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Pharmaceutical factors influencing the rate of gastrointestinal transit in an animal model

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Summary

Suspensions of 99mTc labelled ion exchange resin particles were administered to fasted mice At predetermined time intervals each was sacrificed, the gastrointestinal (G.I.) tract removed, and the distribution of the isotope found One hour after administration a bimodal distribution was observed, one peak in the stomach and one in the small intestine Two values were calculated, the percentage particles retained in the stomach, and the percentage distance travelled by the second peak through the G I. tract After 3 h, particles were still present in the stomach. Gastric emptying was inhibited by increasing the suspension viscosity, whilst intestinal transit rate increased when the suspension was administered without prior fasting. An adsorbed film of the mucosa-adhesive polymer Carbopol 934P resulted in almost complete retention of the resin particles within the stomach at the end of the 1 h experimental time.

Introduction

In recent years there has been much interest in the evaluation and design of controlled release oral drug delivery systems. Control of the gastrointestinal (G.I.) transit of these dosage forms could allow drug delivery for periods in excess of the usual limit of 12 h, or targeting of drugs to their site of action or 'window of absorption'.

The investigation of G.I. transit of dosage forms using gamma scintigraphy has been reviewed by Davis (1986). It has been reported that gastric emptying is a controlling factor in G.I. transit. In fasted subjects, pellet and single unit formulations were reported to have gastric residence times of about 1 h. The presence of food increased the residence time to a far greater extent for single unit (10–12 h) than multiple unit dosage forms (3–4 h). The calorific value (Davis et al., 1984), the viscosity (Levy and Jusko, 1965) and the food composition, e.g. the presence of oils (Palin et al., 1982), were found to affect the rate of gastric emptying. Other physiological factors (exercise, body position) were reported to have a limited effect. Transit through the small intestine was consistent, between 3 and 4 h for both single-unit and multiple-unit dosage forms, and independent of the presence of food (Davis et al., 1986).

Mucosa-adhesive coatings have been proposed as a method of regulating G.I. transit. Some hydrophilic macromolecules containing numerous

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hydrogen bond-forming groups were found to be mucosa-adhesive (Smart et al., 1984; Park and Robinson, 1985). Mucosa adhesion by particles of polycarbophil (polyacrylic acid cross-linked with divinyl glycol) was reported to reduce their rate of gastric emptying in rats (Ch'ng et al., 1985). A suspension of polycarbophil particles administered to dogs via an oral gastric tube, had reduced rates of gastric emptying in comparison with other gel meals (Russell and Bass, 1984). These particles were found, on autopsy, not to be adhesive and could be easily removed from the stomach antrum. A physiological mechanism, related to the indigestible polycarbophil particles inducing 'fed state-like' motility in the stomach, was proposed (Russell and Bass, 1985). Polycarbophil particles, when included in a capsule formulation and inserted into the stomach of anaesthetised rats, reduced the rate of gastric emptying of chlorothiazide carrying albumin beads (Longer et al., 1985). Subsequent work using similar systems administered to humans (Khosla and Davis, 1987; Fell et al., 1987) did not reproduce this effect although differences in experimental conditions may account for this.

In this study the distribution of particle suspension within the G.I. tract of mice was investigated, and some of the factors influencing this were determined.

Materials and methods

Materials

Amberlite ion exchange resin IRA 400 (Cl) was obtained from BDH Chemicals, Poole; Carbopol 934P from B.F. Goodrich, Middlesex; sodium carboxymethylcellulose (Courlose Gum P75) from British Celanese Ltd., Derby; and methylcellulose (Methocel K100) from Greef Chemicals Ltd., Croydon. Solutions containing 25–50 MBq [99mTc] sodium pertechnatate were obtained as a gift from the Department of Medical Physics, University Hospital of Wales as required.

Preparation of resin samples

Preliminary investigations confirmed the work of Theodorakis et al., 1982; 99mTc was taken up by quaternary ammonium group-containing ion exchange resins to form a bond that was stable in in-vivo conditions.

Amberlite ion exchange resin IRA 400 (Cl) was milled, sieved and washed, and the Feret's diameter of each sieve fraction obtained by microscopy. A 0.2 g sample was suspended in 2 ml purified water and 1 ml 99mTc solution slowly added with constant stirring. After 5 min the remaining solution was removed by filtration and washed with water. 100 mg sucrose (used as a flavouring and suspending agent) was dissolved in 0.4 ml water, added to the labelled resin and the suspension made up to 1 ml with water.

Adsorbed films were prepared by suspending 0.2 g samples of labelled resin in 50 ml of 0.4% solutions of either P75 sodium carboxymethylcellulose (SCMC) or Carbopol 934P. After 5 min the supernatant was removed by centrifugation and the particles suspended on two further occasions in 50 ml portions of purified water. The presence of an adsorbed film was established by microelectrophoresis, which yielded electrophoretic mobilities of 6.67 $\mu m\ s^{-1}v^{-1}$ cm for uncoated particles, $-2.63\ \mu m\ s^{-1}v^{-1}$ cm for particles with the SCMC adsorbed film, and $-1.85\ \mu m\ s^{-1}v^{-1}$ cm for particles with the Carbopol 934P adsorbed film.

Experiments

Five male mice (40–45 g), bred at the Welsh School of Pharmacy, were fasted overnight. Each was fed 0.1 ml of the sugar flavoured resin suspensions (particle size $9 \pm 3.6\ \mu m$), via a hypodermic syringe. This method was selected to minimise trauma and to allow comparatively large particles to be administered. At set time intervals, usually 1 h, each was sacrificed, and the G.I. tract from oesophagus to rectum removed. The intestine was monitored in 2.5 cm segments using a counting head (NaI(Tl) scintillation crystal, Rank Hilgar) fitted with a lead shield providing a 10 by 30 mm slit. Each section of intestine containing activity was removed and quantitatively assessed using a well counter (NaI(Tl) well crystal produced at Velindre Hospital, South Glam.). This had been calibrated with serial dilutions of 99mTc of known activities to allow the relationship between activity and concentration to be determined. By compar-

ing the concentration in each section to the total concentration within the G.I. tract the percentage distribution of particles was obtained.

The distribution of particles after 1 h, its reproducibility and some of the factors reported to affect this were investigated, along with the effect of adsorbed films of mucosa-adhesive polymers.

Results

After 1 h a bimodal distribution was obtained (Fig. 1), one peak in the stomach and the other about half way along the small intestine. Two values were calculated, viz. the percentage of particles retained in the stomach, and the distance travelled by the second peak expressed as a percentage of the total length from stomach to rectum (on the few occasions when more than one peak was observed in the small intestine, the mean distance travelled was calculated). The mean ± S.D. of these values was calculated for each group of mice. Differences between groups were tested for significance at 95% confidence limits using the Student *t*-test and the Mann-Whitney test for non-parametric statistics.

When 3 groups of 5 mice were tested, the percentage retained in the stomach was 29.7 ± 18.4, and the mean percentage distance through the intestine of the second peak was 54.1 ± 4.7. As indicated in Table 1, particle size did not have a significant effect on the distribution.

The quantity of particles retained within the stomach showed a time-dependent release within the first 0.5 h, but large variations made it difficult to detect further changes. 10–50% of particles were retained for over 3 h (Fig. 2). The second

TABLE 1

The effect of particle size on the distribution of particles in the G I tract after 1 h

Particle size (μm)	Sample size	% Retained in stomach	% Distance travelled through G.I. tract
56 ± 13 3	4	31 8 ± 20 5	49.0 ± 12 0
9 ± 3 6	15	29.7 ± 18 4	54 1 ± 4 7
2 ± 0 3	5	39 6 ± 20.7	54.5 ± 7.7

Values are means ± S.D.

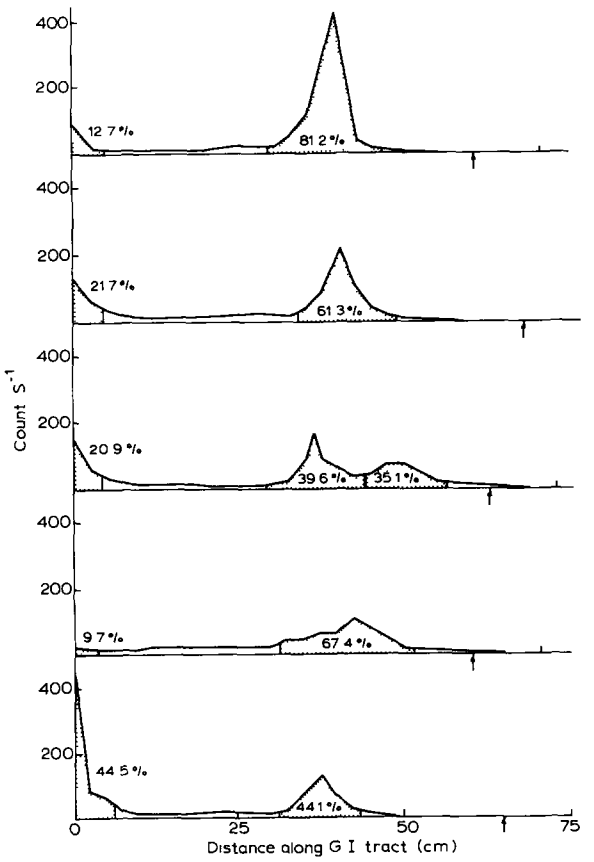

Fig. 1. Distribution of resin suspension within the G I tracts of a group of 5 mice. Arrow indicates position of caecum.

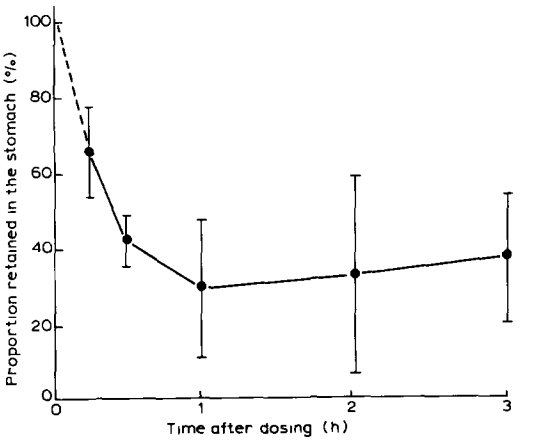

Fig 2. Gastric emptying of resin suspensions with time

TABLE 2

The effect of viscosity on the distribution of particles in G I tract after 1 h

Solution	Viscosity (mPa · s)	Sample size	% Retained in stomach	% Distance travelled by second peak
40% sucrose	3.17	5	84.3 ± 17.4	–
10% sucrose	0.92	15	29.7 ± 18.4	54 1 ± 4.7
0% sucrose	0.69	5	21.6 ± 9.0	54.2 ± 9 7
10% sucrose, 0.4% methylcell.	2 57	5	61 4 ± 20 5	53.5 ± 3 4

Viscosity determined at 37 °C using a U-tube viscometer, apparent viscosity for methylcellulose. Values are means ± S.D.

peak moved rapidly through the first section of small intestine and slowed as it approached the ileocaecal valve (Fig. 3). Two peaks were observed in the small intestine at times 0–1/2 h, but these merged to form a single peak at longer time intervals.

An increase in the viscosity of the suspension resulted in a significant decrease in gastric emptying, but did not affect the distance travelled by the second peak (Table 2).

When the volume of suspension, and hence the number of test particles administered, was halved, there was no significant difference in the distribution (48.9% ± 20.4 retained in stomach, distance travelled by second peak 50.6% ± 6.5 after 1 h).

Omission of the fasting stage did not produce a significant effect on the percentage retained in the stomach (27.1% ± 20.8) but produced a significant increase in the distance travelled by the second peak (87.7% ± 2.0 after 1 h), which had entered the caecum.

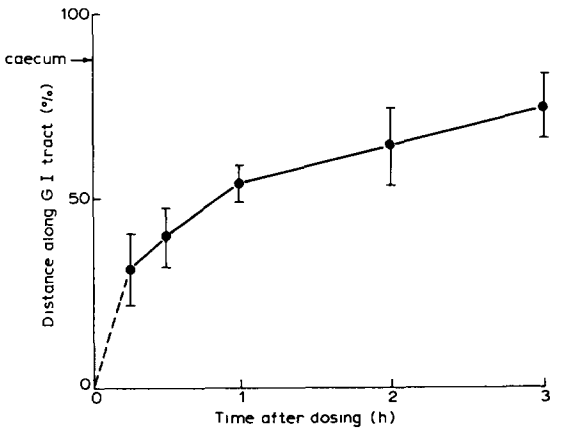

Fig 3. Distance travelled through the G.I. tract by the second peak with time

TABLE 3

The effect of adsorbed films on the distribution of particles in the G I tract after 1 h

Adsorbed film	Sample size	% Retained in stomach	% Distance travelled by second peak
None	15	29 7 ± 18 4	54.1 ± 4.7
SCMC	4	38.7 ± 48 4	54.2 ± 4 2
Carbopol 934P	5	97 7 ± 5.2	–

Values are means ± S.D.

Adsorbed films of SCMC did not produce a significant effect, whilst a Carbopol 934P adsorbed film almost completely arrested gastric emptying, (Table 3).

Discussion

In this study a bimodal distribution, one peak in the stomach and the second in the small intestine, was obtained. Unimodal and bimodal distributions were observed previously in the small intestine in rats (Miller et al., 1981). In fasted humans, pellets were observed to exit rapidly from the stomach (Davis, 1986); in this study significant quantities were retained after 3 h. Physiological differences and considerations of scale could account for these differences.

Gastric emptying is a controlling factor in G.I. transit but large variations made it impossible to draw firm conclusions regarding many of the factors that may affect this. In agreement with other

work (Levy and Jusko, 1965), increased viscosity, (and possibly the osmotic pressure) inhibited gastric emptying.

Intestinal transit rate was seen to decrease with distance travelled. This is illustrated by the linear relationship between the cube of the percentage distance travelled by the second peak and time (Pearsons correlation coefficient > 0.99). Only the presence of food was seen to significantly increase this. Other work has reported that food did not affect intestinal transit (Davis et al., 1986).

An adsorbed film of SCMC did not have a significant effect on GI. transit, whilst the dramatic arresting of gastric emptying by the Carbopol 934P adsorbed film corroborates the work of Ch'ng et al. (1985) and Longer et al. (1985). It is interesting to note that the reduction of G.I. transit with mucosa-adhesive polymers was observed in animal but not in human studies (Khosla and Davis, 1986; Fell et al., 1987). It is possible that other mechanisms, e.g. a physiological mechanism activated by Carbopol, may have reduced gastric emptying. This mechanism could not be the stimulation of fed state-like motility by indigestible particles proposed by Russell and Bass (1985), as this should also occur with uncoated particles. Further work is required before firm conclusions may be drawn.

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