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Effect of resin surface charge on gastric mucoadhesion and residence of cholestyramine

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Abstract

Previous studies performed on excised gastric tissue and in healthy volunteers revealed that the ion exchange resin, cholestyramine, exhibits mucoadherent behaviour. This study was designed to elucidate whether surface charge affected this behaviour. Gamma scintigraphy was performed on fasted normal subjects following oral administration of cholestyramine or the cationic exchanger Amberlite® IRP-69, either uncoated or polymer-coated to mask their charge. Subjects were fed after 4 h. The initial gastric emptying of all formulations was similar (T_{50} values (mean ± S.E.M.): cholestyramine = 85.86 ± 9.16 min; IRP-69 = 76.09 ± 9.23 min; polymer-coated cholestyramine = 72.0 ± 12.64 min; polymer-coated IRP-69 = 70.25 ± 10.57 min: $P = 0.724$). However, after 3 h the emptying pattern of cholestyramine was slower than that of IRP-69. This resulted in greater retention times than IRP-69 (AUC_{0-6} values (relative units) = 15200 ± 1093 versus 9452 ± 811; cholestyramine versus IRP-69: $P = 0.0004$). This effect was reduced by polymer-coating the cholestyramine. Serial images showed that cholestyramine was trapped in the oropharyngeal region and subsequently displaced by the meal, resulting in higher levels of activity remaining at 6 h. Thus, cholestyramine exhibited prolonged gastric residence via mucoadhesion and was distributed throughout the stomach. The surface charge of the resin was found to have a contributory role. These materials may have potential for the delivery of drugs in the topical treatment of the gastric mucosa, for example in the eradication of *Helicobacter pylori*.

Keywords: Cholestyramine; Gastric residence; Ion exchange resin; Amberlite® IRP-69; Gamma scintigraphy; Surface charge

1. Introduction

Current therapies designed for the eradication of *Helicobacter pylori* (*H. pylori*) are usually delivered in tablet or capsule form which, being heavy, tend to fall to the base of the stomach and either empty quickly or remain in the antrum until the occurrence of the next migrating motor

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complex (Washington et al., 1989). Under these circumstances, potential topical drug delivery to the body and fundus of the stomach, where colonies of *H. pylori* are known to exist, is lost. Topical or site-specific drug delivery to the stomach, with reference to *H. pylori* eradication, has been the subject of a few recent investigations (Atyabi et al., 1996; Shah et al., 1999; Yang et al., 1999).

Previous studies have suggested that cholestyramine (Duolite® AP–143) provides extended gastric residence and has the ability to coat the gastric mucosa uniformly (Burton et al., 1995; Thairs et al., 1998); properties which would enhance the topical drug delivery of antibiotics to sites of *H. pylori* colonisation. The mechanism by which cholestyramine acts to increase gastric residence has yet to be fully characterised but previous trials (Burton et al., 1995; Thairs et al., 1998), and recent in vitro investigations (Jackson, 1999; Jackson and Perkins, 2000), have indicated that the resin has potential mucoadhesive properties. The prolonged retention and uniform distribution of cholestyramine has been shown in fed and fasted subjects (Burton et al., 1995; Thairs et al., 1998). This has the advantage over alternate floating systems that rely on the presence of gastric contents to target upper regions of the stomach (Atyabi et al., 1996; Yang et al., 1999).

Anionic polymers have been shown to exhibit greater bioadhesion in vitro when compared to cationic or neutral polymers (Park and Robinson, 1984). However, the ability of anionic polymers to behave as good bioadhesives to mucus/mucosa is likely to be due to factors such as hydrogen bonding. Since cholestyramine has a positive surface charge and the mucus itself is negatively charged at pH 2.8 and above (Longer and Robinson, 1986), any bioadhesive properties exhibited by this resin are more likely due to electrostatic forces. Recent in vitro studies have shown that anion exchange resins exhibit greater mucoadhesion to excised porcine and human gastric mucosa than cation exchange resins indicating a mechanism dependant on surface charge (Jackson and Perkins, 2000). The previous study characterising the effects of surface charge on the in vivo intragastric residence and distribution of cholestyramine concentrated on masking the positive charge of the resin, and their findings indicated that surface charge was not necessary for extended gastric residence (Thairs et al., 1998).

The present study was undertaken to clarify the in vivo behaviour of cholestyramine using gamma scintigraphy, and to determine the role of surface charge in gastric retention not only by masking the surface charge of the resin but by direct comparison to the behaviour of a cationic exchange resin. The effect of inducing a fed pattern of motility on the retention of the resins was also investigated by feeding the subjects 4 h after the administration of the formulations.

2. Materials and methods

2.1. Preparation of ion exchange resins

Cholestyramine (Duolite® AP-143, Rohm and Haas, France SA, particle size 90–125 μm) was regenerated and made suitable for human consumption according to manufacturer's instructions. This method of regeneration has been previously documented (Jackson, 1999; Jackson and Perkins, 2000). Amberlite® IRP-69 (Sigma, Dorset, UK) was regenerated using a similar method of alternate washings in 2 M hydrochloric acid (HCl) and 1.5 M sodium hydroxide (NaOH), with a final soak in 2 M HCl. The resins were rinsed and dried thoroughly.

2.2. Radiolabelling and stability testing of ion exchange resins

Cholestyramine was radiolabelled with Technetium-99m sodium pertechnetate (^{99m}Tc), dispensed by the Radiopharmacy Unit, Department of Medical Physics, Queen's Medical Centre, Nottingham. The required activity was added to the cholestyramine so that each 25 mg dose was radiolabelled with 3 MBq at 0900 h on each study day. Following a 5-min incubation, 20 ml of distilled water was used to rinse any unbound activity from the resin, and as much liquid as possible was decanted from the solid. The radiolabelled resin was then dried thoroughly back to a

dry weight powder, whilst stirring in a direct flow of warm air using a dryer. The same procedure was used to radiolabel each 25 mg dose of IRP-69 with 1 MBq Indium-111 chloride (^{111}In), again obtained from the Radiopharmacy Unit, Department of Medical Physics.

The stability of the radiolabelled resin was investigated over 6 h in acid conditions to simulate the action of gastric juice on the resin over the 6-h study period. Samples of the radiolabelled resins (25 mg) were added to 25 ml volumes of water, 0.03 M HCl, or simulated gastric juice (1 l of 0.03 M HCl with the addition of 24 mg pepsin, Sigma). The solutions were constantly agitated and incubated at 37°C over 6 h. Samples were taken at 2-h intervals and filtered to obtain resin and solution fractions. The masses of the fractions were calculated and the activity in each sample recorded using a gamma camera. The percentage of radiolabel bound to the resin over 6 h was then deduced.

2.3. Polymer coating of ion exchange resins

Ethylcellulose (0.3 g, Sigma) was dissolved in 15 ml dichloromethane (BDH, Poole, UK) and the radiolabelled resin added. The mixture was stirred for 15 min to allow the solvent to evaporate, after which 15 ml hexane (Fisher Scientific UK, Loughborough, UK) was added at a rate of 1 ml/min to precipitate out the particles. Approximately 50 ml hexane was then added to harden the microparticles and the preparation stirred for a further 15 min. The microparticles were filtered using a fast filter and rinsed with distilled water. The coated particles were then allowed to dry thoroughly for 12 h or overnight.

The effect of polymer coating on the surface charge of the resins was determined by measuring the zeta potentials of the resins before and after polymer coating. This was carried out on a Malvern Zetasizer 4 (Malvern Instruments, Worcs., UK) in the Department of Pharmaceutical Sciences, University of Nottingham. An average of three measurements was taken. As pH may affect the zeta potentials of the resins, all measurements were carried out in 0.03 M HCl (pH 1.5) to determine the surface charge under simulated gastric acid conditions.

2.4. Ethical considerations and subject selection

Approval for the trial was obtained from the University of Nottingham Medical School Ethics Committee and the Administration of Radioactive Substances Advisory Committee of the Department of Health.

A total of 12 healthy male and non-pregnant female subjects (four male, eight female; age range 18–59 years, average BMI 24) were recruited from the student and staff population of the University Hospital, Queen's Medical Centre, Nottingham. All subjects were screened by medical questionnaire to ensure their fitness to participate in the study. Exclusion criteria included excessive tobacco and alcohol consumption, history of gastrointestinal problems and consumption of medication considered to influence the study outcome. All subjects were given written and verbal information and written informed consent was obtained prior to the study. All female subjects were pregnancy tested on the morning of each study day.

2.5. Study procedure

The study was designed as a four-way randomised crossover study. Crossover trial days took place 7 days apart to allow for radioactive decay and biological clearance of each formulation.

Subjects were required to fast from 2100 h on the evening prior to the study. A single glass of water was allowed on waking in the morning to prevent dehydration. On the morning of each study day, anatomical markers were prepared from filter paper radiolabelled with 0.05 MBq ^{99m}Tc and sealed in waterproof tape. These were attached, one anterior and one posterior, to the abdomen of each subject in line with the top of the stomach and were used as points of reference to aid in data analysis. The subjects were then given a 25 mg dose in 1 ml water of either radiolabelled cholestyramine, IRP-69, polymer-coated cholestyramine or polymer-coated IRP-69.

Immediately after dosing, anterior and posterior static scintigraphic images of 30 s duration were taken every 25 min. These were repeated for

a total of 6 h. Hourly images of the mouth and oesophagus were also acquired to determine any buccal or oesophageal retention. The images were acquired using a Scintronix Model GRC1 gamma camera, located within the Department of Surgery, with a 48 cm diameter hexagonal field of view and a high-resolution general-purpose collimator. The images were stored on a Sun Sparc 4 workstation running Smart Soft applications (Park Medical, Farnborough, UK).

Subjects were fed a standard meal of ham or cheese filled rolls, a packet of crisps, a chocolate biscuit and a can of cola 4 h after the dose was administered. Eating and drinking were restricted at all other times during the study day.

2.6. Data analysis

Each anterior and posterior image was analysed by creating regions of interest (ROIs) around the whole stomach, the fundus, the body, the antrum and an area for background radiation. The number of counts and pixels within each ROI, displayed by the computer, were transferred to a spreadsheet, via an ethernet link to an Apple Macintosh computer running Microsoft Excel 5.

The counts from each ROI were corrected for background radiation and radioactive decay. The geometric mean for the anterior and posterior counts was then calculated to give the overall activity in the stomach, taking into account the position of the stomach in the body. The data from each individual were then interpolated to produce mean graphs and the standard errors of the mean. The area under the time-activity curve between zero and 6 h (AUC_{0-6}) was calculated to represent the total residence time within the whole stomach. The time taken for 50% of the activity to empty (T_{50}) from the whole stomach was also calculated. The AUC_{0-6} for each region was calculated taking into account the pixel size of each ROI. This compensated for any size variations between ROIs and was used to compare the distribution in each region between formulations.

As the data were normally distributed (determined using Minitab® for Windows Release 10.1 statistical package, Minitab), one way analysis of variance (ANOVA) and 2 sample t-tests were carried out to determine any statistical significant difference between the groups.

Table 1
Percentage of radiolabel bound to the ion exchange resins after 6 h in various dissolution media

Dissolution media	% Radioisotope bound to resin	
	Cholestyramine	Amberlite® IRP-69
Distilled water, pH 4.74	99.42	98.04
0.03 M HCl, pH 1.5	99.39	98.20
Simulated gastric juice, pH 1.5	98.39	98.45

3. Results

3.1. In vitro validation of the stability of the radiolabel

Over 98% of the ^{99m}Tc pertechnetate label remained bound to the cholestyramine resin after 6 h, when placed under simulated gastric conditions (Table 1). Incubation at pH 1.5 with either HCl or simulated gastric juice resulted in the loss of less than 2% of the radiolabel. IRP-69 radiolabelled with Indium-111 chloride also demonstrated a stability of over 98%, again over a 6-h period under the same acid and control conditions.

3.2. Zeta potential measurements

There was no difference in the physical appearance of the polymer-coated resins compared to the uncoated resins. The zeta potential of IRP-69 fell from -7.0 ± 1.5 to -1.2 ± 1.5 mV at pH 1.5 after coating. The reduction in the negative charge indicated that polymer coating had masked the surface charge. The zeta potential of cholestyramine dropped from $+15.8 \pm 1.5$ mV (uncoated) to $+2.2 \pm 1.5$ at pH 1.5 with polymer coating. This also showed a reduction in the positive charge on the resin and therefore indicated a degree of charge masking from polymer coating.

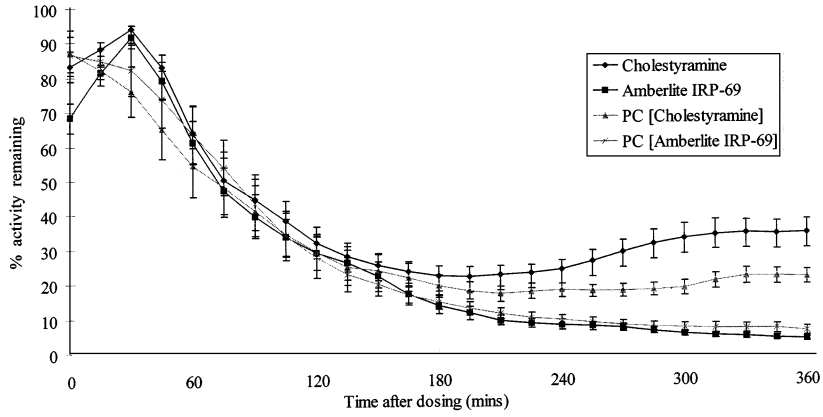

Fig. 1. Mean gastric emptying curves of polymer coated (PC) and uncoated cholestyramine and Amberlite® IRP-69 ($n = 12$: mean ± S.E.M.).

3.3. In vivo results

No adverse events were reported following administration of the radiolabelled formulations to subjects. Some subjects did comment on the unpleasant gritty texture of the resins on swallowing but the formulations were considered tolerable. Oesophageal transit of the doses was observed in some subjects during the first image acquisition, although this was not quantified.

Fig. 1 shows the mean gastric emptying curves for uncoated and coated cholestyramine and IRP-69, when given as a 1 ml suspension to fasted subjects. Gastric filling occurred with both uncoated IRP-69 and cholestyramine with maximum activity achieved within ~45 min, this was not seen with the polymer-coated formulations. From both Fig. 1 and Table 2, it is clear that there was no significant difference in the initial phase of gastric emptying for all formulations ($P = 0.724$). Beyond the first 3 h, the pattern of gastric emptying changed, with cholestyramine emptying more slowly. The overall gastric residence was therefore significantly greater for the coated and uncoated cholestyramine than for the IRP-69 formulations ($P = 0.001$) (Table 2).

A rise in gastric counts after 4 h, when the subjects were fed, was seen in both cholestyramine preparations, rising from 24.08 and 17.89% at 4 h to 34.40 and 21.64% for uncoated and coated cholestyramine, respectively. Although this rise in counts was still seen with the polymer-coated cholestyramine, the effect was reduced. A rise in counts for the IRP-69 formulations was not seen. There was a gradual decrease from 7.88 and 9.26% at 4 h to 3.74 and 5.95% at 6 h for the uncoated and coated doses of IRP-69, respectively.

The images taken of the mouth and oesophagus during the study showed oropharyngeal retention of cholestyramine prior to feeding at 4 h. No evidence of oropharyngeal retention was seen with IRP-69. Fig. 2 shows scintigraphic images taken of the activity in the mouth and oesophagus before and after the meal. Consumption of a meal would appear to significantly reduce the activity in the mouth and oesophagus by dislodging trapped cholestyramine (Table 3).

The distribution throughout the regions of the stomach varied considerably (Fig. 3). The distribution was significantly different between the four

Table 2
T_{50} and AUC_{0-6} values (mean ± S.E.M.) for polymer coated (PC) and uncoated cholestyramine and Amberlite® IRP-69

Resin	T_{50}	AUC_{0-6}
Cholestyramine	85.86 ± 9.16	15200 ± 1093
PC [Cholestyramine]	72.00 ± 12.64	11454 ± 958
Amberlite® IRP-69	76.09 ± 9.23	9452 ± 811
PC [Amberlite® IRP-69]	70.25 ± 10.57	10091 ± 724
P-value	0.724	0.001

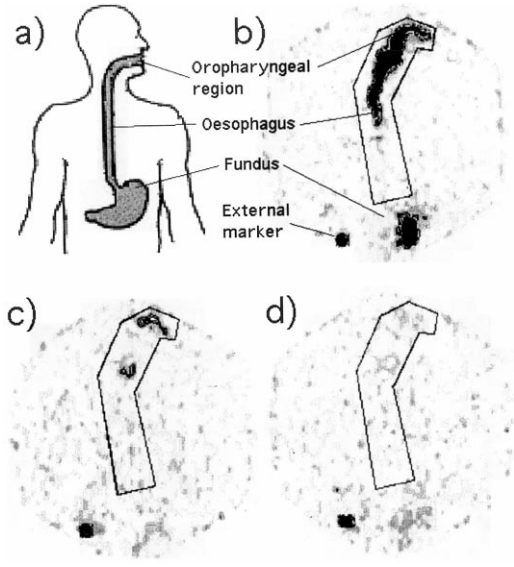

Fig. 2. (a) Orientation of a subject stood in front of the gamma camera whilst acquiring oesophageal images. The head is to one side to give a right lateral view. Typical scintigraphy images showing oesophageal distribution of cholestyramine: (a) at the start of study ($T = 0$ h); (b) immediately before test meal at 4 h; and (c) immediately after test meal.

formulations within the fundus ($P = 0.0001$), the body ($P = 0.001$) and the antrum ($P = 0.019$). Cholestyramine was found in significantly greater quantities than IRP-69 in the fundus ($P = 0.001$) and the body of the stomach ($P = 0.001$) but not in the antrum ($P = 0.069$). This would indicate IRP-69 is not distributed to the fundus or body in any great quantity or for any length of time. Polymer coating the cholestyramine did not significantly alter the distribution in the fundus, body or antrum ($P > 0.05$).

4. Discussion

Previous studies have suggested that cholestyramine has an extended gastric residence and the ability to coat the gastric mucosa uniformly (Burton et al., 1995; Thairs et al., 1998). In vitro investigations by this group would indicate that the resin has potential mucoadhesive properties (Jackson and Perkins, 2000). Factors such as low dosing volumes, the fasted state of the subjects and the characteristics of the resin, such as particle size and surface charge, have also been implicated in the mechanism (Burton et al., 1995; Thairs et al., 1998), although recent in vivo investigations have found gastric retention to be largely independent of dosing volume, particle size and the fasted state of subjects (Jackson, 1999).

Anionic polymers have been shown to exhibit better bioadhesive properties in vitro when compared to cationic or neutral polymers (Park and Robinson, 1984); the ability of anionic polymers to adhere to mucus or the mucosa being due to factors such as hydrogen bonding. Cholestyramine is however a cationic polymer and as such any bioadhesive properties exhibited by this resin are more likely to be due to electrostatic forces as mucus is negatively charged at pH 2 and above. The present findings indicate that cholestyramine exhibits greater in vivo retention than the negative resin, IRP-69. Greater mucoadhesion was also seen during in vitro studies with the positive resins, cholestyramine and Amberlite® CG-400, than with the negative resins, Amberlite® IRP-69, CG-50 and IR-120 (Jackson and Perkins, 2000).

Table 3
Mean percentage activity in the mouth and oesophagus before and after a meal for both polymer coated (PC) and uncoated cholestyramine

	n	Mean (%) activity in mouth and oesophagus	S.E.M.	P-value
Cholestyramine				
Before meal	12	8.50	1.07	0.0003
After meal	12	5.24	0.64	
PC [Cholestyramine]				
Before meal	12	4.61	0.55	<0.0001
After meal	12	2.39	0.37	

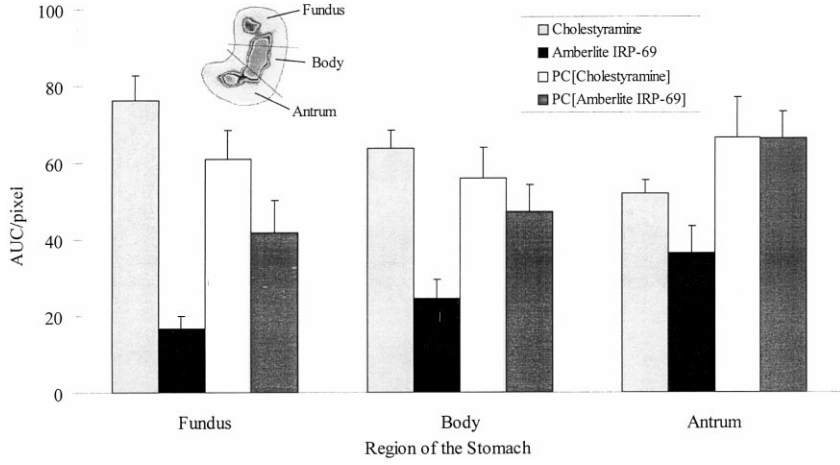

Fig. 3. Distribution of uncoated and polymer coated (PC) resin throughout the regions of the stomach ($n = 12$: mean ± S.E.M.). Inset: Typical scintigraphic image used to produce data, showing distribution of cholestyramine and the regions of interest.

This would indicate that surface charge is important in the gastric retention of cholestyramine and that mucoadhesion is due to the electrostatic forces. Although considered to be beyond the scope of this particular study, physicochemical analysis of the materials, such as polymer coat thickness and integrity and the particle size distributions before and after coating, may have provided additional information and aided in the interpretation of the results herein.

The initial phase of gastric emptying of all formulations was similar but the high level of activity remaining in the stomach with cholestyramine after 3 h, and the rise in counts after 4 h were not seen with the negatively charged resin, IRP-69. Polymer coating of IRP-69 did not significantly affect the gastric emptying or residence of the resin despite the zeta potential being close to zero and the resin exhibiting very little negative charge. Polymer coating of the cholestyramine however, while not affecting the gastric emptying, did significantly reduce the overall residence of the resin. Although, in previous work, polymer coating of cholestyramine did reduce the gastric residence slightly, it was concluded that this was not significant and that, since the polymer coated particles behaved in a similar fashion to the uncoated particles, surface charge was not necessary for mucoadhesion (Thairs et al., 1998). The discrepancy between the two studies may be due to incomplete masking of the resin in the previous study: the polymer-coated resin had a relatively high positive zeta potential ($+18$ mV) compared to the zeta potential of the coated resin used in the present study ($+2.2$ mV). As adherence of particles to mucus is at a maximum when zeta potentials are positive (Ponchel et al., 1997), the polymer-coated particles in the previous study could still have exhibited a high degree of adherence.

In contrast to the Thairs paper, the comparison not only of charge masking but also of cholestyramine to a negatively charged resin, IRP-69, indicates that the gastric retention could be due to surface charge and electrostatic forces. The fact that the diameter range of the IRP–69 particles used was the same as cholestyramine also shows that the prolonged gastric residence of cholestyramine was not due to particle size. This was also evident in the in vitro mucoadhesion assessment of cholestyramine in relation to particle size (Jackson and Perkins, 2000), and an in vivo scintigraphy study, also carried out by the author (Jackson, 1999), in which no significant difference was found between the gastric emptying rates or total residence time of three different particle size fractions, < 40, 40–90 and 90–125 μm, of cholestyramine (T_{50}, $P = 0.075$: AUC_{0-6}, $P =$

0.313). A previous study by another group had also concluded that a small particle size alone did not contribute to extended gastric residence when investigating the gastrointestinal transit of small particles (Brown et al., 1998).

The rise in gastric counts seen at 4 h with cholestyramine was not evident with IRP-69. Validation studies performed prior to the in vivo studies showed at least 98% stability of the radiolabel, indicating that it would be unlikely for the radiolabel to become dissociated from the resin. Theodorakis et al. also quoted a stability of 95% binding of pertechnetate ions to anionic exchange resins in simulated gastric juice (Theodorakis et al., 1982). Micronised resin however had been seen in the mouth and oesophagus in previous trials (Washington et al., 1989; Burton et al., 1995) and periodic scans of the oropharynx in this study showed hotspots of activity, indicating trapped resin, which disappeared after eating. It was concluded therefore that the rise in counts at 4 h was due to the clearance of trapped resin from the mouth and oesophagus.

There was a distinct difference in the distribution of the cationic and anionic exchange resins, another indication that surface charge had some effect on the behaviour of cholestyramine. Greater quantities of cholestyramine compared to IRP-69 were found in the fundus and body of the stomach, indicating that IRP-69 was not distributed to those regions in any great quantity or for any length of time. Polymer coating the cholestyramine did not significantly alter the distribution in the fundus, body or antrum.

Overall, cholestyramine has shown a tendency to develop intimate contact with the gastric mucosa in vivo, targeting all regions of the stomach and extending gastric residence. In excess of 20% of the cholestyramine was still present in the stomach at 6 h, compared to less than 6% of the IRP-69. It has been shown that cholestyramine initially trapped in the mouth and oesophagus and dislodged by subsequent feeding contributes to this high level of resin remaining. Once the resin had adhered to the mucus layer, it would seem that the only limiting factor would be mucus turnover. The adherent resin did not appear to be dislodged by the normal contractions of the fed stomach or by constant washings from food, drink or gastric secretions. Particle aggregation, also possible under these circumstances and having an affect on distribution, did not appear to occur. Scintiscans taken throughout the study showed no evidence of focal 'hotspots' indicative of the accumulation of particles.

From the results presented here, cholestyramine was distributed throughout the stomach and its adherent behaviour was considered responsible for the prolonged gastric residence. It was concluded that, as the oppositely charged IRP-69 resin did not possess the same characteristics as cholestyramine, and that polymer coating the resin reduced the effects, the surface charge of the resin played a significant role in mucoadhesion and the subsequent retention. The findings indicate that cholestyramine has potential as a drug delivery system for the topical treatment of the gastric mucosa, for example in the delivery of antibiotics for the eradication of *H. pylori*.

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