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Intragastric Distribution of Ion-exchange Resins: a Drug Delivery System for the Topical Treatment of the Gastric Mucosa

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Abstract

Previous studies by this group on freeze-dried oral dosage forms containing finely-divided ion-exchange resins revealed prolonged gastric residence and uniform distribution within the stomach. The present study was carried out to ascertain whether this was due to freeze-drying, properties of the radiolabelled ionic exchange resin, or the small dosing volume used. ^{99m}Tc-labelled cholestyramine resin was administered in two dosage forms, a freeze-dried tablet which dissolved in the oral cavity (orally dissolving tablet; ODT) and a 1·5 mL aqueous suspension. Two resin particle sizes (20–40 and 90–125 μm) were studied. Oesophageal transit and intragastric distribution and residence were followed by gamma scintigraphy. In a second study, in six subjects, gastric emptying of the water-soluble fraction of the ODT and 1·5 mL of water, was measured using ^{99m}Tc diethylenetriaminepentaacetic acid.

Oesophageal transit of a water-soluble marker and resin in suspension was rapid, but the transit of the resin in the ODTs was significantly prolonged. Regardless of particle size or dosage form, the resin was evenly distributed throughout the stomach with 20–25% remaining for 5·5 h. In contrast, the water-soluble marker cleared from the stomach rapidly from both dosage forms.

We suggest that oral dose forms containing finely-divided ion-exchange resins may form a useful system for topical treatment of the gastric mucosa, for example in targeting to *Helicobacter pylori* infection.

Very few drug delivery systems have been designed which are specifically targeted to the stomach. The majority of oral dosage forms are intended simply to achieve controlled gastrointestinal absorption; since the stomach is rarely a useful site of absorption, methods of efficiently targeting it have been neglected. Recently, however, the microorganism *Helicobacter pylori* has been identified as a major factor in the development of gastric ulcer, leading to a requirement for efficient targeting of antibiotics to the gastric mucosa. A recent study by Atherton et al (1995) demonstrated that in 60% of *Helicobacter* sufferers, the organism was found in the fundal region of the stomach, with 45% demonstrating the presence of the organism in the body and 14% in the gastric antrum (32% having more than one region affected). Difficulties arise in the local treatment of this organism with conventional tablets or capsules, since these fall to the base of the stomach from where they are emptied (Wilson & Washington 1989). Little, if any, drug is delivered to the body or fundus of the stomach. Systemic administration followed by local secretion in the gastric juice has been considered as an option for drug delivery to the bacterium. Unfortunately, only strong bases will diffuse into the stomach and the antibiotics used in *H. pylori* treatment are weak acids and bases, and hence will not easily enter the acid environment. This may be the reason why amoxycillin monotherapy is largely ineffective in the treatment of *H. pylori*, even though in-vitro tests demonstrate that the bacteria is sensitive to it (Glupczynski et al 1988; Rauws et al 1988). Amoxycillin suppresses *H. pylori*—i.e. tests to detect the organism are negative at the end of treatment; however, when repeated one month later the tests are found to be positive, and it has been suggested that organisms are in sanctuary sites which evade both the amoxycillin and detection by the test, which then re-colonize the stomach after treatment has been discontinued (Atherton et al 1995). It is possible that a dosage form with a uniform gastric distribution may target these sites more effectively and optimize antibiotic monotherapy of *H. pylori*.

Previous work by this group has demonstrated that radiolabelled ion-exchange resin delivered by a freeze-dried fast dissolving oral dosage form (Expidet, Wyeth Laboratories) produced a prolonged residence in fasted subjects when compared with conventional dosage forms (Washington et al 1989). However, the mechanism responsible for this behaviour was unclear. It is possible that the mucosal-coating effect observed was due to the freeze-drying process which allowed the formulations to disperse in the mouth before swallowing, an inherent bioadhesive property of the resin, or the small particle size of the resin. It is also possible that the small volume of administration of these formulations was of importance.

In the current study, the formulations studied were either small-volume suspensions or tablets which disintegrated in the oral cavity (orally dissolving tablets or ODTs) and were thus swallowed with a small volume of saliva. The object of the study was to clarify the mechanism of gastric distribution of this type of formulation, using ^{99m}Tc-labelled ion-exchange resin and ^{99m}Tc-labelled diethylenetriaminepentaacetic acid as an aqueous phase marker.

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Two separate studies were performed to measure the oesophageal transit and gastric emptying of the resin and aqueous components of a range of ion-exchange resin formulations. In the first, the anionic exchange resin cholestyramine was labelled with ^{99m}Tc and administered in two dosage forms, a freeze-dried ODT formulation, or a 1·5-mL aqueous suspension of resin. Two different resin particle sizes (20–40 and 90–125 μm) were studied in each formulation. Twelve healthy volunteers participated in a four-way cross-over separated by one week intervals. The oesophageal transit and intragastric distribution and residence were followed by gamma scintigraphy.

The second study measured the gastric emptying of the water-soluble fraction of the ODT, using ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA), a water soluble marker. If the resin component was mucoadhesive, there should be distinguishable differences in the gastric retention of the labelled resin and corresponding aqueous component.

Materials and Methods

Preparation of resin fractions

Anionic ion-exchange resin (Duolite AP-143, Rohm and Haas UK Limited) was sieved into a number of size bands using standard calibrated sieves (Engelhard UK) and size fractions of 90–125 μm and 20–40 μm were selected for the present study.

Labelling and stability of radiolabel binding to ion exchange resin

Both [^{99m}Tc]pertechnetate and ^{99m}Tc diethylenetriaminepentaacetic acid (DTPA) were obtained from the Radiopharmacy Unit, University Hospital, Nottingham.

The ion exchange resin was tested for integrity of the radiolabel, [^{99m}Tc]pertechnetate. Two MBq of radiolabel was adsorbed onto 0·5 g of resin which was incubated, in turn, in four separate 100-mL buffers in the pH range 1–7. Samples of the solution were taken periodically for up to 4 h. These were then centrifuged at 3900 rev min^{-1} for 5 min, the supernatant and pellet were weighed and the activity was counted in a well counter (Mini-Assay type 6–20, Mini Instruments), to calculate the percentage of radiolabel retained on the resin.

Preparation of the dosage forms

Orally dissolving tablet (ODT). Three freeze-dried formulations were prepared, containing either 5 mg ion-exchange resin with particle size of 90–125 μm or 20–40 μm labelled with [^{99m}Tc]pertechnetate, or 2 MBq of the water-soluble marker ^{99m}Tc DTPA. The specific activity of all dose forms was calculated to be 3 MBq per tablet at the time of dosing.

Five hundred milligrams of the labelled resin was added to 100 mL of a 1% gelatin and 0·167% sucrose solution. This was well stirred and 1 mL samples were placed in tablet moulds and frozen on dry ice. When frozen, the samples were removed and ground with 2·5 g ascorbic acid and returned to the moulds for re-freezing. The formulations were freeze-dried overnight (Edwards Freeze Dryer Modulyo).

The ODTs with the water-soluble marker were radiolabelled by the addition of the ^{99m}Tc DTPA to the gelatin solution before freezing and the remaining procedure was identical for those which contained resin.

Suspension/liquid. To study the effect of dosing the resin in a small liquid volume, a suspension of 5 mg labelled resin in 1·5 mL of distilled water was made which was administered to the subject on a spoon.

The gastric-emptying characteristics of the aqueous phase were studied using 3 MBq ^{99m}Tc DTPA added to 1·5 mL distilled water.

Ethical considerations and volunteer selection

Eighteen healthy subjects, 8 male and 10 female with an age range of 20 to 24 years, were recruited from the University of Nottingham student population. Subjects were screened by a fully qualified medical practitioner and the female subjects were pregnancy-tested on the morning of each study day.

Volunteers were given both written and verbal information on the nature of the trial. Before entering the study, written informed consent was obtained from all subjects. Approval was obtained from the Nottingham University Hospital Ethical Committee. Permission to administer isotopes was obtained from the Department of Health, the total radiation exposure being 0·15 mSv per subject for the subjects participating in the four-way cross-over and 0·075 mSv for those participating in the two-way cross-over.

Study protocol

Study 1. Twelve subjects participated in a four-way cross-over in which the following formulations were studied: ODT containing 5 mg of 20–40 μm labelled resin (20 μm ODT); ODT containing 5 mg of 90–125 μm labelled resin (90 μm ODT); 1·5 mL water containing 5 mg of 20–40 μm labelled resin (20 μm suspension); 1·5 mL water containing 5 mg of 90–125 μm labelled resin (90 μm suspension);

Study 2. Six subjects participated in a two-way cross-over to study the distribution of the aqueous components of the formulations: ODT containing ^{99m}Tc DTPA as an aqueous marker; 1·5 mL water containing ^{99m}Tc DTPA.

The study protocol was identical for both study groups. Assignment to the different dosage forms was randomized. Radiolabelled reference markers were placed on the anterior and posterior surfaces of the body of each subject to allow alignment of the images. All subjects were dosed after an overnight fast. Dosing was carried out by one investigator who was responsible for the randomization code, but who did not take part in the data acquisition or analysis. The code was not revealed to the other investigators until after the analysis was completed.

Gamma scintigraphy

Gamma scintigraphy was carried out using an IGE Maxicamera II (IGE Ltd, Herts, UK), fitted with a low energy collimator. The view was focused on the 141 keV photopeak for ^{99m}Tc. All the images were stored for later analysis. Oesophageal transit was observed using dynamic imaging over a 10-min period. This was immediately followed by a 30-s static anterior image of the stomach followed by a 30-s static posterior image. Subsequent static 2-min anterior and

posterior images of the stomach of each subject were taken every 20–25 min up to 5·5 h post-dose.

Data analysis

The data analysis was carried out blind. The oesophageal transit of each formulation was analysed by obtaining the number of radioactive counts, over a 10-min period, from two regions of interest (ROIs) on the image: the oesophagus and background area.

To assess activity in the stomach and gastric-coating properties of the formulations, the number of radioactive counts from five ROIs were measured, the whole stomach, fundus, body, antrum and background.

The data were then entered into a spreadsheet (Microsoft Excel) on an Apple Macintosh computer. Corrections were made for frame time, background activity and radioactive decay. The geometric mean of the anterior and posterior images was calculated to correct for front-to-back movement of the isotope. Data from individual subjects were interpolated on to a common time axis in order to calculate the mean gastric emptying curves.

Oesophageal transit was analysed by examining the time taken (s) for 80% (T80) of the formulation to be cleared from the oesophagus. Gastric emptying was assessed by calculating the time taken for 50% of the radiolabel to empty (T50) and area under the curve in the range 0 to 5·5 h ($AUC_{0-5.5}$).

As these parameters did not prove to be normally distributed, the non-parametric Wilcoxon Signed Rank test was used to compare paired data and the Mann Whitney U-test to compare unpaired data.

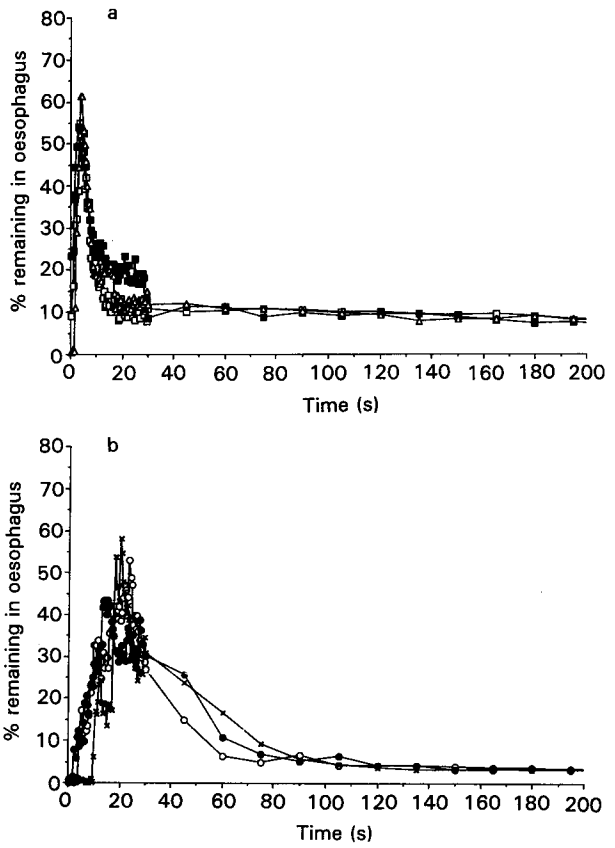

FIG. 1. a. Oesophageal transit of suspension dose forms (□ 20 μm, ■ 90 μm) and aqueous marker (△). b. Oesophageal transit of ODT freeze-dried dose forms (○ 20 μm, ● 90 μm) and aqueous marker (X).

Results

Radiolabel stability on ion exchange resin

The retention of the radiolabel on the resin in-vitro was independent of the pH of the incubation medium. Over 99% of the radiolabel remained associated with the resin after 4 h over the pH range studied.

Oesophageal transit

The oesophageal transit of the resin in the suspension, and labelled water, were rapid, whereas there was a slight delay in the resin transit of the ODTs as they broke up in the mouth before being swallowed with saliva. The transit of the resin in the ODTs was prolonged compared with the resin in the suspension (Fig. 1a, b). The time for 80% of the radiolabel to clear from the oesophagus and the statistical comparison of clearance times for the different formulations are summarized in Table 1. Transit of the dosage forms through the oesophagus was not dependent on the particle size of the resin.

Gastric emptying

Fig. 2 shows the mean gastric emptying of both particle sizes of resin in both dosage forms. The emptying is compared with the liquid-phase marker ^{99m}Tc DTPA delivered as a solution and in a rapidly disintegrating tablet.

There was no significant difference in the emptying of any label (resin or aqueous) using the standard parameter of time to 50% gastric emptying (T50), demonstrating that the initial phase of emptying was similar for all formulations. However, the area under the gastric emptying-time curve demonstrated prolonged and increased residence of all resin-containing formulations compared with those containing aqueous radiolabel, and highlighted the prolonged retention of a fraction of the resin in all resin-containing formulations (Table 2).

Distribution of the marker throughout the stomach is shown in Fig. 3. A significantly greater proportion of resin was located in all fractions of the stomach compared with the aqueous marker, regardless of method of delivery or particle size ($P > 0{\cdot}01$). In particular the proportion of labelled resin in the fundus was significantly higher than the fraction of aqueous label.

Discussion

Oesophageal transit was influenced by the nature of the dosage form, but not by the particle size of the resin, or of the radiolabelled component within it. The freeze-drying process was responsible for the rapid dispersal of the ODTs in the mouth, and the relatively lengthy oesophageal transit was due to clearance of the dosage form from the mouth by a series of swallows. Dosage forms which disperse in the mouth also demonstrated prolonged oesophageal transit in

Table 1. Time for 80% of the formulation to clear the oesophagus (T80, s).

Subject	Orally dispersing tablet		Suspension		Water-soluble fraction	Water
	90 μm	20 μm	90 μm	20 μm		
1	26	43	13·5	7		
2	80	42	13	11		
3	50	50	29	10		
4	29	26	12	8		
5	56	27	6·5	5		
6	38	35	7·5	7·5		
7	49	28	9	6		
8	74	52	6	15		
9	10	12	7	7		
10	18	24	30	5		
11	19	52	9	6		
12	31	44	7	13		
13					29	17
14					78	8·5
15					25	8
16					24	7
17					28	8
18					24	10·5
Median	34·74	38·50	9·09**	7·49**	26·50	8·25*
Interquartile range	24–52	27–46	7–13	8–10	24–28	8–10

*$P < 0.05$, **$P < 0.01$.

supine subjects compared with a 10-mL bolus of water (Wilson et al 1988). Interestingly, the oesophageal transit of the ODTs was slower in the current study even though the subjects were upright. For example, the average T80 of the resin in the 90 μm ODT was 46·5 ± 8·21 s (± s.e.m.) compared with 14·1 ± 2·7 s in the supine subjects. This could be attributed to prolonged dispersion time in the mouth. These types of formulations may thus be suitable for treatment of diseases of the oesophagus or for patients with swallowing difficulties such as dysphagia in whom intake of solid dosage forms such as tablets and capsules pose great difficulties.

In contrast to oesophageal transit, gastric emptying of the resin was significantly prolonged regardless of particle size and dose form when compared with a corresponding aqueous label. The first 60–70% of the resin cleared at the same rate as an aqueous phase, but the remaining 30–40% of the resin was retained for 1·5–2 h after administration, whereas the aqueous phase continued to empty. The distribution of the resin was uniform throughout the fundus, body and antrum of the stomach, with approximately 10% remaining in each area for the 5·5-h imaging period.

Previous studies have demonstrated that most conventional dosage forms, such as large tablets or capsules, are treated as indigestible solids and as such have variable

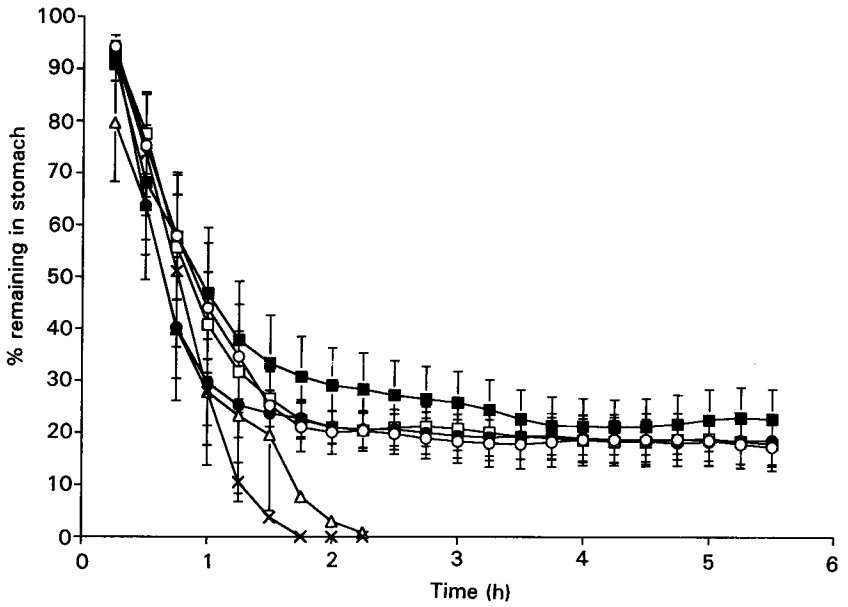

FIG. 2. Gastric emptying from whole stomach of resin in ODT (○ 20–40 μm, ● 90–125 μm) and suspension dose forms (□ 20–40 μm, ■ 90–125 μm), and aqueous label in solution (△) and ODT (X).

Table 2. Gastric emptying values measured as time to half-emptying (T50) and area under the gastric emptying-time curve (AUC).

Formulation (particle size)	T50 (h)	AUC (% h)
Tablet (20 μm)	0·85 (0·52–1·39)	136·99 (112–158)
Tablet (90 μm)	0·65 (0·45–0·83)	116·46 (102–164)
Suspension (20 μm)	0·76 (0·63–1·06)	142·67 (116–185)
Suspension (90 μm)	0·76 (0·54–1·66)	134·68 (121–232)
Water-soluble fraction	0·76 (0·49–0·98)	59·92 (41–80)
Water	0·63 (0·45–0·79)	48·15 (27–67)

Median (interquartile range).

gastric residence times which are dependent on the occurrence of migrating myoelectric complex (MMC) (Washington et al 1989; Wilson et al 1989). As the subjects were fasted, it would be expected that during the current study they would have experienced at least one MMC since these occur at approximately 2-h intervals (Wingate 1981). This should have resulted in the emptying of the resin unless mucoadhesion had occurred. It has been suggested that ion-exchange resins contained in the dosage form may have inherent bioadhesive properties similar to those of highly charged polyanions (Borodkin 1991). It is possible that the remaining 20–30% of the resin was bound to the gastric mucus and would only be sloughed off as the mucus turned over. The turnover time of the mucus gel layer in chronically isolated intestinal loops in the rat during perfusion with isotonic saline has been estimated to be between 47 and 270 min (Lehr et al 1991). This may underestimate the true mucus turnover time since manipulation of tissue is known to stimulate mucus production. Hence the unstimulated mucus turnover may be longer, and furthermore it has not been measured in the intact human stomach and the present experiment may provide a realistic estimate of this parameter.

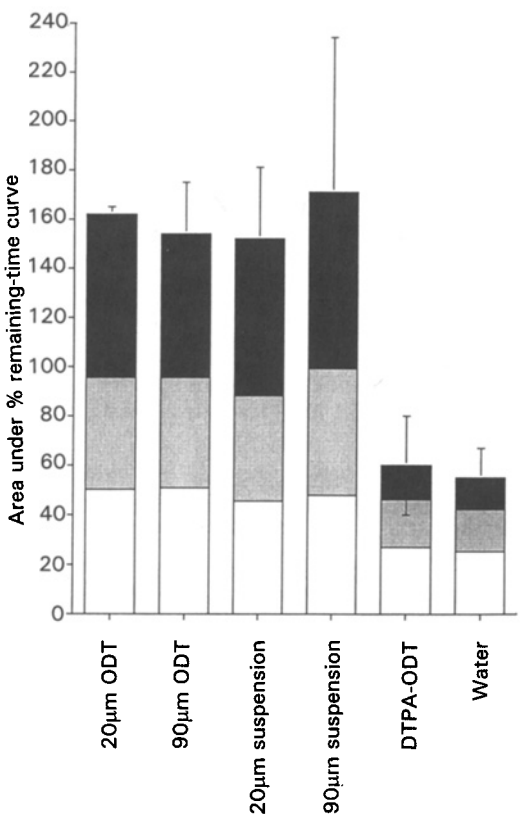

FIG. 3. Gastric emptying from individual regions of the stomach (fundus ■, body ▨, and antrum □) of labelled resin and aqueous markers in suspension/solution and ODT dose forms.

It may be suggested that the enhanced delivery of the resin to the fundus was due to the dispersion of the dosage form in the mouth, with subsequent swallowing with only saliva as a dispersant. This hypothesis is demonstrably false, since the aqueous suspension of the resin also delivered resin uniformly to the stomach even though it was swallowed as a bolus, and emptying of the corresponding aqueous label was rapid.

The majority of studies of gastric emptying have been performed using relatively large volumes of stomach contents, and very few data in the literature exists concerning the gastric-emptying rates of small volumes of liquid. Ten to twenty millilitres of liquid antacids or anti-reflux agents empty within 1 h when given to fasted subjects (Jenkins et al 1983; Washington et al 1990). Studies carried out on 50 and 200 mL of liquid found that antral interdigestive phasic activity affected gastric-emptying rate (Oberle et al 1990). The results demonstrated that smaller 50-mL volumes were influenced by phase I and phase II activity of the MMC and had slower emptying rates than larger volumes. In this study, the emptying of 1·5 mL of water was complete in just over 2 h. This may reflect the normal emptying of secretions from the fasted stomach.

Consequently we suggest that ion-exchange resins may be useful mucoadhesive systems for topical treatment of the stomach, for example for the treatment of *H. pylori* infections. Prolonging the gastric residence of the antibiotics commonly used to treat *H. pylori*, by administering them with food, has the disadvantages that the drug will be diluted if local delivery is required, and that absorption will be reduced and slowed for systemic delivery. Food also does not completely fill the stomach since radiological studies demonstrate an air pocket above the barium-fill line. Thus food will not deliver drug to the fundus as efficiently as the present resin formulations.

Ionic resins are already in use as drug delivery vehicles (Borodkin 1991). Drug release from the resin occurs through the replacement of the drug by another ion of the same charge. The present study suggests the need for further

study of this system with the view to optimization of the delivery of drugs in the treatment of *H. pylori*. Incomplete delivery of diagnostic agents in the detection of *H. pylori*, such as [^{13}C]urea in the breath test, may be responsible for false-negative results, and thus it is evident that ion-exchange resins could also be valuable for the delivery of diagnostics.

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