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A gamma scintigraphic study of gastric coating by Expidet, tablet and liquid formulations

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Summary

The gastric residence time and gastric coating properties of 10 mg of radiolabelled micronised resin incorporated into Expidet formulations, chewable tablets and 10 ml of a liquid formulation were measured by gamma scintigraphy in twelve fasted, healthy subjects. All preparations emptied from the stomach in a similar manner for the first 1.5 h; however, the final 10% of the activity from the Expidet formulation emptied considerably more slowly than the initial phase. The total mean gastric emptying times for the three formulations were 2.3, 2.5 and 5.5 h for the tablet, liquid and Expidet formulation, respectively. The amount of activity following administration of the tablet or Expidet formulation was the same in the three regions of the stomach, but the coating of the mucosa by the Expidet formulation within each area was observed to be more uniform due to the greater dispersion of the dose form. The tablet broke up into a number of small discrete pieces. The gastric residence time of ^{99m}Tc-labelled resin delivered in an Expidet formulation is significantly longer than the same marker administered in a tablet or in 10 ml of a liquid formulation. Moreover, coating of the gastric mucosa was more uniform with the Expidet formulation than the other two formulations studied.

Introduction

The delivery of drugs for the local treatment of the stomach appears a simple problem, but in reality numerous difficulties occur. The gastric residence times of pharmaceutical dosage forms administered to fasted subjects is known to be erratic and difficult to control; small volumes of liquids empty from the stomach within 30 min (Jenkins et al., 1983; Washington et al., 1986), but single large non-disintegrating units may be emptied from the stomach between 5 min and 3 h after administration (Kaus et al., 1984; Wilson et al., 1984). In addition, the fasted stomach only has a low volume of fluid available for the dispersion of dose forms and this generally pools in the base of the greater curvature. Studies in the early 1960s conducted by Levy (1963) established that the degree of mixing in the fasted stomach is low and materials which fall to the base of the greater curvature remain there. The gastric retention times of oral dose forms are also dependent upon their size and shape, and the calorific value of any food in the stomach when the dosage form is ingested. Consequently, consistent local treatment of the

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stomach is difficult, and there is much interest in drug delivery systems which can target this region.

The Expidet formulation has a similar size, shape and appearance to standard tablets, but is light-weight, consisting of an open matrix of polymer strands or sheets which hold the drug uniformly throughout the matrix. The dose form is freeze-dried and designed to disintegrate rapidly in small volumes of water or in the mouth, facilitating rapid delivery to the absorption site. The major advantage of this preparation is that it can be taken without water and it avoids the problems of oesophageal retention common to other solid dosage forms such as capsules and tablets (Wilson et al., 1988).

Pilot studies on the Expidet formulation using gamma scintigraphy demonstrated that a radiolabelled micronised resin delivered in this formulation to fasted volunteers demonstrated a surprisingly long gastric residence time. A gamma scintigraphic study was, therefore, carried out to quantify the gastric distribution and clearance of the Expidet formulation in normal volunteers by the addition of a small quantity of micronised radiolabelled resin.

Materials and Methods

Preparation of radiolabelled dosage forms

Technetium-99m pertechnetate was eluted from a generator and adsorbed onto micronised "Amberlite CG400" ion exchange resin (mean particle diameter size less than 20 μm). The resin was oven dried for 1 h at 105 °C and added to each of the formulations as described below. The activity was calculated for each dose to be 2–3 MBq at the time of administration.

Expidet formulations. The radiolabelled micronised resin (10 mg) was added to the standard Expidet formulation and the Expidet (12 mm diameter, 0.25 ml) manufactured in the usual manner.

Chewable tablet. A chewable tablet base consisting of a 50/50 mix of Tabfeine D 97HS (dextrose) and Emdex (dextrose) was prepared and mixed with 10 mg of labelled resin and 0.25% magnesium stearate. The mix was compressed on a single punch machine to produce tablets with a final weight of 250 mg.

Liquid formulation. The liquid, a placebo antacid formulation, was prepared to the following formulation:

Xanthan gum	4.0 g
Titanium dioxide	3.5 g
Sodium benzoate	4.5 g
Sodium cyclamate	1.0 g
Saccharin sodium	0.148 g
Alcohol 96%	0.84 g
Benzoic acid	0.50 g
Menthol laevo U.S.P.	0.048 g
Peppermint oil	0.18 g
Glycerin	31.20 g
Strong ammonia solution	0.02 g
Sodium hypochlorite solution	0.06 g
Deionised water	to 1 litre

Ten mg of the radiolabelled resin was added in each 5 ml dose of the liquid formulation. The 5 ml dose of liquid was then diluted with 15 ml of water.

Protocol

Twelve healthy male or female volunteers aged between 18 and 30 years were recruited from the student population of the University of Nottingham. Exclusion criteria included weight outside the range of $\pm 10\%$ of group mean weight, consumption of medications which could influence the results of the study, excessive tobacco or alcohol consumption or participation in a similar study within the previous 12 months. Approval from the University of Nottingham Ethical Committee had been obtained and the study was performed in accordance with the guidelines for the Declaration of Helsinki (Venice Amendment) 1984. A certificate permitting the administration of the radioisotopes to healthy volunteers was obtained from the DHSS. Written informed consent was obtained from each volunteer prior to the start of the study.

The subjects were fasted overnight. An open unblind format was used and the order in which the formulations was presented to each subject was randomised. The subject was placed in front

of the gamma camera and the formulations were administered in the following manner:
(a) the Expidet formulation was placed on the tongue after the subject had ingested 50 ml of water;
(b) the tablet was crushed in the mouth and washed down with 50 ml of water;
(c) the liquid was ingested with a single swallow.

Scans were taken dynamically for 40×15 s followed by 15 s static images taken at regular intervals for up to 5 h.

Data evaluation

Scans were evaluated for:
(a) Residence times in the stomach and rate of clearance of the formulation into the small intestine.
(b) The stomach was divided in three regions, fundus, body and pylorus of approximately equal area. The distribution of radiolabelled resin marker in each area was quantified; the counts were corrected for background radiation and radioactive decay of the isotope.
(c) Profiles of activity from the fundus to pylorus were created on the computer to examine the distribution of activity.

The statistical significance of the data was calculated using a paired *t*-test.

Results

Gastric residence of the three formulations

The three formulations emptied from the stomach in a similar fashion for the first 1.5 h as shown in Fig. 1. The mean time ($\pm$S.E.) taken for half the formulation to empty from the stomach (T_{50}) was 61 ± 7 min for liquids, 54 ± 11 min for tablets and 68 ± 12 min for Expidet formulations. There was no significant difference between these times, however, the total gastric residence time for the Expidet formulation was clearly greater than for the other two formulations. The mean T_{90} (the time for 90% of the formulation to leave the stomach) for the formulations was 111 ± 11 min for the liquid, 80 ± 11 min for the tablet and 211 ± 20 min for the Expidet formulation. Ten percent of the activity in the Expidet formulations remained in the stomach for a significantly longer time than for the tablets and liquids ($P < 0.01$, $P < 0.001$, respectively).

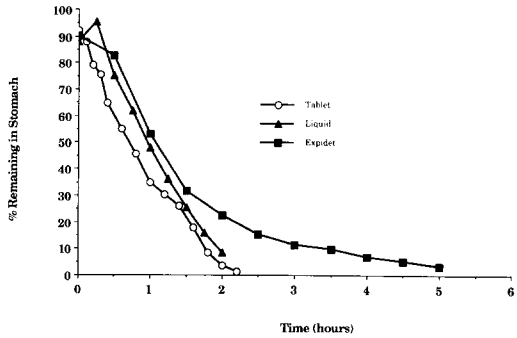


Fig. 1. Emptying of the three formulations from the stomach.

Gastric distribution and coating of the formulations

Liquid. Fig. 2 shows the distribution of the liquid formulation as a percentage in the fundus, body and antrum of the stomach. The liquid moved from the fundus to the antrum within 15 min of administration and emptied over a period of 2.5 h. The difference in distribution at 1 h between the fundus and antrum was significant ($P < 0.01$).

Tablet. Fig. 3 shows the mean percentage of tablet within the three regions of the stomach. There was no significant difference between the distribution in the three regions.

Expidet formulation. There was no significant difference in the distribution of the Expidet formulation within the regions of the stomach (Fig. 4).

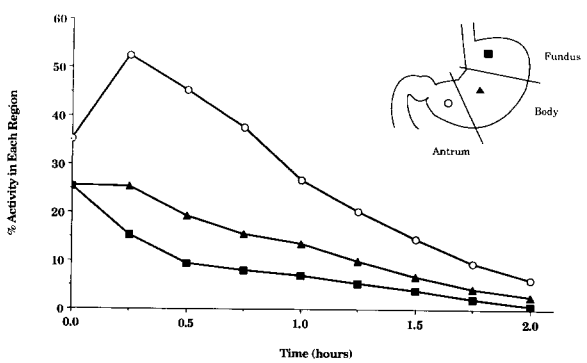


Fig. 2. Gastric emptying of the liquid formulation from the fundus, body and antrum. Inset illustrates the division of the stomach into the three regions of interest.

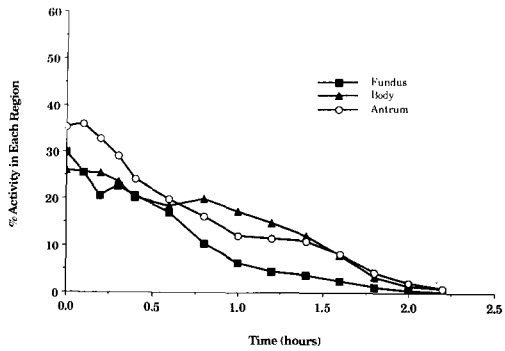


Fig. 3. Gastric emptying of the tablet formulation from the fundus, body and antrum.

No significant difference was found between the percentage of the resin within each of the three regions of the stomach when administered in the three formulations.

Data from the activity profiles could not be averaged, since the longest straight path from fundus to pylorus was chosen and this varied in length from subject to subject. In addition some tablet fragments did not lie on the path and hence would not be counted in the analysis.

Discussion

Earlier gamma scintigraphic studies have shown an unexpected degree of coating of the oesophagus and the stomach during routine dosing with Expidet formulations containing small quantities of radiolabelled micronised resin. This behaviour contrasted with most other dose forms, including liquid products, as these mainly disperse in the lower part of the stomach. An explanation for this phenomenon may be that the enhanced dispersion of the micronised resin from the Expidet formulation, coupled with the low volume of fluid required for dosing, leads to a more efficient coating of the mucosa.

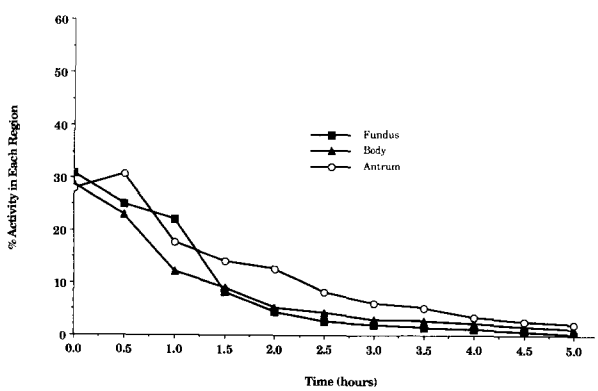
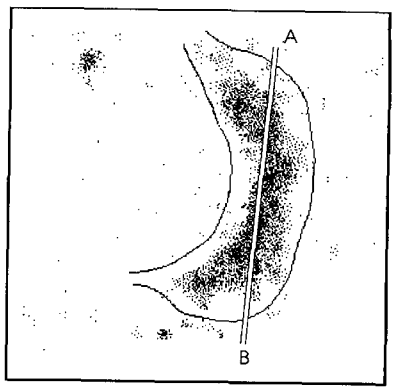


Fig. 4. Gastric emptying of the Expidet ® formulation from the fundus, body and antrum.



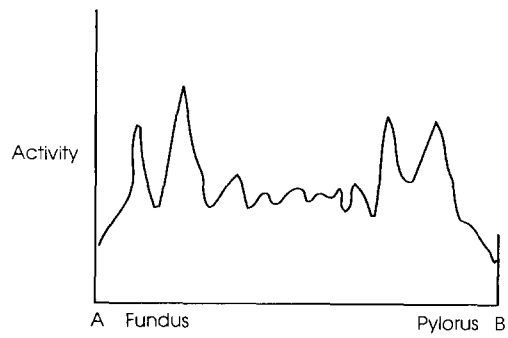


Fig. 5. A typical scintiscan of the gastric distribution of the micronised resin delivered in the Expidet formulation and the profile of activity taken approximately from fundus to antrum.

The distribution of counts in the upper, middle and lower stomach was not significantly different for either the Expidet or tablet formulations, although the overall emptying time for the Expidet formulation was greater than that for the tablet from each region. The Expidet formulation produced a more uniform coating of the gastric mucosa (Fig. 5), whereas the tablet disintegrated into smaller but discrete pieces (Fig. 6). The tablet was crushed in the mouth and hence the fragments

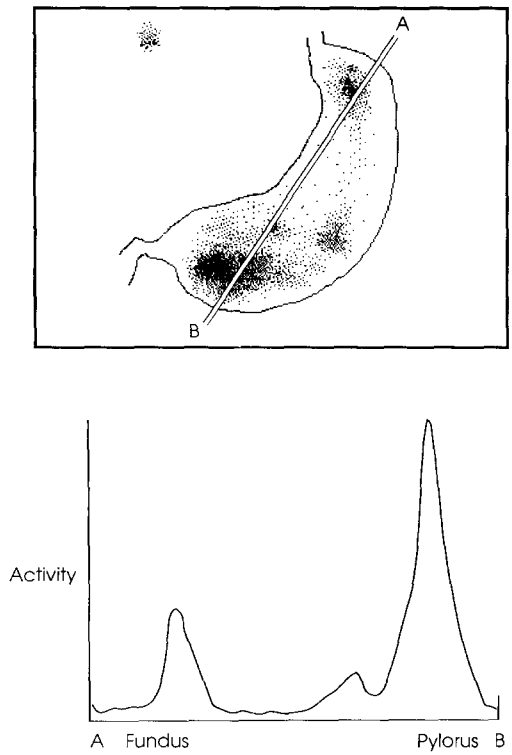


Fig. 6. A typical scintiscan of the gastric distribution of the micronised resin delivered in the tablet and the profile of activity taken approximately from fundus to antrum.

were distributed through the three regions of the stomach as the pieces were swallowed. The individual distributions were varied since the degree to which the tablet was crushed in the mouth, and hence the number and particle size of the fragments, were random. This method of delivering drugs locally to the stomach is unsatisfactory since local areas of high concentration of drug will result, whilst other areas will remain untreated. The possibility of delivering drugs accurately to focal erosions, especially in the proximal stomach, will be unpredictable. If the drug is administered in a rapidly dissolving tablet, then the volume of fluid available for dissolution in the fasted stomach is low and localised in the pylorus; again there is limited availability of the drug to the upper regions of the stomach.

The gastric emptying pattern from the Expidet formulation fits an exponential curve, and the tablets and liquid empty in a linear manner. This behaviour is unusual for liquids, since it has been reported that liquids empty in an exponential pattern (Minami and McCallum, 1984; Hunt, 1956). In addition, the gastric emptying of the liquid from the fasted subjects is slower than would be expected for a 20 ml bolus which contained few calories. Emptying of neutral, iso-osmolar and calorifically inert materials is rapid; e.g. half of a 500 ml load of isotonic saline is emptied from a human stomach in 12 min (Hunt, 1956). The emptying of small volumes (10 ml) of various liquid antacid formulations has been shown to be complete within 70 min (Jenkins et al., 1983; Washington et al., 1986). It is possible that large volumes of liquid empty in a different manner to small volumes, since receptive relaxation will not occur unless the stomach is filled beyond a certain point. It is common practice in our trials to administer small volumes of water (30–50 ml) labelled with ^{99m}Tc-diethylenetriaminepentaacetic acid to outline the stomach. The label is observed to empty rapidly in a monoexponential pattern. It is possible that the unusual behaviour observed for the liquid may be attributed to the resin and does not reflect the behaviour of the remainder of the formulation. Hunter and co-workers have studied the dispersion of milled resin when administered in a hard gelatin capsule (Hunter et al., 1980, 1983). It was found that the dispersion of the resin in fasted volunteers, was greatly reduced if it was milled from 25 μm to 9 μm. Hunter proposed that this may be due to changes in the hydrophobicity of the surfaces, due to chemical and physical variations in the resin through the bulk of the particle. It is equally likely that milling changes the wettability of the material due to variations in particle surface roughness. Decreasing the wettability would decrease the ability of a powder to disperse. In these trials, the resin in the liquid is prewetted, and the resin in the Expidet formulation wets very readily despite the small particle size because it is so well dispersed. The hydrophobic nature of the resin may then cause it to adhere to or become entrapped within the mucus; subsequent clearance would then be dependent on the digestion rate of the mucus layer.

The Expidet formulation delivered the resin uniformly through the stomach and the extremely

long gastric residence time may reflect the differences in rate of clearance between the proximal and distal parts of the stomach. The Expidet formulation would not be expected to alter the fasting gastric motility pattern since the amount of liquid administered was equivalent to a few swallows and there were no large particles which might cause mechanical stimulation. It is concluded that the Expidet formulation is ideally suited to the local delivery of drugs to the gastric mucosa, especially hydrophobic materials such as prostaglandins.

Acknowledgement

"Expidet" is a registered trademark of American Home Products Corporation.

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