International Journal of Pharmaceutics, 34 (1987) 213–216
Elsevier

IJP 01160

The influence of food on the gastric emptying of multiparticulate dosage forms

Sheila O'Reilly, Clive G. Wilson and John G. Hardy

Department of Physiology and Pharmacology and Department of Medical Physics, Queen's Medical Centre, Nottingham (U.K.)

(Received 21 July 1986)
(Accepted 5 August 1986)

Key words: Gastric emptying; Multiparticulate system

Summary

Gastric emptying of multiparticulate systems has been monitored in healthy volunteers. Particles dosed before a meal emptied exponentially, whilst those taken along with and after a meal exhibited a linear pattern of emptying. Although dosing before eating resulted in an initially faster emptying rate, the overall half-times of about 3–4 h were similar for all the dosing regimens. Particles dosed predispersed with the food emptied from the stomach at the same rate as those taken in a capsule.

Introduction

Sustained-release oral dosage forms are commonly prescribed as single unit or multiparticulate preparations. The patient may be instructed to take the formulation at meal times, but it may not be made clear whether this means before, during or after eating. The presence of food in the stomach inhibits the emptying of large capsules and tablets, and reduces the rate of emptying of small particles (Davis et al., 1984). Conversely, dosing before a meal may result in the preparation being swept from the stomach in advance of the food emptying.

Transit of particles through the small intestine takes typically 3–4 h (Davis et al., 1986). Thus with rapid gastric emptying, sustained-release products may have only a relatively short duration of action. Hunter et al. (1983) found that the dispersion of capsule contents was enhanced by taking the capsule after a meal. Multiparticulate preparations tend to empty from the stomach along with food fragments. It seems likely, therefore, that the bioavailability of drugs from sustained-release multiparticulate preparations could be prolonged by dosing on a full stomach.

In the present study, the gastric emptying of a multiparticulate preparation has been investigated. Attention has been focused on the timing of capsule administration relative to eating. The effect of encapsulation of the particles, when taken with food, has also been considered.

Materials and Methods

Materials

Anion exchange resin (Amberlite IRA 410) pellets, 0.7–1.3 mm diameter, and having a density of 1.2 $g \cdot cm^{-3}$ were radiolabelled with technetium-99m, by the addition of [^{99m}Tc]sodium pertech-

Correspondence: J.G. Hardy, Medical Physics Department, Queen's Medical Centre, Nottingham NG7 2UH, U.K.

netate solution. The pellets were dried, and 300 mg doses each containing approximately 500 particles were incorporated into hard gelatin capsules. At the time of administration each dose was radiolabelled with 3 MBq technetium-99m. In vitro studies showed that $< 1\%$ of the radioactivity was lost from the resin after 3 h at 37°C in human gastric juice.

Subjects

Twelve healthy male subjects aged 20–22 years participated. None was taking any medication and all were non-smokers and had abstained from alcohol for at least 24 h before dosing. The study was approved by the Medical School Ethical Committee and each subject provided written informed consent.

Methods

The investigation was undertaken in two parts, with 6 subjects participating in each. The first study involved each subject swallowing a capsule on 3 separate occasions: before, during and after a meal. In the second part of the investigation each subject was dosed during a meal on two separate occasions: once with encapsulated pellets and once with the pellets predispersed amongst the food. The dosing regimens were randomly allocated for both sets of experiments.

The subjects fasted overnight and were dosed at 12.30 h. During each experiment they consumed a 3800 kJ lunch comprising: one cheese roll, one ham roll, fruit yoghurt and 150 ml orange juice. During the first part of the study the capsule was taken with orange juice either 10 min before eating, midway through the meal or 10 min after eating. During the second part of the investigation the non-encapsulated particles were sprinkled over the contents of both rolls, and the capsule was taken after eating the first roll.

The distributions of the particles were monitored using a gamma camera and the data recorded by computer for subsequent analysis. Each subject had ^{99m}Tc-labelled reference markers taped to his skin anteriorly and posteriorly to the right of the stomach. Anterior and posterior images, each of 60 s duration, were recorded at 15 min intervals over 4 h. Throughout each study the subjects remained in upright postures and were imaged standing.

Images of the dispersed particles were displayed on a television monitor and the location of the stomach established relative to the positions of the reference markers. A region of interest was defined over the stomach region in each image and a count rate obtained. The count rates were corrected for background counts and for radioactive decay. The geometric means of the count rates from corresponding pairs of anterior and posterior images were calculated (Tothill et al., 1978) and the results expressed as proportions of the count rates from the stomach immediately after dosing.

Results

During each experiment the particles were released from the capsule within a few minutes after dosing. In comparison with the encapsulated particles taken before the meal, those dosed during and after the meal tended to remain for longer in the upper half of the stomach. The average rates of gastric emptying for the three dosing regimens are shown in Fig. 1. The particles administered before eating initially exhibited an exponential pattern of emptying, whilst for those taken during and after the meal the rate of emptying was approximately linear. There was no significant dif-

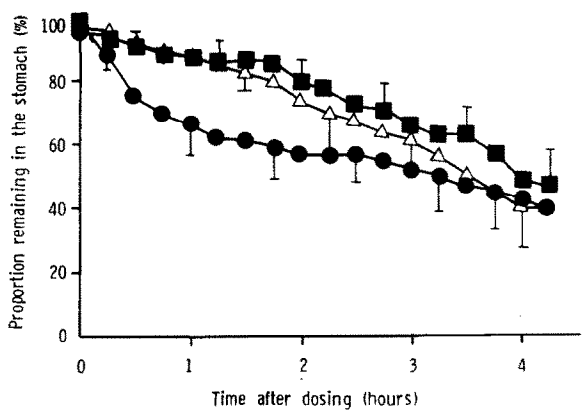

Fig. 1. Gastric emptying of a multiparticulate preparation dosed: before (●), during (■), and after (△) a meal (mean ± 1 S.E.M., $n = 6$).

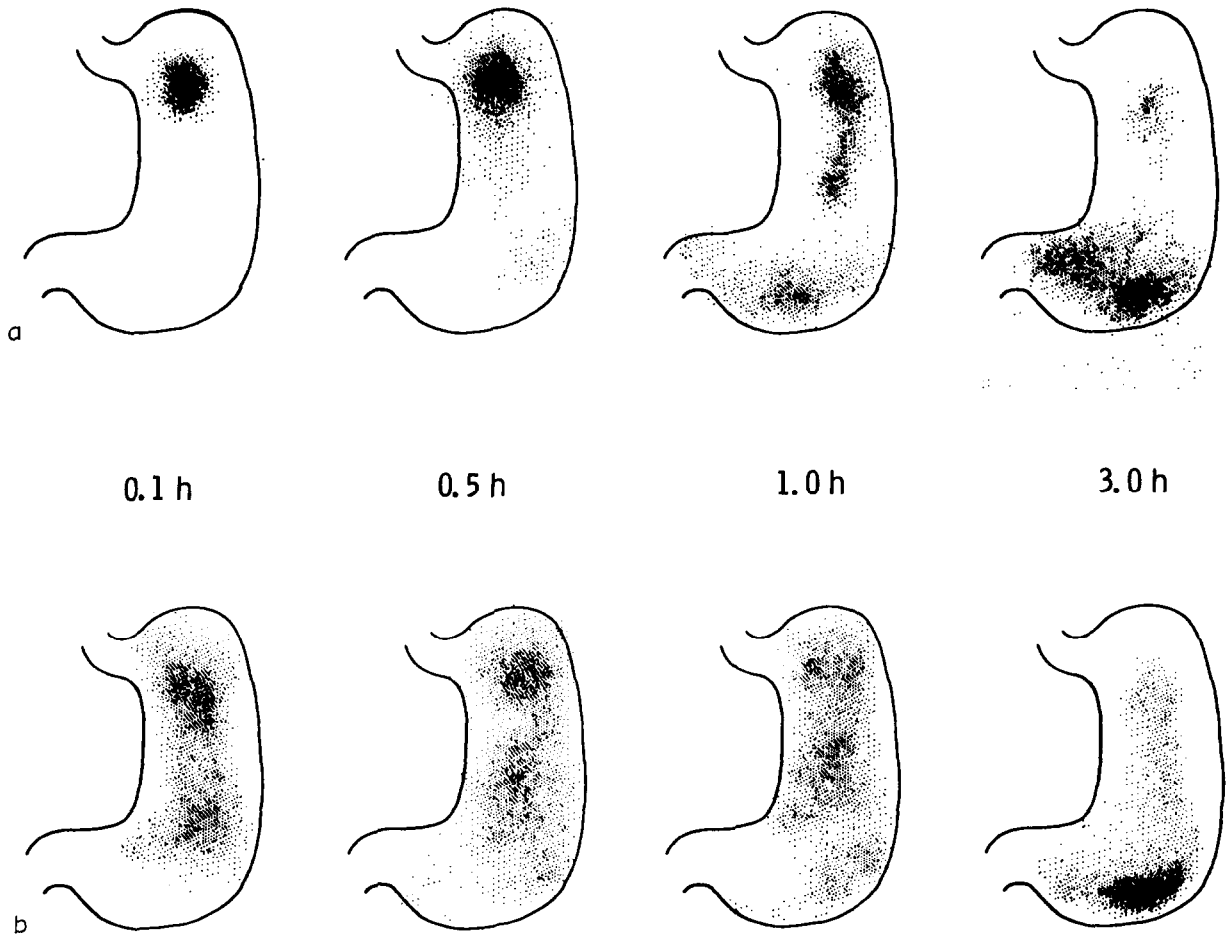

Fig. 2. Distribution of particles in the stomach after dosing the same subject: (a) with encapsulated particles, and (b) with predispersed particles.

ference between the emptying rates of the particles taken during and following the meal. Over the initial 100 min, however, the particles taken before the meal emptied fastest ($P < 0.05$). The mean half-times for gastric emptying, however, were similar for all the studies: the values for particles dosed before, during and after the meal being 3.3 h, 3.5 h and 4.0 h, respectively.

In the second part of the investigation, dispersion of the particles within the stomach was more rapid for those sprinkled onto the food (Fig. 2). For both preparations, however, gastric emptying approximated to a linear pattern and there was no significant difference between the emptying rates (Fig. 3).

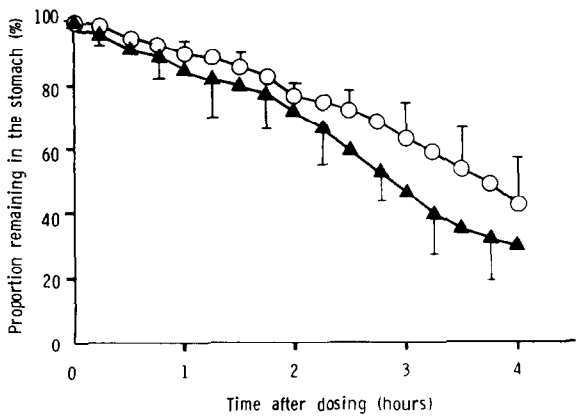

Fig. 3. Gastric emptying in subjects dosed during a meal with encapsulated (▲) and predispersed (○) particles (mean ± S.E.M., $n = 6$).

Discussion

Following capsule disintegration, the particles became dispersed within the stomach. The particles administered during or soon after the meal exhibited an approximately linear pattern of gastric emptying. This was found for both the preparation dosed in capsules and the particles sprinkled onto the food. Solid food characteristically empties in this manner (Tothill et al., 1978) and these findings indicate that the particles became intimately mixed with the solid components of the meal. In contrast, the initial phase of gastric emptying of the particles taken before the meal was approximately exponential. This pattern is typical of liquid emptying from the stomach (Tothill et al., 1978). Thus a proportion of the particles may have emptied with the orange juice in advance of any mixing with the solid food.

Overall, the half-times for gastric emptying of the particles were similar irrespective of the dosing regimens. The values of 3–4 h are in agreement with those reported by Davis et al. (1986) for particles taken after a breakfast of about the same calorific value as the meal consumed during the present study. Particles taken by fasting subjects empty more rapidly, with half-times of about 1 h (Hardy et al., 1985; Davis et al., 1986). Christian et al. (1980) found that changing the meal size from 300 to 1692 g increased the half-time for solid phase gastric emptying from 77 min to 277 min, and for the liquid phase from 38 min to 178 min. It is apparent, therefore, that the rate of entry of particles into the duodenum can be modulated by varying food intake.

The efficacy of multiparticulate sustained-release preparations may be influenced by the food content in the stomach at the time of dosing. Taking a preparation before a meal results in rapid initial gastric emptying, which may cause an early high peak blood level of the drug. Administration of the particles during or soon after a meal is likely to prolong the duration of action of the preparation, whilst minimizing fluctuations in bioavailability. Sprinkling the particles onto food may be appropriate for patients unable to swallow capsules, since the gastric emptying rate was the same as for the encapsulated dose. This procedure has the disadvantage, however, that the patient may not consume the whole meal, and thus only receive a proportion of the required dose.

References

Christian, P.E., Moore, J.G., Sorenson, J.A., Coleman, R.E. and Welch, D.M., Effects of meal size and correction technique on gastric emptying time: studies with two tracers and opposed detectors. *J. Nucl. Med.*, 21 (1980) 883–885.

Davis, S.S., Hardy, J.G., Taylor, M.J., Whalley, D.R. and Wilson, C.G., A comparative study of the gastrointestinal transit of a pellet and tablet formulation. *Int. J. Pharm.*, 21 (1984) 167–177.

Davis, S.S., Hardy, J.G. and Fara, J.W., Transit of pharmaceutical dosage forms through the small intestine. *Gut*, 27 (1986) 886–892.

Hardy, J.G., Wilson, C.G. and Wood, E., Drug delivery to the proximal colon. *J. Pharm. Pharmacol.*, 37 (1985) 874–877.

Hunter, E., Fell, J.T. and Sharma, H., The gastric emptying of hard gelatin capsules. *Int. J. Pharm.*, 17 (1983) 59–64.

Tothill, P., McLoughlin, G.P. and Heading, R.C., Techniques and errors in scintigraphic measurements of gastric emptying. *J. Nucl. Med.* 19 (1978) 256–261.