

The effects of alginate molecular structure and formulation variables on the physical characteristics of alginate raft systems

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Abstract

A study has been conducted in order to assess the effects of alginate molecular structure and formulation variables on alginate raft strength and dimensions. In addition, the use of texture analysis as a novel means of characterising alginate raft systems has been investigated. Five alginates of known molecular composition were used (LFR 5/60, LF 120M, LF 10/40RB, LF 20/200 and LF 200DL), while two gas-forming agents (sodium and potassium bicarbonate) and two divalent cationic salts (calcium carbonate and zinc carbonate) were studied. The effects of acid strength on raft formation was also investigated. It was noted that the inclusion of divalent cations and the use of the lowest molecular weight alginate sample (LFR 5/60) increased the volume of the resulting rafts. Texture analysis measurements allowed both the maximum breaking strength and the work involved during the rupture process to be quantified. Inclusion of divalent cations (particularly calcium) increased the raft strength, while inclusion of potassium carbonate resulted in stronger rafts than did sodium carbonate. Alginates with higher guluronic acid contents resulted in stronger rafts, with the exception of LFR 5/60 which yielded weaker rafts despite the high G ratio, probably as a result of the lower molecular weight of this material. Raft volume and strength increased with decreasing pH of the raft forming media. © 1997 Elsevier Science B.V.

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1. Introduction

Alginates are polysaccharides obtained from brown algae which have found wide applicability in the food, textile and pharmaceutical industries (McDowell, 1986). These molecules are block co-polymers of D-mannuronic (M) and L-guluronic

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(G) acids, the proportion and block distribution of the M and G residues having a profound effect on the gel-forming properties of the alginates, which in turn may affect the corresponding product performance.

Amongst other pharmaceutical applications, alginates may be used as raft-forming systems for the treatment of reflux oesophagitis. These products differ from traditional antacids by virtue of the fact that they form a viscous 'raft' layer on top of the stomach contents, which protects the oesophagus from acid reflux, either by the establishment of a physical barrier to reflux or by the raft itself being preferentially refluxed (Washington, 1990). Raft-forming mixes contain two principle components: an alginate (as the sodium salt) and a gas-forming agent. Sodium alginate precipitates on ingestion in the acid conditions of the stomach to form a gel of alginic acid. The gas-producing substance, a bicarbonate, forms carbon dioxide on contact with the stomach contents. The gas bubbles are entrapped by the alginate gel and the resulting viscous foam (gas dispersion) rises to the surface of the stomach contents and floats. Calcium carbonate may be added in order to aid the gelation of the alginate, as in acid conditions the salt dissociates to release divalent calcium cations which interact with the alginate. This interaction has been extensively studied (e.g. Haug and Smidsrød, 1965, 1968; Grant et al., 1973; McDowell, 1986) and involves chelation between adjacent blocks of guluronic acid to form an 'egg-box' structure, thereby considerably increasing the viscosity of the system. Additional antacids may also be included in the mixture, although standard materials such as aluminium hydroxide or magnesium carbonate may have the effect of reducing raft strength (Washington et al., 1986).

A method for the evaluation of raft-forming products was suggested by Washington et al. (1986) who developed an apparatus designed to measure the breaking strength of alginate rafts *in vitro*. The apparatus consists of a horizontal wire probe suspended under the raft

from one end of a beam balance. The vertical load on the probe is increased via a stepping motor attached to the other end of the balance via a length of chain. The apparatus gives a measure of the force required to break the raft, this being dependent on the size and shape of the probe which must be standardised. The method therefore allows quantitative assessment of raft strength which is essential for raft product development. However, the fact that the apparatus has to be individually built from non-standard pieces of equipment means that reproducibility of results between laboratories is difficult, thus comparison of data is not entirely reliable.

One of the problems associated with the use of alginate products in pharmaceutical preparations has been that the molecular characteristics of the alginate used are frequently not stated, particularly in terms of the MG ratio and block distribution. In this investigation, a series of alginate samples which have been previously characterised in terms of molecular structure (Johnson et al., 1997) have been prepared as raft-forming mixtures in order to assess the effects of choice of alginate and other formulation variables, particularly the choice of gas-forming agent and divalent cation salt, on raft characteristics. In addition, the use of texture analysis as a novel means of assessing raft characteristics has been investigated. This method involves the insertion and withdrawal of a probe into a sample and the measurement of the forces involved during the cycle; hence, the method is a form of penetrometry. The method has found an increasing number of applications within the pharmaceutical field, including the assessment of bioadhesion (Tobyn et al., 1996; Jones et al., 1997) and the rheological properties of creams (Tamburic et al., 1996). It is therefore logical to investigate the use of this equipment to measure the force and work required to break the various rafts. This has been performed in order to quantify the effects of formulation variables on raft characteristics and as an assessment of the applicability of the method as a quality control tool.

2. Method

2.1. Materials used

The alginate samples used were obtained from Pronova Biopolymers A/S, Drammen, Norway. Five samples were used as received (LFR 5/60, LF 120M, LF 10/40RB, LF 20/200, LF 200DL), with molecular characteristics given in a previous publication (Johnson et al., 1997). In brief, the guluronic acid ratios for the alginates are as follows: LFR 5/60, 67.2%; LF 120M, 42.4%; LF 10/40RB, 50.9%; LF 20/200, 67.0%; LF 200DL, 55.1%. In addition, LFR 5/60 is a lower molecular weight grade of alginate. Sodium and potassium carbonate were used as gas-generating agents and calcium and zinc carbonate were used as sources of divalent cations. All carbonates and bicarbonates were obtained from BDH. All raft-forming materials contained 2.5% w/v alginate and 2.5% w/v bicarbonate (potassium and sodium, as stated). Where stated, calcium or zinc carbonates were added at a concentration of 0.75% w/v. Calcium was chosen for its gelling properties with alginates and because it is currently used in some commercial raft products; zinc was chosen as an alternative chelating agent. These cations were used in the form of the carbonate salts which are insoluble at neutral pH, hence the divalent ions were only released in the presence of acid, thereby preventing premature gelation.

2.2. Measurement of raft thickness

The raft-forming mixture (2 ml) was added to 10 ml HCl at 37°C in a 25-ml pyrex cylinder. The raft was allowed to form for 10 min without agitation. The thickness of the raft was measured at three places around the cylinder. Three measurements were made for each raft and three rafts were studied from each formulation. Multiple repeats showed that the reproducibility was within a coefficient of variation of approximately 10%, although the uneven physical characteristics of the rafts rendered specific quantitative assessment extremely difficult. The data is therefore discussed in terms of gross differences between formulations.

2.3. Texture analysis

Calibration of the TA.XT2 texture analyser (Stable Microsystems) was by means of external standard weights. The probes used were as follows: stainless steel ball (10 mm diameter), stainless steel ball (5 mm diameter), plastic cylinder (10 mm diameter, flat end), plastic cylinder (10 mm diameter, rounded end), stainless steel disk (20 mm diameter). The rafts to be tested were formed in 100-ml pyrex beakers containing 20 ml hydrochloric acid, maintained at 37°C in a water bath. The acid used was 0.1 M HCl except where stated otherwise. The TA.XT2 texture analyser was used in the tension mode; thus, the rafts were formed with the probe in situ at the start position, just above the bottom of the beaker. The rafts were formed by the addition of 4 ml of the raft forming mixture to the acid from a 5-ml syringe. The mixture was expelled from the syringe onto the surface of the acid surrounding the probe. The beaker was allowed to stand for 10 min without agitation to permit raft formation. The texture analyser was set up in tension mode to travel a distance of 30 mm at a constant speed of 1 mm/s and then return to the start at the same speed. Data were collected at a rate of 50 points/s via the Xtra dimension software, with five repeats being performed for each sample except for the probe shape studies which were run in duplicate.

3. Results

3.1. Effect of probe characteristics on raft strength

A variety of probe types were considered for use with the TA.XT2 texture analyser, as outlined in the previous section. It was decided that the most suitable probe arrangement would be the one which gave the greatest resolution between a raft sample and the acid alone. A variety of probe materials and shapes were examined and the maximum force exerted on each probe before breakage of the raft/surface was determined with an alginate raft formed with LFR 5/60 and sodium bicarbonate. The maximum force recorded for the

Table 1

Comparison of maximum breaking strengths of alginate rafts formed with LFR 5/60 sodium alginate and sodium bicarbonate using a variety of probe materials and shapes

Probe type	Blank max (mN)	Raft max (mN)	%
Metal ball (10 mm diameter)	16.9	23.1	73.2
Metal ball (5 mm diameter)	5.3	7.1	74.6
Plastic cylinder (flat end)	21.3	29.3	72.7
Plastic cylinder (round end)	14.2	17.8	79.8
Metal disc	26.7	44.6	59.8

blank sample (acid alone) is a reflection of the surface tension of the liquid and the mechanics by which the probe disrupts that surface. The maximum forces for the blank and the raft sample with each probe are given in Table 1; the blank maximum force is expressed as a percentage of the sample maximum. It can be seen from these results that the highest values and most favourable raft to blank ratio was obtained with the metal disc probe. This is a reflection of the fact that pulling a probe of these dimensions through a sample inevitably involves major disruption of the raft, while, for example, spherical probes could conceivably be pulled through the sample with relatively little breakage of the floating gel. This probe was therefore used for all subsequent studies.

3.2. The effect of raft-forming mixture composition

3.2.1. Raft dimensions

Table 2 shows the thicknesses of the rafts formed from the various mixes using the five alginate samples under investigation. Greater thicknesses were seen on addition of either calcium or zinc carbonate compared to rafts formed with the alginate and bicarbonate alone. No clear trend could be seen between raft thickness and choice of alginate, other than the observation that the low molecular weight LFR 5/60 generally produced thicker rafts. It may therefore be concluded that in terms of choice of alginate, there appears to be a stronger link between raft dimensions and molecular weight (and hence viscosity) than there is with G ratio.

3.2.2. Texture analysis

A typical set of texture analysis force–time profile for an alginate raft is shown in Fig. 1. As the probe is pulled through the raft the force increases as the gas dispersion deforms up to a maximum value at which rupture has taken place. The force decreases beyond this point up to the 30 s time limit, at which the probe starts to descend into the beaker. One might initially expect the value to remain constant after rupture due to the force simply reflecting the weight of dispersion remaining on the probe. However, due to the semisolid nature of the system, the gel was continuously being shed from the probe; hence, a steady decrease was seen in force up to the 30 s change in direction. The further decrease seen at approximately 50 s reflects the immersion of the probe within the liquid surface. Clearly, a number of processes are involved in the cycle, hence the two parameters chosen to quantitatively describe the raft characteristics were the maximum breaking strength and the total area under the curve which reflects the energy required to subject the raft through the probe cycle. A correction is made for the differences in the initial force prior to the probe coming into contact with the raft, these values being due to unreacted raft forming mixture remaining on the probe.

Table 3 shows the maximum breaking strengths of rafts formed with the five alginates under investigation, with Table 4 showing the corresponding work values. A simple ordinal method of ranking the various systems may be used whereby for each formulation, the various alginates are given scores between 5 and 1 depending on their rank order. Similarly, for a single alginate, the different formulations may be ranked between 6 and 1. The

Table 2

The thickness (cm) of rafts prepared using a range of alginates, carbonates and bicarbonates (% guluronic acid (G) content data taken from Johnson et al. (1997))

Alginate	% G	NaHCO ₃	KHCO ₃	NaHCO ₃ /CaCO ₃	KHCO ₃ /CaCO ₃	NaHCO ₃ /ZnCO ₃	KHCO ₃ /ZnCO ₃
LFR 5/60	67.2	3.0	2.2	4.4	4.4	2.9	3.2
LF 20/200	67.0	2.0	1.7	2.2	2.4	2.8	2.6
LF 200DL	55.1	1.6	1.5	1.9	2.3	1.5	2.2
LF 10/40RB	50.9	3.0	2.1	3.5	2.4	3.3	2.6
LF 120M	42.4	2.0	1.9	3.1	1.9	2.6	2.4

total of these rankings allows an overall comparison between both different alginates and different formulations.

An overall rank order for the breaking strength values between the alginates was observed such that

$$\begin{aligned} \text{LF 20/200 (28)} &> \text{LF 10/40RB (25)} \\ &> \text{LF 120M (16)} > \text{LF 200DL (13)} \\ &> \text{LFR 5/60 (8)} \end{aligned}$$

The total rank scores are given in parenthesis. The values show that for the majority of the samples, LF 20/200 shows the greatest breaking strengths while LFR 5/60 shows the lowest. This latter observation may be a function of the low molecular weight of this material. Discounting LFR 5/60 for this reason, the rank order shows a rough correlation with the G ratio, with LF20/200 (67.0% G) having the highest breaking strength

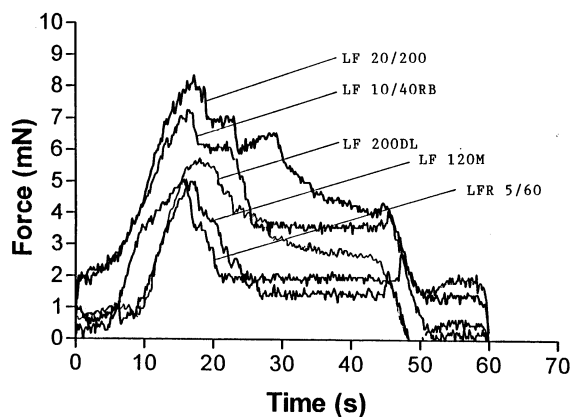


Fig. 1. Force–time profiles for rafts produced using five alginate samples with KHCO₃ as the gas-forming agent.

while LF 120M (42.4% G) consistently has one of the lowest breaking strengths of the group. It is perhaps surprising, however, that LF 10/40RB shows consistently high strength values (second only to LF 20/200) given its low G content of 50.9%. Comparison with intrinsic viscosity values (Johnson et al., 1997) again shows a reasonable correlation, with LF 20/200 showing the highest and LFR 5/60 the lowest value of $[\eta]$. Smidsrød et al. (1973) have suggested that the molecular flexibility of alginate molecules is determined by the uronic acid composition and sequencing, with G blocks being more rigid than M blocks. The manner in which this relates to the behaviour of gel systems, particularly those formed by precipitation from acid, is less clear, although gels formed in the presence of calcium show greater stiffness when the G ratio is high due to the interaction between G blocks and the divalent cations (Smidsrød and Haug, 1972). The data shown here suggest that both molecular weight and G ratio may be of importance in determining raft strength, with higher values of both tending to lead to stronger rafts.

There was an approximate rank order in strength and work of rupture between samples containing different carbonate and bicarbonate combinations such that, for the breaking strength values,

$$\begin{aligned} \text{K/Ca (27)} = \text{K/Zn (27)} &> \text{Na/Ca (21)} \\ &> \text{Na/Zn (13)} > \text{K (12)} > \text{Na (5)} \end{aligned}$$

This can be seen in Fig. 2 where the force–time profiles for LF 10/40RB rafts are shown. The effects of different divalent ions on the properties of alginate solutions has been investigated by

Table 3

Mean maximum breaking strengths of rafts formed using a range of alginates, carbonates and bicarbonates, measured using texture analysis

Additions to alginate solutions	Breaking strength (mN) \pm S.D.				
	LFR 5/60	LF 20/200	LF 200DL	LF 10/40RB	LF 120M
NaHCO ₃	44.6 \pm 1.2	63.0 \pm 5.1	50.0 \pm 2.2	57.1 \pm 7.1	41.6 \pm 3.4
KHCO ₃	45.5 \pm 3.5	79.8 \pm 6.1	56.7 \pm 2.4	75.6 \pm 4.1	51.6 \pm 3.5
NaHCO ₃ + CaCO ₃	58.9 \pm 1.6	90.5 \pm 3.7	63.5 \pm 3.4	80.1 \pm 9.6	74.4 \pm 2.5
KHCO ₃ + CaCO ₃	62.8 \pm 5.4	87.7 \pm 2.9	78.4 \pm 3.9	109.9 \pm 3.4	89.8 \pm 3.9
NaHCO ₃ + ZnCO ₃	56.5 \pm 3.2	85.2 \pm 4.8	54.1 \pm 2.0	66.9 \pm 2.3	58.0 \pm 2.2
KHCO ₃ + ZnCO ₃	67.1 \pm 2.3	91.2 \pm 7.2	72.2 \pm 3.3	82.5 \pm 5.2	75.7 \pm 3.1

Table 4

Mean work performed in cycling a probe through rafts formed using a range of alginates, carbonates and bicarbonates using texture analysis

Additions to alginate solutions	Mean work performed in cycling rafts (N·mm) \pm S.D.				
	LFR 5/60	LF 20/200	LF 200DL	LF 10/40RB	LF 120M
NaHCO ₃	0.41 \pm 0.07	0.80 \pm 0.20	0.65 \pm 0.18	0.56 \pm 0.11	0.35 \pm 0.04
KHCO ₃	0.50 \pm 0.01	1.03 \pm 0.24	0.85 \pm 0.10	0.83 \pm 0.16	0.50 \pm 0.05
NaHCO ₃ + CaCO ₃	0.71 \pm 0.04	1.50 \pm 0.15	1.21 \pm 0.075	0.96 \pm 0.22	0.70 \pm 0.12
KHCO ₃ + CaCO ₃	0.94 \pm 0.09	0.95 \pm 0.23	1.98 \pm 0.21	1.78 \pm 0.15	1.09 \pm 0.22
NaHCO ₃ + ZnCO ₃	0.51 \pm 0.03	1.14 \pm 0.28	1.01 \pm 0.11	0.68 \pm 0.09	0.52 \pm 0.03
KHCO ₃ + ZnCO ₃	0.80 \pm 0.03	0.72 \pm 0.071	1.67 \pm 0.21	1.32 \pm 0.29	0.68 \pm 0.06

Haug and Smidsrød (1965), who showed a rank order of the concentrations of the ions needed to bring about gelation, this being Ba < Pb < Cu <

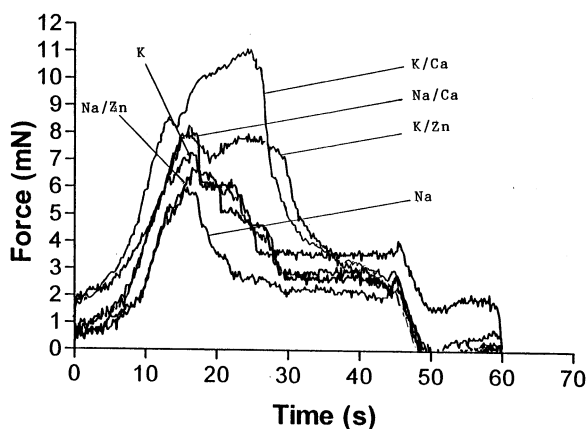


Fig. 2. Force–time profiles for rafts containing LF 10/40RB sodium alginate containing sodium and potassium bicarbonates and calcium and zinc carbonates.

Sr < Cd < Ca < Zn < Ni < Co < Mn < Mg;

hence, the greater gelation properties of calcium compared to zinc predicted by this rank order are reflected here. However, it is less clear why the choice of the sodium or potassium salts should have an effect. Given that the same weight, rather than molar quantity, of the salts were used, there will be marginally greater quantities of the sodium salts in the rafts. Nevertheless, the clear trend showing potassium salts to result in stronger rafts than sodium salts is unexpected.

3.3. The effects of acid strength

Table 5 shows the effect of acid strength on the thickness of rafts formed showing that, in general, raft thickness increased with an increase in the molarity of HCl. This differs from the observations of Patel (1991) who found that the thickness of the rafts formed by two of the commercial preparations investigated, Gaviscon and Algitec,

Table 5

The effect of acid strength on raft thickness of LFR 5/60 alginate raft formulations containing sodium and potassium bicarbonates and calcium and zinc carbonates

Additions to LFR 5/60 solution	Raft thickness (cm)		
	0.1 M HCl	0.07 M HCl	0.05 M HCl
NaHCO ₃	3.0	1.6	1.0
KHCO ₃	2.2	2.0	1.5
NaHCO ₃ +CaCO ₃	4.4	2.4	1.3
KHCO ₃ +CaCO ₃	4.4	2.5	1.3
NaHCO ₃ +ZnCO ₃	2.9	1.5	0.8
KHCO ₃ +ZnCO ₃	3.2	1.9	1.1

Table 6

The effect of acid strength on the breaking strength of LFR 5/60 alginate raft formulations containing sodium and potassium bicarbonates and calcium and zinc carbonates

Additions to alginate solution	Breaking strength (mN) \pm S.D.		
	0.1 M HCl	0.07 M HCl	0.05 M HCl
NaHCO ₃	44.6 \pm 1.2	40.3 \pm 1.3	33.2 \pm 1.0
KHCO ₃	45.5 \pm 3.5	43.5 \pm 1.9	36.4 \pm 1.9
NaHCO ₃ +CaCO ₃	58.9 \pm 1.6	49.7 \pm 2.6	45.2 \pm 2.5
KHCO ₃ +CaCO ₃	62.8 \pm 5.4	59.4 \pm 2.0	46.5 \pm 3.2
NaHCO ₃ +ZnCO ₃	56.5 \pm 3.2	43.3 \pm 1.8	35.3 \pm 1.5
KHCO ₃ +ZnCO ₃	67.1 \pm 2.3	52.6 \pm 4.1	37.5 \pm 0.6

tended to decrease with an increase in molarity of HCl and the third product investigated, Algicon, was not significantly affected by the strength of the acid. It is not immediately clear as to why this discrepancy should have arisen, although both the formulations and the raft-forming conditions were different for the two studies. It is also interesting to note that the formulations are not equally affected by the change in the pH of the acid medium. The rafts containing either calcium or zinc carbonate show a greater increase in raft thickness with acid strength than the rafts formed without the addition of a carbonate.

Table 6 shows the effect of acid strength on the breaking strength of LFR 5/60 rafts of various compositions. The breaking strength generally increases with increasing acid strength, as was found by Patel (1991). In addition, the proportional changes in strength were greater for rafts containing divalent cations, as was found for the raft thickness.

4. Conclusions

There were two principal objectives to this study. Firstly, the use of texture analysis as a means of characterising alginate rafts has been examined. The data presented here have demonstrated that this method is highly useful; the equipment may be easily calibrated and standardised while also allowing assessment of the entire breaking process, giving information not only on the maximum breaking strength but also on the work involved. This may be particularly important when one considers the likely biological fate of these raft systems, as the resistance to deformation may be just as important as rupture strength in an *in vivo* situation.

The second objective was to assess the effects of formulation variables on raft characteristics. The study has clearly shown that the choice of alginate may have a profound effect on raft strength, with both the molecular configuration and molecular

weight being of importance. In general, it would appear that high molecular weight, high G ratio alginates are optimal in forming strong rafts. In addition, the choice of gas-forming agent has been investigated, with potassium bicarbonate forming stronger rafts than sodium bicarbonate systems. This may be a function either of the bubble-forming characteristics of these materials or due to the effect of the monovalent ions on the characteristics of the precipitated gel. The presence of the divalent cations resulted in the expected increase in raft strength, although it is interesting to note that zinc is comparable in this effect to the more widely studied calcium. The pH of the medium was also shown to be of considerable importance, with increased acid strength resulting in thicker and stronger rafts.

Overall, the study has demonstrated that the characteristics of alginate rafts are highly sensitive to formulation factors and the choice of alginate, and that these systems may be usefully studied using the novel technique of texture analysis. There are almost certainly several factors which determine raft thickness and breaking strength including the extent of precipitation, structure of the precipitated gel and characteristics of the bubbles produced by the various agents. By delineation of the formulation variables, it is hoped that rational design of these products and, eventually, elucidation of the relationship between raft strength and in vivo performance may be facilitated.

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