0001$	
	Maalox	$p < .0001$	
Raft acid neutralization capacity (ANC)	Rennie Duo	$p = .0025$	ANC is used to determine the total capacity of the raft to neutralize acid. GDA is significantly superior to all comparator products except for Rennie Duo
	GDA		
	GO	$p = .0024$	
	Peptac	$p = .0014$	
	Mylan	$p = .0007$	
	Maalox	$p = .0005$	
	Algycon	$p = .0003$	
Raft neutralization profile	GDA		GDA is significantly superior to all comparator products
	GO	$p = .0001$	
	Rennie Duo	$p < .0001$	
	Peptac	$p < .0001$	
	Maalox	$p < .0001$	
	Mylan	$p < .0001$	
	Algycon	N/A	

\*Each product has been ranked in terms of performance with the top position indicating the best performer and bottom position the worst performer.

All rafts displayed one or two transition peaks for the decomposition of the biopolymer alginate and alginate, respectively, within the range of 190–340 °C, except for Algycon and GDA raft where only one peak was observed; however, this could be due to lack of resolution between the two signals.

### Fourier transform infrared spectroscopy

The characterization of the isolated rafts and the alginate and calcium carbonate references was evaluated by FT-IR and the representative bands are shown in Figure 5. Rafts displayed the characteristic bands of alginate reference. A broad band with minimum transmittance in the range of 3211–3320  $\text{cm}^{-1}$  was observed in all the rafts providing information of O–H bond stretching vibrations. The peak in the range of 2922–2938  $\text{cm}^{-1}$  is characteristic of methylene ( $-\text{CH}_2$ ) stretching vibrations. The asymmetric and symmetric stretching vibrations of  $-\text{COO}^-$  can be assigned to the peaks in the range of 1582–1649 and 1405–1426  $\text{cm}^{-1}$ , respectively. In the fingerprint region, there are several alginate specific absorbance bands at 1155–1163, 1072–1083, 1010–1027, and 945–969  $\text{cm}^{-1}$ , respectively, and can be attributed to CO and OH bond stretching. The absorbance peak in the range of 796–813  $\text{cm}^{-1}$  displayed information about C–C skeletal vibrations.

Table 4. Overall ranking of the products.

Product	Overall score
GDA	20
GO	17
Peptac	11
Rennie	14
Mylan	10
Maalox	6
Algycon	6

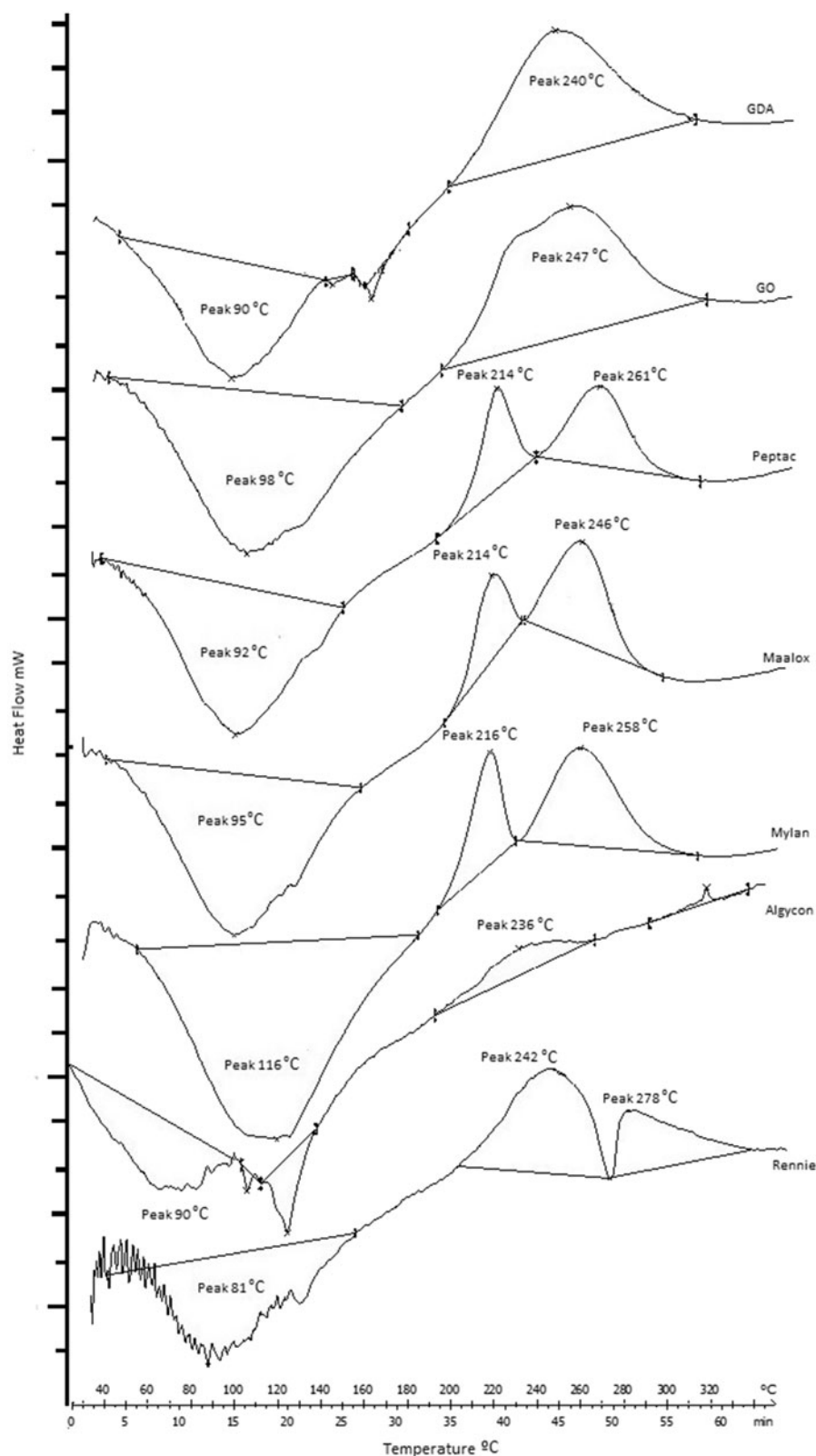


Figure 4. DSC thermograms of isolated rafts.

Calcium carbonate displayed three main absorbance peaks at 1790, 870, and 712  $\text{cm}^{-1}$  associated to  $\text{CO}_3^{2-}$  vibrations that can be observed in Rennie isolated rafts. All isolated rafts showed an absorbance peak in the range of 872–878  $\text{cm}^{-1}$  attributed to  $\text{CO}_3^{2-}$  asymmetric deformation vibration, with the exception of Algycon.

## Discussion

The products evaluated represented a wide range of alginate products from across European and global markets, and these are illustrated in Table 1. The main active ingredient across the products evaluated was sodium alginate at the maximum dose of

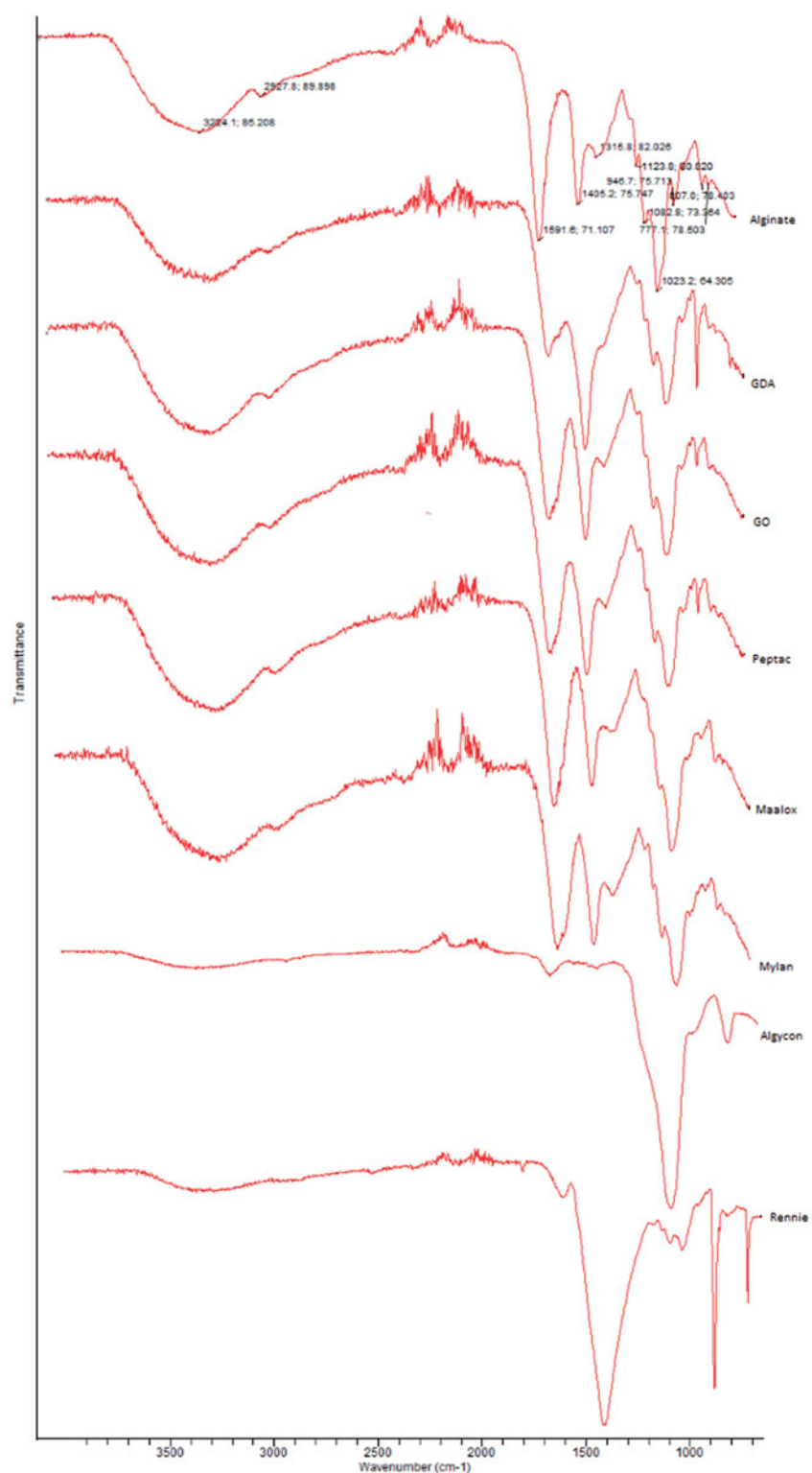


Figure 5. FT-IR scans of product rafts.

1000 mg. The exceptions were seen with Rennie Duo which contained a lower concentration of sodium alginate (300 mg per maximum dose) but contains a far greater concentration of the antacid component calcium carbonate (1200 mg) in comparison with the other products tested, and Maalox which contained 500 mg sodium alginate and 164 mg calcium carbonate within the maximum dose. All the products evaluated contained some

antacid usually calcium carbonate and sodium bicarbonate as seen in Table 1. The product tested with the greatest differences in formulation was Algycon, a tablet-based product containing 600 mg alginic acid and the antacids aluminum hydroxide and magnesium carbonate. While there are formulation differences between the products, the manufacturer's on-pack claims are the same for all, although strictly speaking Algycon is not a



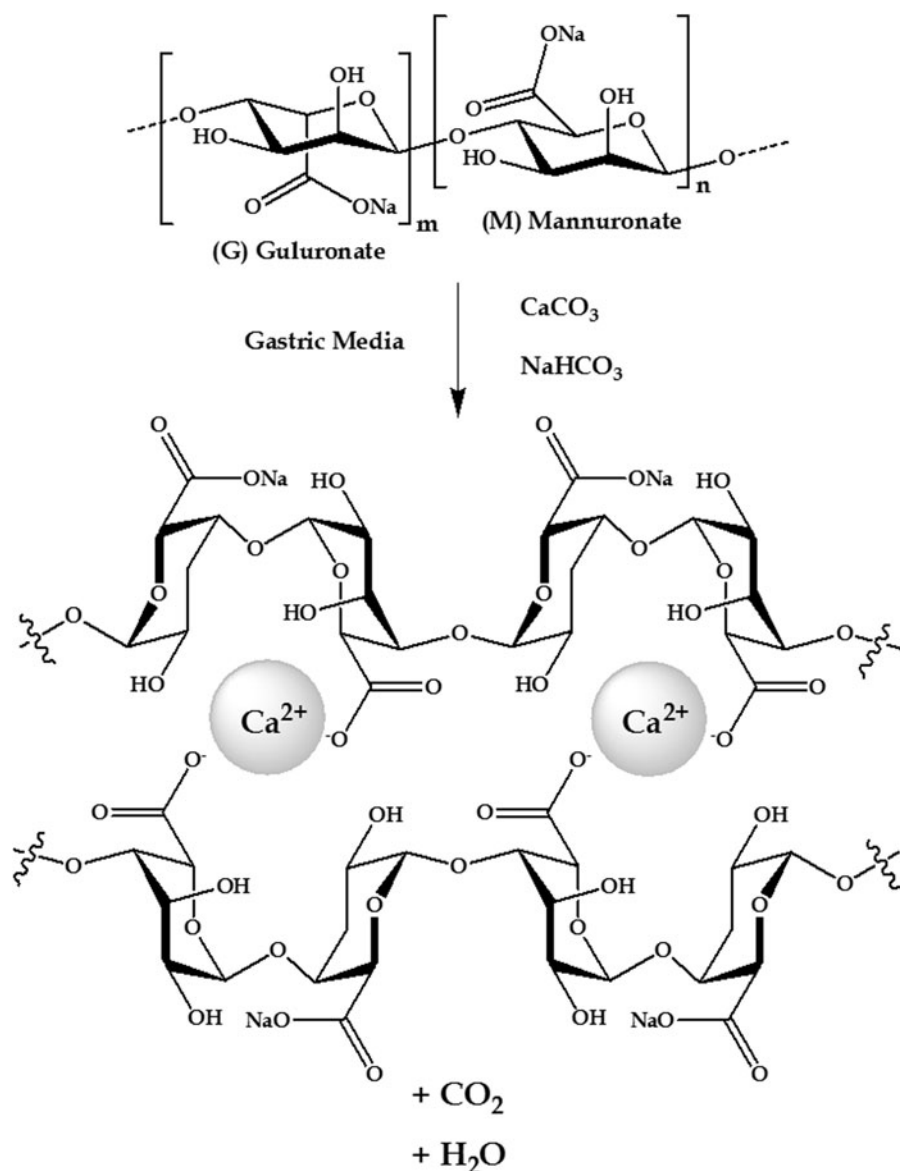


Figure 6. Discussed chemical reactions.

raft-forming alginate product as clearly demonstrated in the current studies.

Previous *in vitro* studies [4,5] have mainly investigated the physical properties of the alginate-based products such as raft strength. Raft strength has always been a key differentiator between alginate-based products [4], whereas the *in vitro* studies described here are focused on the chemical characteristics of the raft, particularly the alginate content within the raft as this is key for a superior product performance, and the neutralization profile of the rafts.

The effects that the variation in the amounts and ratios of the active ingredient sodium alginate (alginic acid in the case of Algycon) and the antacids, mainly calcium carbonate and sodium bicarbonate, has on the raft formation have been well described and documented in earlier patents [11,12] and publications [13–16]. However, there has been little published on how the alginate content within the raft can influence how well the product maintains raft performance in terms of integrity and strength and utilizes the antacid components within the formulation. This is important as the presence of the alginate within the raft allows for antacid entrapment which in turn provides a pH neutral barrier

preferentially refluxed ahead of any gastric acidity into the esophagus.

Recently, some interesting studies were published by Hanif and Abbas [17] and Abbas et al. [18] describing the development of alginate–pectin rafts using Box–Behnken response surface design to optimize alginate polymeric formulations to achieve symptomatic relief from GERD. Rafts formed were characterized by their strength, weight, volume, resilience, reflux resistance, thickness, buffering capacity, neutralization capacity, floating lag time, and total floating time. FT-IR spectroscopy was performed to check the interaction between the polymers and other excipients and showed no interaction between sodium alginate, pectin, and other excipients.

The scope of this current research was to focus on the chemical characteristics of the alginate-based rafts to compliment all the extensive previous studies centered on the physical properties. It has been well established in previous research work how the source of alginate and the alginate biopolymer composition as measured by the ratio of mannuronic to guluronic acid components (M–G ratio) has an impact on the formulation. In addition to this, the alginate within the raft is important firstly because this

affects the integrity and strength of the rafts formed and secondly because alginate present in the raft allows for the raft to entrap antacid within its matrix. This in turn will lead to a longer duration of neutralization as demonstrated in the present series of studies.

The alginate content within the raft was determined by a newly developed method by HPLC as described in the methods section. In the current series of studies, the alginate content within the raft was shown to be statistically superior for GDA and GO in comparison with all other products evaluated.

Previous *in vitro* and *in vivo* studies have suggested that alginate rafts have the capacity of entrapping CO<sub>2</sub> and antacid within the matrix of the raft but until now this has not been measured. A new method has been developed to measure the actual ANC of the raft and the method is first described in this paper.

All the products tested contain antacid components, and in the case of Rennie Duo, the antacid is the main active ingredient within the formulation. The fact that each product has some antacid within its formulation will cause some initial but often transient neutralization of the acid pocket. For products to be truly effective antacids, they need to demonstrate not only a high ANC but a long duration of neutralization. This is where the importance of the raft structure/alginate content plays a key role in entrapping the antacid to ensure longer duration of neutralization. This is not seen with classical antacid products which are only capable of short duration neutralization as they have no means to retain unreacted material [19]. The present studies clearly demonstrate that a product formulated in the way GDA has been, will not only have superior alginate raft content but also a significantly longer duration of neutralization owing to the alginate entrapping the antacid within the raft.

It was of interest to compare GDA with Rennie Duo. The Rennie Duo formulation contains a greater concentration of antacid but far less sodium alginate, resulting in a raft ANC of 12.8 compared to an ANC of 7.9 for GDA, but because of the superior alginate content within the raft GDA had a longer duration of neutralization 93 min compared to 27 min for Rennie Duo.

In the current study, a further series of experiments were designed to show how the raft structure influences how efficiently the ANC within the raft can be utilized. The main characteristic is having the optimum of raft porosity which allows the acid passing through the raft to be in contact with the antacid now trapped within the raft, which in turn accounts for the period of time for the neutralization reaction to take place. Rennie Duo was too porous allowing acid to filter through and spend insufficient time within the raft to react with the antacid present. Both GDA and GO had an absorbent raft structure which was reflected in their superior duration of neutralization. In contrast, Peptac, Maalox, and Mylan had a nonabsorbent raft structure allowing the acid to pass through the outside channels of the raft structure rather than through the raft, which avoided the acid coming into contact with the antacid within the formulation which was reflected by the short neutralization times associated with these products. Algycon has no raft structure and therefore the lowest ANC and zero duration of neutralization.

The introduction of the two characterization techniques complemented the chemical characterization already reported [20]. DSC confirmed the decomposition temperature of the biopolymer in all the samples corroborating the presence of alginic/alginate in the rafts. This highlights that different formulation compositions will result in rafts presenting different chemical and thermal properties.

Rennie Duo showed the biggest different thermal profile among all the samples with an exotherm for the alginate decomposition at 278 °C. This can be attributed to the important contribution of inorganic compounds in the isolated raft (high carbonate content in the raft indirectly measured by the ANC) which is consistent with Rennie showing the highest ratio ANC versus total alginate content within the raft among all the samples. The ratio ANC versus alginate content has been calculated as ANC/alginate in percentage. This has resulted in a ratio of 6.8 for Rennie against a ratio interval of 0.4–1.4 for the rest of the samples.

The FT-IR spectra provided evidence of the alginate- and carbonate-based structures of the isolated rafts. For the alginate, the characteristic chemical groups COO<sup>-</sup>, OH, CH, and CH<sub>2</sub> were identified in all the products and results were confirmed from both pure alginate and by reported literature [18,21]. GDA, GO, Maalox, Mylan, and Peptac showed FT-IR profiles very similar to pure alginate. In all of these rafts, the CO<sub>3</sub><sup>2-</sup> group was identified (872–878 cm<sup>-1</sup>), demonstrating that rafts were entrapping insoluble carbonates during the raft formation and providing these structures with neutralizing capacity. Furthermore, this band was significantly higher in the case of GDA confirming the higher neutralizing capacity observed in this product.

Algycon and Rennie Duo showed different profiles that can be mainly attributed to the important contribution of inorganic compounds in the isolated raft. It should be emphasized that these products consist of alginic acid rather than alginate. In the case of Rennie Duo, the main peaks observed in the spectrum at 712, 872, and 1795 cm<sup>-1</sup> can be clearly attributed to the calcium carbonate which is present in a high content. This high calcium carbonate content was expected as the ANC of Rennie was highly superior to the rest of the products.

Algycon profile can be mainly attributed to aluminum hydroxide compound entrapped in the raft. Accordingly, a strong peak at 1072 cm<sup>-1</sup> can be assigned to O–H vibrations.

## Conclusion

Alginate-based products are complex formulations as they require three chemical reactions to take place simultaneously, alginate transforming to alginic acid, sodium carbonate reacting to form carbon dioxide, and calcium carbonate releasing free calcium ions to bind with alginic acid and provide strength to the raft. Small differences in the way products are formulated can have a significant effect on the kinetics of these reactions taking place asynchronously and leading to significant differences in product performance. The chemical reactions then control and influence three key processes: (i) the efficient utilization of the alginate within a formulation, (ii) the subsequent alginate content within the raft, and (iii) the neutralization profile of the raft itself. The discussed chemical reactions are illustrated in Figure 6.

This research on the chemical properties of the raft complements previous research work focus on the physical properties of the raft [4,5]. Previously, GDA has demonstrated to be superior in terms of raft strength and raft resilience as a result of how the product is formulated and type of alginate utilized. In addition to this, this research has shown the product to be superior in the chemical properties of the raft that are relevant to the efficacy of the product, by trapping a superior amount of alginate within the raft, allowing for antacid to be trapped within the raft and consequently providing a longer duration of neutralization.

### Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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### Geolocation information

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