An implication of these results is that rates of solubilization from mixtures of these types of oil would be an average of the rates of an individual oil. Preliminary measurements (O'Rourke 1983; Faulkner 1985) indicate this to be the case, in contrast to the observation of selection in equilibrium solubilization (Nagarajan & Ruckenstein 1983) and rates of solubilization (Ward et al 1985) in mixtures of oils with large differences in polarity.

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The effect of polycarbophil on the gastric emptying of pellets

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The influence of the putative bioadhesive, polycarbophil, on the gastric emptying of a pellet formulation, has been investigated in three fasted subjects. The pellets were radiolabelled with technetium-99m. Gastric emptying was measured using the technique of gamma scintigraphy. The pellets emptied from the stomach rapidly and in an exponential manner. Polycarbophil did not retard the gastric emptying of the pellets.

The design of oral controlled release dosage forms continues to attract the attention of formulation scientists. Several technically ingenious systems have been developed, (e.g. osmotic devices) that are capable of well-defined controlled drug release. The performance of these systems in-vivo however, is sometimes limited to the relatively short, and variable gastrointestinal transit times in man (8–10 h) (Ch'ng et al 1985). A device designed to deliver its dose over 24 h, may have emptied from the stomach, traversed the small intestine, and entered the colon in half that time. This could result in a reduced systemic level and a significant fraction of the dose being wasted. Control of the gastrointestinal transit of controlled release systems would be a clear advantage.

The gastric emptying of dosage forms is variable, and influenced by factors such as diet and the type of dosage form administered (Davis et al 1984b). Conversely, small intestine transit appears to be regular and unaffected by these factors (Read et al 1982; Davis et al 1984a). Control of the gastric emptying of dosage forms, therefore, represents the preferred option. A number of strategies have been proposed for this purpose, such as particle size (Meyer et al 1985), particle density (Bechgaard & Ladefoged 1978), and intermittent feeding (Meyer et al 1985). Another approach is the use of so called bioadhesive polymers, which adhere to the mucin/epithelial surface of the gastrointestinal tract (Park & Robinson 1984; Peppas & Buri 1985). Controlled release devices formulated with such polymers, could provide a 'localized platform', in the gastrointestinal tract, for drug release (Longer et al 1985). A variety of polymeric materials has been investigated (Smart et al 1984; Park & Robinson 1985), and anionic, water-insoluble polymers have been proposed because of their low toxicity and greater flexibility of use (Park & Robinson 1984). In particular, polycarbophil, a hydrophilic, granular, acrylate polymer, used as both an antidiarrhoeal, and a bulk-forming laxative (Russell & Bass 1985), has been shown to adhere to the rat stomach and small intestine (Ch'ng et al 1985). Furthermore, a sustained release formulation, containing polycarbophil and albumin beads, provided a longer duration of drug action in rats than formulations without the polymer (Longer et al 1985). It was suggested that polycarbophil rapidly hydrated in-vivo, retaining the beads and adhering to the mucin coating of the rat stomach. No studies have been reported for man.

The gastric emptying of pellets, labelled with a gamma-emitting radionuclide, can be measured in human subjects, using the technique of gamma scintigraphy (Davis 1983). This method has been used in the present study, to investigate the gastric emptying of a pellet formulation containing polycarbophil, in fasted, healthy male subjects. Our results indicate that poly-

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carbophil does not influence the gastric emptying of the pellets.

Materials and methods

Preparation of formulations. The formulations were prepared in a manner to mirror the systems employed by Longer et al (1985). Pellets (0·5–1·0 mm, density 1·17 g cm^{-3}) of Amberlite IRA410 anionic resin (BDH) were labelled by soaking 6 g in 10 mL [^{99m}Tc]sodium pertechnetate solution (CIS (UK) Limited, London). Size 0 hard gelatin capsules (Capsugel), disintegration time <10 min (BP 1980), were packed with a mix of dried, labelled pellets (310 mg) and 100 mg polycarbophil (0·5–1·0 mm) (Lee Laboratories, Petersburg, USA). Each capsule had an activity of about 3 MBq technetium-99m at the time of administration. The integrity of the binding of the label to the resin, was checked by appropriate in-vitro tests, under relevant conditions of temperature and pH.

In-vivo study. The study was approved by the Ethical Committee of the University of Nottingham and conducted in accordance with the declaration of Helsinki Guidelines for Ethics in Research.

Three, healthy, male volunteers, age range 19–25, height range 1·7–2·0 m, weight range 64–75 kg, participated with informed consent. Each subject abstained from ethanol for 24 h, and had fasted for 10 h before the study. The subjects did not smoke, and were not on medication. On the morning of the study, each subject swallowed one capsule with 100 mL water.

Anterior and posterior images, each of 60 s duration, were taken at regular intervals, using a gamma camera (General Electric Maxicamera, Type II) having a 40 cm field of view and fitted with a low energy (160 keV) parallel hole collimator. The subjects stood in front of the camera for imaging, and remained in upright positions between images. The data were recorded, and stored on computer (Nodecrest). Anatomical reference markers containing technetium-99m, were taped to the skin, anteriorly and posteriorly, over the liver to the right of the stomach. The volunteers were given a standard light lunch (cheese roll, 150 mL orange juice) after 5 h of imaging. After this time they were allowed to eat and drink as normal.

The recorded images were analysed by drawing regions of interest around the position of the stomach.

Table 1. Gastric emptying (t 50% min) of pellets.

Volunteer	Polycarbophil study	Control study
1	53	80
2	23	47
3	80	70
Mean (n = 3)	52	66
s.e.m.	13	8

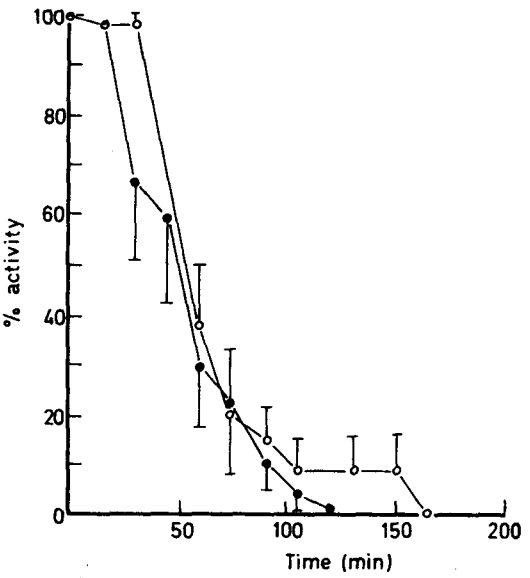

FIG. 1. Gastric emptying of radiolabelled pellets (mean ± s.e.m., n = 3). Key: (●) polycarbophil formulation; (○) control formulation.

The activity in these regions was quantified, and then corrected for background activity and radioactive decay. The error due to the variation in depth of radionucleotide in the stomach, was corrected by calculating the geometric mean of corresponding anterior and posterior views (Tothill et al 1978; Hardy & Perkins 1985).

A control study was conducted one week later, using capsules containing pellets only.

Results and discussion

Gamma scintigraphy was found to be an ideal method for measuring the gastric emptying of the pellet formulations, in fasted subjects. Release of the pellets from the capsule occurred within 15 min of administration and the dispersion of the pellets enabled ready identification of the stomach region for subsequent creation of regions of interest. The images obtained were similar to those presented before (Christensen et al 1985; Hardy & Perkins 1985).

Gastric emptying data have been expressed as the time for 50% (t50) of the pellets to leave the stomach (Table 1). The pooled data have been plotted in Fig. 1, as the mean ± s.e.m. for the three subjects.

The mean t50 gastric emptying time for the polycarbophil formulation, 52 ± 13 min, and for the control formulation, 66 ± 18 min, are in good agreement with previous investigations that have used gamma scintigraphy to measure gastric emptying. Hardy & Perkins (1985) report a t50 gastric emptying of 45 min (n = 4), for pellets given to fasted subjects. The mean t50 gastric

emptying for pellets given to subjects who had taken a light breakfast, was 99 ± 7 min (n = 8) (Christensen et al 1985). Davis et al (1984a) obtained t50 gastric emptying values ranging from 30 to 150 min (n = 6), for pellets taken by subjects who either fasted or had received breakfasts of different calorific values. This influence of food on the gastric emptying of pellets has been well illustrated by Davis et al (1984b). Gastric emptying was slower, 285 ± 45 min, when the subjects (n = 6) received a heavy breakfast, than when given a light breakfast, 119 ± 15 min. Thus, rapid gastric emptying in the present study, can be attributed to the absence of food in the stomachs of the subjects.

Our data show that both formulations empty exponentially (Fig. 1). It has been suggested that particles small enough (≤2 mm) to pass through the 'closed' pylorus, empty more as a liquid than as a solid (Kelly 1981). The rate of emptying of a liquid can be described as an exponential function, and typical t50 gastric emptying times range from 10 to 50 min (Bechgaard 1982). Malagelada et al (1984) report gastric emptying values between 20 and 60 min for radiolabelled water given to fed subjects. Emptying followed approximately an exponential pattern. Similarly, the mean t50 gastric emptying for radiolabelled water, given to subjects who had received a light breakfast, was 18 ± 4 min (n = 5) (Christensen et al 1985). Our results suggest, therefore, that the pellets emptied from the fasted stomach in a pattern similar to that for the gastric emptying of liquids.

The similar rate of emptying for both formulations, indicates that their admixture with polycarbophil does not retard the gastric emptying of pellets in fasted subjects. Longer et al (1985) investigated the gastrointestinal transit of a similar formulation of polycarbophil and albumin beads in rats. Approximately 90% of the beads remained in the stomach 6 h after administration. In the absence of polycarbophil, the beads emptied rapidly. Russell & Bass (1984) have reported that only 8% of a polycarbophil meal emptied from the stomachs of dogs within 90 min. A further investigation of canine gastric emptying of polycarbophil (Russell & Bass 1985) reported that 50% of a 90 g polycarbophil meal emptied within 4 h. However, in this study no attempt was made to attribute the slow emptying to adhesion of the polycarbophil to the gastric mucosa. The amounts of polycarbophil used in those studies, in rat and dog, were greater than that used in the present study and those larger amounts may have elicited motor activity of the fed stomach, which would result in a slower rate of gastric emptying (Russell & Bass 1985).

Our results show that pellets empty rapidly, and with an exponential pattern from the fasted stomach. Admixture of pellets with polycarbophil does not reduce the rate of gastric emptying.

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