ELSEVIER

International Journal of Pharmaceutics 105 (1994) 97–101

international journal of pharmaceutics

Research Papers

A comparison of the gastric retention of alginate containing tablet formulations with and without the inclusion of excipient calcium ions

N.M. Davies [1], S.J. Farr, I.W. Kellaway *, G. Taylor, M. Thomas [2]

Welsh School of Pharmacy, UWCC, Cardiff CF1 3XF, UK

(Received 19 August; Accepted 8 October 1993)

Abstract

Gamma scintigraphy has been used to monitor the gastric residence of tabletted alginate preparations. It was found that a new formulation of Gaviscon tablets containing calcium carbonate as an excipient formed a raft which persisted in the stomach for approx. 2 h. In contrast, the raft formed from Gastrocote tablets readily dispersed and emptied with the food contents of the stomach. In vitro experiments illustrated a greater raft breaking strength for the 'new' Gaviscon tablets but raft thickness and time of raft formation were similar for both preparations. The study suggests that new Gaviscon tablets may display superior anti-reflux activity and that the ability to form a strong persistent raft may be influenced by the ion content of the formulation.

Key words: Gastric retention; Alginate raft; Gamma scintigraphy

1. Introduction

The inherent gelling properties of alginates are utilised in formulations for preventing oesophageal reflux. After ingestion, alginates can produce raft-like structures that float on the stomach contents. These may serve as mechanical barriers inhibiting reflux or provide neutral material for preferential discharge, should such an episode occur. 'Liquid Gaviscon' forms a strong raft in vitro which has also been shown to remain in the upper part of the stomach for 1–2 h (Washington et al., 1986). However, alginate formulations may occasionally contain high proportions of Mg^{2+} or Al^{3+} ions. Whilst these ions are included for their buffering activity, they also appear to reduce raft strength. In contrast, Ca^{2+} ions are important to the alginate gelling mechanism (Rees, 1972). Alginates contain or comprise polyguluronate chains which form linear corrugated shapes. When packed together, interstices occur in the structure in which suitable cations may be accommodated. Stability is enhanced by the presence of sufficient oxygen atoms suitably placed on each chain producing a complete coor-

* Corresponding author.

[1] *Present address:* School of Pharmacy, University of Otago, P.O. Box 913, Dunedin, New Zealand.

[2] *Present address:* Glaxo Group Research Ltd, Park Road, Ware, Herts SG12 0DP, U.K.

SSDI 0378-5173(93)E0313-F

dination sphere. This arrangement is described by Rees (1977), as the 'egg box model'. The configuration results in a screening of the electrostatic charge that would otherwise cause the chains to repel, thereby enhancing the formation of a cross-linked matrix. It is believed that hydrated Mg^{2+} and Al^{3+} ions are unable to fit into this packing arrangement.

To date, reports in the literature regarding in vivo raft formation experiments have been largely based on liquid preparations. Therefore, the aim of the present study was to evaluate the performance of tabletted alginate preparations. A randomised cross-over study in 12 volunteers was performed, comparing raft formation in vivo of alginate preparations containing Mg^{2+} and Al^{3+} ions, with and without the presence of excipient Ca^{2+} ions. The behaviour of the formulations in relation to raft formation and gastric retention was monitored by gamma scintigraphy over a 3 h period.

To further characterise the properties of the raft, in vitro studies that included breaking strength, time for raft formation and raft thickness were also performed on the tabletted preparations.

2. Materials and methods

2.1. Materials

Two Gaviscon tablets (Reckitt & Colman Products), labelled with 3 MBq ^{113m}In and two Gastrocote tablets (MCP Pharmaceuticals Ltd) labelled with 2 MBq ^{113m}In were used.

2.1.1. Test meal

The test meal consisted of the following: two slices (60 g) toasted white bread; 200 ml unsweetened orange juice; 25 g butter; 30 ml milk; and two scrambled eggs labelled with 3 MBq ^{99m}Tc tin colloid (total calorific value 2554 kJ (611 kcal)).

The meal was labelled according to an established method (Washington et al., 1987) by addition of 3 MBq ^{99m}Tc to the eggs prior to cooking.

Gaviscon and Gastrocote tablets were each labelled by the addition of 2 MBq ^{113m}In. 1 ml of ^{113m}In eluate was diluted to 10 ml with absolute ethanol. The quantity of diluted eluate required to give the correct activity at the time of administration was added to each tablet in 100 μl aliquots. Approximately one quarter of the total was applied to each side of each tablet and the solvent evaporated by warm air. This technique did not affect the physical aspects of the tablets and the ^{113m}In has been shown to remain bound to the alginate component under in vitro test conditions.

2.2. In vitro studies

2.2.1. Assessment of ^{113m}In binding to the dosage form

Two tablets labelled as described above were crushed using a small mortar and pestle. The resulting powder aggregates were mixed with 10 ml of water before transference to a 100 ml measuring cylinder. 0.1 M HCl was added carefully so as not to disperse the alginate raft. Gamma camera images were taken in order to assess the activity associated with the raft over 3 h. The results are illustrated in Fig. 1.

2.2.2. Raft strength

The apparatus consisted of a stainless-steel wire probe (diameter 1.6 mm) the end of which was formed into a loop (diameter 18.3 mm) and set at a 90° angle to the shaft. The probe was motor driven which ensured a constant rate of travel through the liquid. Half a 'new' Gaviscon or one Gastrocote tablet was finely ground and wetted with 5 ml of distilled water. This mixture was added to a 100 ml beaker containing 60 ml of 0.03 M HCl, previously warmed to 37 ± 1°C. After stirring for 30 s, the beaker was placed on a top pan balance and the probe lowered so that the loop was situated beneath the alginate material. The raft was allowed to form for 5 min before taring the balance and commencing the experiment. As the probe was raised through the raft, force fluctuations were recorded by a programmed BBC micro-computer, and the peak value was taken as the breaking strength of the raft.

2.2.3. Time for raft formation

125 ml of 0.03 MHCl in a 250 ml beaker was warmed to 37 ± 1°C and half a new Gaviscon or Gastrocote tablet was prepared as above and added to the acid. The time for the majority of the alginate material to move to the top half of the beaker was recorded.

2.2.4. Raft thickness

The gel suspension from above was returned to a 37°C water bath and after raft formation had been allowed to take place for 20 min, the thickness of the raft was measured in four places and the mean calculated.

2.3. In vivo study

2.3.1. Scintigraphic test procedure

12 healthy volunteers (Caucasian, male or female, aged 18–40 years) participated with informed consent. The protocol was approved by the South Glamorgan Joint Ethics Committee and conducted in accordance with the Declaration of Helsinki.

An open cross-over study was performed, allowing a 7 day washout period between treatments. Following an overnight fast, volunteers had radioactive anterior and posterior markers placed on the thorax opposite the stomach to allow accurate alignment of subsequent images. They then consumed the standard ^{99m}Tc-labelled meals, followed 30 min later by two ^{113m}In-labelled Gaviscon tablets or two labelled Gastrocote tablets chewed with 100 ml water.

Volunteers stood in front of a G.E.C. Maxicamera II fitted with a medium-energy, parallel-hole collimator (400 keV maximum) immediately after consuming the meal. Anterior and posterior images of 30 s duration were taken at 10 min intervals for 3 h post tablet administration. Indium and technetium channels were monitored simultaneously.

2.3.2. Data analysis

Images from each channel were analysed by creating two regions of interest; one around the whole stomach and a second to assess background activity. The count rates from the region of interest around the stomach were corrected for background radiation and decay of the isotope. The ^{99m}Tc count rates were also corrected for ^{113m}In scatterdown into the technetium channel. The activity in the stomach was calculated as the geometric mean of the anterior and posterior images. This corrected for the movement of the isotope from the fundus to the antrum, since the fundus is closer to the posterior of the body (Hardy and Perkings, 1985).

Graphs of per cent of meal and Gaviscon or Gastrocote formulations remaining in the stomach with time were constructed for each subject for the initial and final tests.

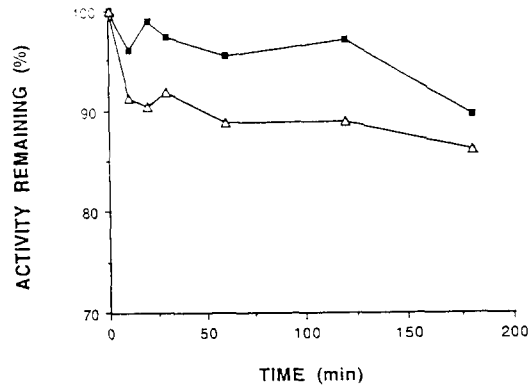

Fig. 1. In vitro assessment of the ^{113m}In labelling efficiency of alginate rafts. (■) Gaviscon raft; (△) Gastrocote raft.

3. Results and discussion

Fig. 1 illustrates that the labelling procedure efficiently binds the isotope to the alginate content of both dosage forms for at least 3 h under in vitro test conditions.

The small SE values displayed in Fig. 2a and b illustrate that there was little intersubject variation in the data. The results for gastric residence (expressed as AUC 0–180 min) of each radiolabelled component were analysed using two-way ANOVA and Duncan's Multiple Range Test ($p < 0.05$). The results indicated that gastric emptying of the meal was the same in the presence of each formulation. It was also evident from the scintigraphs that new Gaviscon tablets formed a

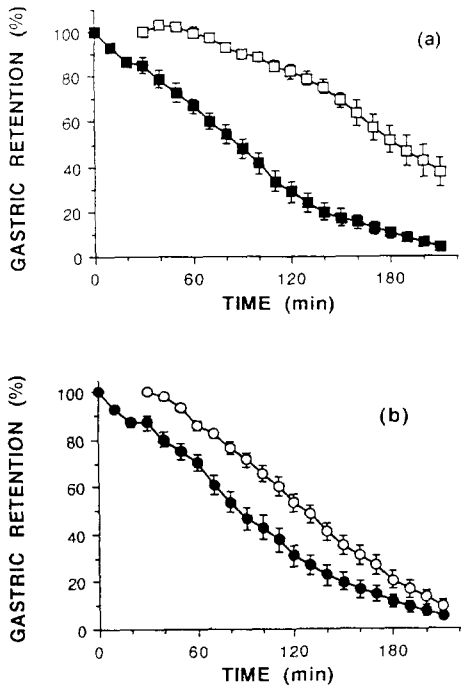

Fig. 2. Gastric retention (±SE) of alginate containing tablet formulations in relation to a standard meal in healthy volunteers. (a) Gaviscon: (□) test meal, (■) ($n = 11$); (b) Gastrocote: (○) test meal, (●) ($n = 12$).

raft which persisted for approx. 2 h, when 80% of the activity remained within the stomach. In contrast, only 40% of the Gastrocote activity, which appeared to be dispersed within the food, was detectable in this area after 2 h. These observations were supported by significant differences in AUC values between new Gaviscon (^{113m}In) and both food (^{99m}Tc) and Gastrocote (^{113m}In). Consequently, the gastric residence of Gastrocote was similar to that of the labelled meal, whereas Gaviscon was significantly slower. It was only after a substantial amount of food had left the stomach, i.e., after 110 min, that the Gaviscon raft descended to the lower regions and in comparison to the earlier stages of the study, a faster rate of alginate emptying was observed.

In order to form a physical barrier between the oesophagus and stomach contents, the alginate material must not only form a persistent coherent mass but also position itself correctly in the upper gastric area. The reaction between $NaHCO_3$ present in the formulation and gastric acid releases carbon dioxide which elevates the raft. However, it has been shown (Washington et al., 1987) that in addition to interfering with the cross-linking process of the gel, particulate antacids in the formulation may compete with the $NaHCO_3$ for H^+ ions. Table 1 illustrates that both formulations contain approximately equal quantities of $Al(OH)_3$ and $Mg(OH)_2$. However, Gaviscon contains a higher quantity of $NaHCO_3$ and in addition the ratio of particulate antacids to alginic acid is approx. 1:2 for Gastrocote and 1:4 for new Gaviscon tablets. In the latter, a supply of Ca^{2+} ions are available from a subtherapeutic amount of calcium carbonate in the formulation which may further strengthen the raft. Since it is possible that the superior behaviour of new Gaviscon tablets in vivo may be due to the higher amount of alginic acid, in vitro studies were performed comparing half a Gaviscon tablet with one Gastrocote tablet. Time for raft formation and raft thickness (Table 2) were similar for both formulations, but breaking strength was far greater for Gaviscon tablets. It was observed during these studies that, in comparison to Gastrocote, the raft formed by Gaviscon tablets appeared a much more coherent mass. On a theoretical basis, this was assumed to be the result of a higher degree of cross-linking achieved in the Gaviscon raft. Therefore, the in vitro data suggest

Table 1
Composition of new Gaviscon and Gastrocote tablets

Tablet	Alginic acid	Dried aluminium hydroxide	Magnesium trisilicate	Sodium bicarbonate	Calcium carbonate
Gaviscon	500 mg	100 mg	25 mg	170 mg	40 mg
Gastrocote	200 mg	80 mg	40 mg	70 mg	0

Table 2
In vitro results for new Gaviscon and Gastrocote tablets ($n = 5$)

Tablet	Mean raft strength (g)	SX	Mean raft time (s)	SX	Mean raft thickness (cm)	SX
Gaviscon (half tablet)	2.86	0.30	34	3	1.5	0.2
Gastrocote (one tablet)	1.60	0.14	38	8	1.3	0.2

that the poor raft formation in vivo displayed with the Gastrocote preparation appears to be due to the ionic composition of the formulation as opposed to the amount of alginic acid present.

In conclusion, from the above study on the residence of tabletted alginate preparations, it would appear that the new formulation of calcium strengthened Gaviscon has a longer gastric residence than the Gastrocote preparation. This suggests that the former may display superior anti-reflux activity. The study also indicates that the ability of an alginate to form a strong persistent raft in vivo may be influenced by the ion content of the formulation.

4. References

Hardy, J.C. and Perking, A.C., Validity of the geometrical mean correction in the quantification of whole bowel transit. *Nucl. Med. Commun.*, 6 (1985) 217–224.

Rees, D.A., Polysaccharide gels. A molecular view. *Chem. Ind.*, 19 (1972) 630–636.

Rees, D.A., *Polysaccharide Shapes*, Chapman & Hall, London, (1977) pp. 51–52.

Washington, N., Washington, C., Wilson, C.G. and Davis, S.S., The effect of inclusion of aluminium hydroxide in alginate containing raft-forming antacids. *Int. J. Pharm.*, 28 (1986) 139–143.

Washington, N., Washington, C. and Wilson, C.G., Gastric distribution and residence time of two anti-reflux formulations *Int. J. Pharm.*, 39 (1987) 163–171.