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Effect of dose size, food and surface coating on the gastric residence and distribution of an ion exchange resin

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Abstract

Ion exchange resin displays prolonged gastric residence and uniform distribution over the gastric mucosa when given in a small volume of water to fasted subjects. The aim of this study was to explore factors which could influence the observed gastric retention, for example the quantity of resin administered, the fed state of the subject, and the surface charge of the resin. The study was performed as a single blind, three-way crossover in 12 healthy volunteers using gamma scintigraphy to visualize the distribution of the resin in the stomach. On the first two occasions each subject received either a 25 mg or 250 mg dose of cholestyramine (an anionic exchange resin) in 1 ml of water. On the last occasion each volunteer received 250 mg of cholestyramine coated with the inert polymer ethylcellulose, to determine if the gastric residence of the resin was influenced by the surface properties of the particles. For all formulations, half of the subjects were fed 4 h after dosing to determine the effects of inducing a fed pattern of motility on the gastric retention of the resin. Gastric retention was measured as the area under the stomach activity–time curve (AUC). Median AUC values (relative units) for the 25 mg, 250 mg and polymer coated 250 mg doses were 139.6, 199.6 and 146.0 respectively, for fasted subjects and 164.1, 256.9 and 176.1 for fed subjects. Approximately 20% of the resin persisted in the stomach for the entire 6 h of the study in every case, and this was distributed evenly throughout the fundus, body and antrum. Statistical analysis of the data showed no significant differences between the gastric emptying and distribution of any of the data sets. It can be concluded that the prolonged gastric residence and uniform distribution of ionic resins is not influenced by the dose size and that the binding of the dose to the mucosa is sufficiently strong to retain the dose during feeding 4 h after administration. The mechanism by which resin becomes mucoadherent is not clear; however, these results indicate that it is unlikely to be due to a charge-based attraction.

Keywords: Stomach; Drug delivery; Ion exchange resin; Cholestyramine; Gastric emptying; Bioadhesion; Mucoadhesion

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1. Introduction

Although the stomach is one of the most accessible structures of the gastrointestinal tract, it is paradoxically one of the most difficult to treat in a range of diseased conditions. In particular, treatments targeting the gastric mucosa have a poor success rate with most therapeutic regimens due to erratic emptying and poor distribution of the dosage forms used. A means for achieving efficient topical treatment of the whole stomach would be of value in the treatment of all diseases of the upper gastrointestinal tract, but in particular for *Helicobacter pylori* (*H. pylori*) infection.

H. pylori is a highly virulent pathogen of the stomach and duodenum which infects up to one in four people in the adult population. It has been shown to cause both acute and chronic gastritis (Slomiany and Slomiany, 1992) and recently it has been implicated in the occurrence and relapse of peptic ulcer disease and possibly the development of gastric cancer (Barreto-Zuniga et al., 1997). The bacterium colonizes the gastric mucus throughout the stomach (Quigley and Turnberg, 1987) and has proven extremely difficult to eradicate. Spontaneous eradication of *H. pylori* appears to be quite rare despite a seemingly adequate local and systemic immune response. It is most often found in the antrum of the stomach within the mucous layer, above the mucosa or along the luminal surfaces of those cells lining the gastric pits (Slomiany and Slomiany, 1992). The difficulty of eradicating *H. pylori* can be directly linked to the absence of a suitable therapeutic procedure for attaining a bactericidal concentration of antibiotics at the gastric mucosa over a suitably extended period, together with increasing bacterial resistance to the antibiotics used (Glupczynski and Burette, 1990). Current treatments include a triple therapy consisting of colloidal bismuth, which has a direct effect on the pathogen, together with two antibiotics such as amoxycillin and metronidazole; more recently clarithromycin is preferred. The tablets and capsules used to deliver these drugs are however distributed unevenly throughout the stomach, with the majority of the dose being delivered to the base of the stomach and relatively little drug reaching the fundus. Therapeutic concentrations of antibiotics have to be attained via systemic absorption, and the advantages of local topical effects are lost.

The optimum delivery system for the treatment of *H. pylori* infection would evenly distribute the drug throughout the stomach and would remain in close contact with the gastric lining for a prolonged time. Work by this group has shown that targeted delivery to the gastric mucosa can be achieved using small doses of finely powdered ion exchange resins. When administered in small volumes to fasted subjects, these have prolonged gastric residence with remarkably uniform coating of the gastric mucosa (Washington et al., 1989). The aim of this study was to investigate whether administering larger doses of resin, feeding subjects after dosing with resin or masking surface charges on the resin particles using an inert polymer had any effect on the coating and distribution properties of the resin in the stomach. In order to assess the effect of surface charge interactions on gastric adhesion, a sample of ion exchange resin was coated with ethylcellulose. This was expected to mask the surface charge, and if the binding to the mucosa was ionic in nature, this should reduce the extent of gastric retention.

2. Methods

2.1. In vitro studies

2.1.1. Stability of resin radiolabelling

The binding of technetium-99m (Tc-99m) to the cholestyramine resin in hydrochloric acid was determined as an indication of the labelling stability in the stomach. Cholestyramine, the cationic resin used in this study, was Duolite AP-143, sieved to a particle size 90–125 μm (Rohm and Haas, France. B.P. No. 48). Radiolabelled resin was made by adding 3 MBq Tc-99m pertechnetate solution to 250 mg of resin and drying thoroughly before sieving. This was then added to 50 ml of 0.03 M HCl and three 1-ml samples were removed and filtered using a 0.2-μm syringe filter every 2 h for 6 h. A gamma detector (Novo Memolog 600 system, Vertec Scientific, Reading, UK) was used

to determine the extent of radiolabelling of the resin and supernatant. All samples taken were counted at the end of the experiment to account for isotopic decay. The weight of resin and the supernatant were recorded, and the percentage of radioisotope remaining bound to the resin was calculated.

2.1.2. Polymer coating

Ethylcellulose (1.5 g) was dissolved in 15 ml dichloromethane. Approximately 18 ml of hexane was added dropwise to the solution whilst stirring until a slight cloudiness was observed; 4.5 g radiolabelled cholestyramine was added to this and the resulting mixture was stirred until most of the solvent had evaporated. Hexane (250 ml) was then added to harden the microcapsules, and stirred for 10 min. The residue was then filtered off and thoroughly washed with hexane. The residue was left to air dry before being passed through a 178-μm sieve to remove the larger aggregated particles.

2.1.3. Surface modification of resin by polymer coating

The effects of polymer coating on the surface properties of the resin were determined by measuring the zeta potential before and after coating. Since the zeta potential of the resin probably varies with pH, it was necessary to measure it in an acid environment corresponding to the gastric pH. Samples of both coated and uncoated resins were suspended in 0.01 M hydrochloric acid (pH 2) and the largest particles were allowed to sediment (approximately 5 min) prior to injecting the suspension into a Doppler electrophoresis instrument (Malvern Zetasizer 4, Malvern Instruments, Worcs., UK). Four separate measurements were made and averaged for each sample.

2.2. In vivo studies

2.2.1. Ethical considerations and volunteer information

Seven males and five non-pregnant females between the ages of 18 and 45 were recruited from the student population of the University of Nottingham and the staff of the Queen's Medical Centre. The subjects completed a medical questionnaire prior to entry into the study to ensure their fitness to participate. All volunteers received written and verbal information concerning the trial. Approval was gained from the Nottingham University Ethical Committee. An ARSAC licence to allow the administration of radioisotopes to healthy volunteers was issued by the Department of Health. All females were pregnancy tested on the morning of each study day.

2.2.2. Measurement of the gastric residence and distribution of ionic resins

Anterior and posterior markers containing a small amount of isotope (< 0.2 MBq) were placed on the thorax opposite the stomach to allow accurate alignment of subsequent images.

The subjects were randomized to receive either a 25 mg dose or a 250 mg dose of radiolabelled cholestyramine resin with the cross-over being performed 1 week later. On the last day 250 mg of polymer coated resin was administered to all 12 subjects. Each dose was radiolabelled with 3 MBq Tc-99m as previously described. Six volunteers were fed a light meal every week 4 h after being dosed. The same subjects were fed every week.

An IGE Maxicamera II (IGE, Herts., UK) was used to image the passage of the resin through the stomach. A low energy collimator was fitted to the gamma camera and the view was focused at the photopeak of 141 keV. Images were taken anteriorly and posteriorly for 30 s at approximately 20-min intervals for a total of 6 h after dosing. All images were stored as a 64×64 matrix on a Nuclear Diagnostic (Gravesend, Kent, UK) computer system for analysis.

2.2.3. Data analysis

Counts and pixel area for five regions of interest (ROI) were calculated. These were the whole stomach, fundus, body, antrum and a background area. The activity in the stomach was calculated as the geometric mean of the anterior and posterior images to correct 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 Perkins, 1985). These values were then corrected for background radiation and iso-

topic decay prior to normalization and interpolation. The area under the percent remaining-time curve ($AUC_{0-6\,h}$) for each ROI was used as a measure of total gastric residence time, and the Mood's Median test for non-parametric data was used to compare the gastric emptying times of the following groups:

1. Dose sizes 25 and 250 mg;
2. Polymer coated and uncoated 250 mg dose;
3. Fasted and fed subjects.

3. Results

3.1. In vitro studies

3.1.1. Stability of resin radiolabelling

Over 99.9% of the Tc-99m label was retained on the resin after 6 h at pH 1.5. Consequently, it is unlikely that the label became dissociated from the resin during the course of the experiment.

3.1.2. Surface modification of resin particles

The coated resin had a similar appearance to the uncoated material. The particle size was not directly measured after coating, although the powder could still pass through a 125-μm sieve. The surface potentials of the uncoated and coated resins were $+38 \pm 3$ and $+18 \pm 3$ mV at pH 2 respectively, indicating a significant degree of charge masking by the coating.

3.2. In vivo studies

Subjects tolerated the study well; however, the resin was reported to be unpleasant to swallow, particularly at the largest dose and in the polymer coated form. Oesophageal transit of the resin could be observed in most subjects in the first image. In some subjects resin was still visible in the oesophagus after 20 min.

3.2.1. Gastric emptying of ionic resins

The mean emptying patterns for both fasted and fed subjects are shown in graphical form in Figs. 1 and 2. The times taken for 50% of the resin to empty from the stomach of fasted and fed subjects are shown in Table 1 and statistical analysis showed no significant differences between these results. The AUCs for each region of interest are shown in Table 2. Differences in the AUCs of both doses of uncoated and coated cholestyramine from each region of interest were also not significant. The percentages of resin remaining in the stomach of fasted subjects after 6 h were 15.7, 23.5 and 22.4 for 25 mg uncoated, 250 mg un-

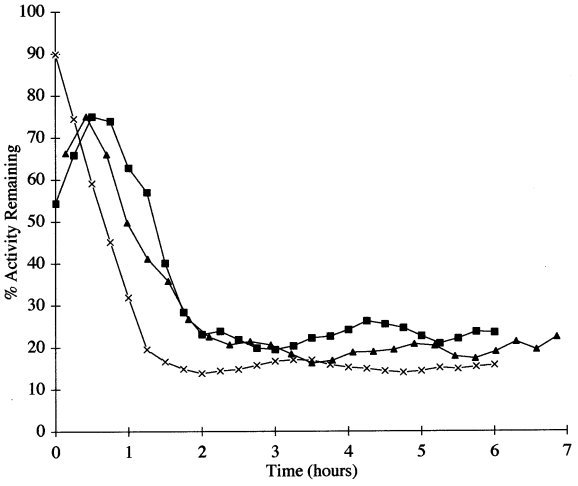

Fig. 1. The mean emptying patterns (% activity vs. time) for fasted subjects. ×, 25 mg resin dose; ■, 250 mg resin dose; ▲, 250 mg polymer coated resin dose.

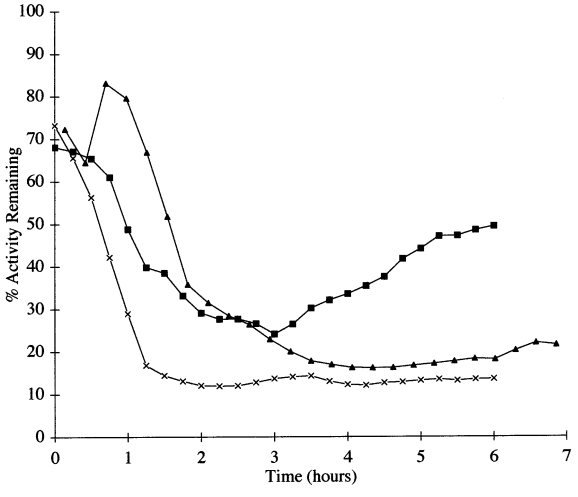

Fig. 2. The mean emptying patterns (% activity vs. time) for fed subjects. ×, 25 mg resin dose; ■, 250 mg resin dose; ▲, 250 mg polymer coated resin dose.

Table 1
Time taken (h) for 50% of resin to leave stomach

	Fasted	Fed
25 mg	0.51 (0.27–1.06)	0.77 (0.50–1.07)
250 mg	1.3 (0.70–1.61)	0.79 (0.46–1.41)
PC-250 mg	0.73 (0.52–1.45)	1.08 (0.76–1.56)

Values are median with interquartile range in parentheses.

coated and 250 mg polymer coated resin respectively. The corresponding values in fed subjects were 13.6, 49.5 and 21.6%.

3.2.2. Distribution of the ion exchange resin

Fig. 3 shows the percentage of activity remaining in the antrum, body, and fundus of the three treatment groups, averaged over the period 2–6 h, during which the activity due to the bound resin was in the plateau phase. The body of the stomach showed slightly greater binding than the fundus or antrum due to its larger area, and the 250 mg uncoated formulation showed greater binding than the 25 mg or coated 250 mg formulations. However, due to the wide degree of variation between the subjects, the differences did not approach the 95% confidence level.

4. Discussion

Previous work by this group has suggested that ion exchange resins have an extended gastric residence time and coat the gastric mucosa uniformly (Burton et al., 1995). The mechanism by which this occurs has not yet been characterized but one possibility is that these properties could be due to ionic mucoadhesion of the resin in combination with the fasted state of the subjects. The results of this study suggest that this is not the case, since adhesion of the resin was observed for all the formulations studied, although some differences in behaviour were noted.

Anionic polymers such as cholestyramine have been shown to display better mucoadhesive properties in vitro when compared to cationic polymers (Park and Robinson, 1984). This was thought to be due to ionic interactions between the highly charged surface of the polymers and the mucus. However although some type of mucoadhesive mechanism is likely for the behaviour of ionic resin in this study, surface charge is not a necessity since the polymer coated resin displayed similar characteristics to the uncoated resin.

The interaction between the resin and the mucus appears to be very strong, since in the 6-h period in which the subjects were studied, the adherent resin was not removed by migrating myoelectric complexes in the fasted volunteers, nor was it dislodged by food in the fed subjects. Mucus turnover is thought to occur in 4–5 h, but the bound activity enters a plateau phase after 2 h. This suggests that the resin is not dislodged by mucus loss, or, more likely, that the mucus turnover times are significantly higher than those proposed in the literature. This may be due to hypersecretion after tissue irritation, occurring as a result of the technique employed to measure turnover (Washington et al., 1989). Nevertheless some loss of resin due to turnover would be expected during the course of the study. Feeding stimulates mucus production by mechanical abrasion, and it may be expected that this would increase the emptying of the resin in the fed subjects compared to the fasted group, but this was not observed.

Saturation of the gastric mucosa with resin is not a possibility at these dose sizes as a constant percentage of resin remained in the stomach rather than a finite amount. It is possible that the resin travels through the stomach as a bolus and only resin coming into contact with the mucus will stick to it. The small volume of water administered with the resin encourages slow gastric transit, further enabling good stomach coating and ensuring that a fed pattern of motility is not induced (Oberle et al., 1990). The water, and the resin not making contact with the stomach lining, will empty with the gastric secretions which are being continuously passed into the duodenum.

The fact that the resin that was coated with an inert polymer also displayed extended gastric retention demonstrated that this behaviour is not solely a property of ionic resins. Due to the chemical nature of ethylcellulose, hydrogen bonding between the polymer and mucus is possible. It

Table 2
Gastric emptying time in each region of interest, demonstrated by AUCs

	Fasted			Fed		
	25 mg	250 mg	PC-250 mg	25 mg	250 mg	PC-250 mg
Whole stomach	139.6 (96.1–185.4)	199.6 (138.6–260.4)	146.0 (118.8–229.2)	164.1 (143.9–226.3)	256.9 (172.6–318.8)	176.1 (159.9–249.5)
Fundus	36.6 (28.1–56.5)	60.4 (34.6–74.8)	42.4 (24.7–49.4)	52.1 (23.6–71.6)	92.0 (64.2–132.3)	52.1 (23.6–71.6)
Body	47.4 (40.4–67.2)	69.7 (50.4–123.1)	61.2 (37.4–111.7)	74.7 (59.9–95.3)	113.8 (68.7–138.2)	92.3 (68.1–119.1)
Antrum	23.5 (17.4–71.8)	51.3 (27.2–111.0)	32.4 (19.6–68.6)	40.6 (26.3–78.0)	46.6 (29.7–69.9)	28.2 (16.9–47.0)

Values are median with interquartile range in parentheses.

may also be that any small particle, when given in a small volume of water, could adhere to the mucus. In the present study the fine particles will not sediment to the base of the stomach and will have an extended opportunity to coat the stomach wall uniformly.

In fed subjects at the 250 mg dose an increase in activity remaining in the whole stomach was seen after feeding, although this was not statistically significant over the whole group. Previous studies have shown that a proportion of finely milled resin, administered in a small volume of water, remains trapped in the papillae of the tongue (Washington et al., 1989) and in the oesophagus (Burton et al., 1995). This is probably the reason that the resin does not appear rapidly in the stomach after administration; the oesophageal transit of liquids is less than 1 min, but the resins studied here show maximum gastric activity only on or after the second image was taken at 30 min after dosing. A further clearance effect may be the cause of the increase in gastric activity in the 3–6 h region for the 250 mg dose of the uncoated resin. It is even possible that this material is cleared from the mouth by reflex salivation, since the increase in gastric activity is observed in the image slightly prior to feeding. The effect is not seen with the coated resin, suggesting that a degree of control over the effect may be achievable by appropriate formulation.

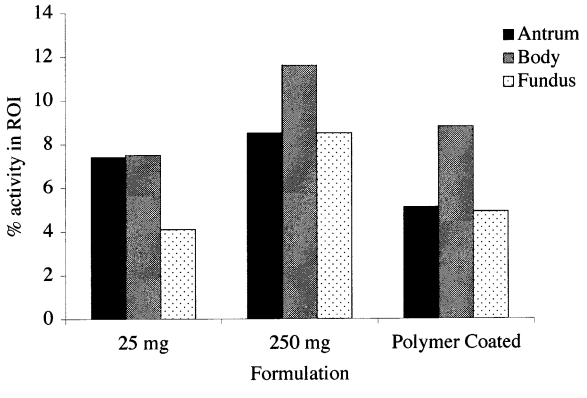

Fig. 3. Percentage of activity remaining in the antrum, body, and fundus of the three treatment groups, averaged over the period 2–6 h.

In the fasted state the stomach is collapsed with many prominent rugaes particularly in the distal stomach. If resin simply became trapped in these folds then one would expect both housekeeper sequences and ingestion of food to either sweep the resin out of the stomach or into the antrum. This, together with the uniform intragastric distribution of the resin, suggests that simple mechanical trapping of this type is not occurring.

Another group has used a different approach to increasing the gastric residence time of ion exchange resins (Atyabi et al., 1996). This group loaded resins (Amberlite IRA 400 mean particle size 400 μm and Dowex 2 $\times$ 10 mean particle size 279 μm) with sodium bicarbonate and coated the resin with Eudragit RS. In this case the system was designed to float as the sodium bicarbonate reacted with the gastric acid to produce bubbles

of carbon dioxide which became trapped within the semipermeable membrane. Gastric residence of the resin was demonstrated to be enhanced when coated, but this was through floatation and not coating the mucosa.

The findings of the current study indicate that ion exchange resins have possible therapeutic value as drug delivery vehicles in topical treatment of the stomach due to their extended gastric residence and uniform coating of the stomach. Ion exchange resins have long been used in pharmaceutics and medicine. Drugs may be absorbed on the resin to form complexes which can then be used to mask the bitterness of some drugs, and to provide sustained or controlled release of others (Borodkin, 1991). With regard to *Helicobacter pylori* this has possible use in both the diagnosis and treatment of bacterial infection. False negative cultures are common in antral mucosa biopsies taken immediately after cessation of treatment, partly due to the reduced numbers of bacteria and the patchy nature of their distribution. Recrudescence of the infection is common and long-term eradication is often not achieved. The urea breath test, commonly used in diagnosis, could be made more reliable by the use of ionic resins as carriers for the urea, thus allowing all areas of infection to be reached.

5. Conclusions

Approximately 20% of the resin persists in the stomach for the entire 6 h of the study regardless of dose size, polymer coating or feeding. This was distributed evenly throughout the fundus, body and antrum. These results indicate considerable potential for the application of these materials as drug delivery systems for the stomach.

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