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# Simultaneous measurement of gastric emptying of the soluble and insoluble components of a formulation using a dual isotope, gamma scintigraphic technique

LYDIA KAUS, H. SHARMA, J. T. FELL*, *Departments of Pharmacy and Medical Biophysics, University of Manchester, Manchester M13 9PL. U.K.*

The gastric emptying of a soluble and an insoluble component of a capsule formulation has been monitored by gamma scintigraphy using a dual isotope technique. There was no significant difference between the emptying rates for the two components or between fasting and non-fasting conditions ($P > 0.01$).

The gastric emptying of a drug can be the rate-limiting step in drug absorption (Heading et al 1973). Several studies have been made using short-lived radionuclides to assess in-vivo disintegration and dispersion of solid dosage forms (Casey et al 1976; Hunter et al 1980; Lagas et al 1980; Daly et al 1982). The method of continuous monitoring by means of a γ-camera offers qualitative and quantitative estimation of the behaviour of solid dosage forms in the gastrointestinal tract.

Studies on the emptying of foods from the stomach have shown that different components empty at different rates; liquids, for example, leaving faster than solids (Heading et al 1976: Grimes & Goddard 1977; Weiner et al 1981). In solid pharmaceutical dosage forms, a liquid component would not normally exist as such, but combinations of readily soluble and insoluble components would commonly occur. The present study uses a dual isotope technique to investigate the in-vivo behaviour of formulations containing a soluble and an insoluble component in fasting and non-fasting patients.

## *Materials and methods*

*Materials.* The two components of the formulation used were sodium chloride (Analar, BDH Ltd) to represent a readily soluble material, and Amberlite resin (CG. 400 Cl, chromatographic grade BDH Ltd) as an insoluble, but readily wetted material. They were labelled with $^{113m}$In and $^{99m}$Tc respectively.

*Labelling and capsule filling.* Amberlite resin (0·6 g) was stirred into 30 ml of distilled water. Approximately 500 μCi of $^{99m}$Tc sodium pertechnetate were eluted from a generator with 0·9 M NaCl. This was mixed with the ion exchange resin suspension and stirred. The labelled resin was recovered from the suspension by filtration followed by drying of the filtrate.

To label the sodium chloride, 0·5 g was dissolved in 30 ml of distilled water in an evaporating dish. Approximately 1 m Ci $^{113m}$In indium chloride was eluted from a generator with 0·1 M hydrochloric acid. This was mixed with the solution of sodium chloride and the labelled solution slowly evaporated to dryness and sieved through a 250 μm sieve.

Samples of 60 mg labelled ion-exchange resin and 50 mg indium (113 m) chloride were mixed together, and packed by hand into No. 4 hard gelatin capsules.

*Disintegration time.* This was measured by the BP (1980) method, using single capsules, with distilled water as the test fluid. The result, the mean of five determinations, was 1 min 37 s.

*In-vivo experiments.* Each of 11 healthy male volunteers (ages 20–24 years) took a capsule with 100 ml water after a night-long fast or immediately after a standard breakfast of 200 ml milk, 40 g cornflakes and 6 g sugar. Immediately after ingestion of a capsule, the subject lay supine on a stretcher, allowing an anterior view of the abdominal region to be monitored by a γ-camera linked to an on-line computer (MED II, Nuclear Data Inc.). Data for each isotope, accumulated for 60 min at 1 min intervals, were stored. Counts were adjusted for the contribution of $^{113m}$In to the $^{99m}$Tc channel and for decay of the individual isotopes.

## *Results and discussion*

Plots of log % radioactivity in the stomach against time were constructed. As these plots exhibited different

Table 1. The areas under the curves of % radioactivity in the stomach against time to 30 min, expressed as a fraction of the maximum counts, for eleven subjects.

| | Fasting | | Non-fasting | |
|---|---|---|---|---|
| Subject No. | Insoluble | Soluble | Insoluble | Soluble |
| 1 | 0·71 | 0·71 | 0·25 | 0·34 |
| 2 | 0·40 | 0·65 | 0·79 | 0·72 |
| 3 | 0·74 | 0·69 | 0·66 | 0·54 |
| 4 | 0·41 | 0·35 | 0·46 | 0·27 |
| 5 | 0·63 | 0·61 | 0·57 | 0·49 |
| 6 | 0·60 | 0·66 | 0·82 | 0·69 |
| 7 | 0·96 | 0·85 | 0·82 | 0·84 |
| 8 | 0·38 | 0·37 | 0·65 | 0·56 |
| 9 | 0·67 | 0·76 | 0·48 | 0·53 |
| 10 | 0·45 | 0·39 | 0·26 | 0·29 |
| 11 | 0·31 | 0·36 | 0·61 | 0·57 |

* Correspondence.

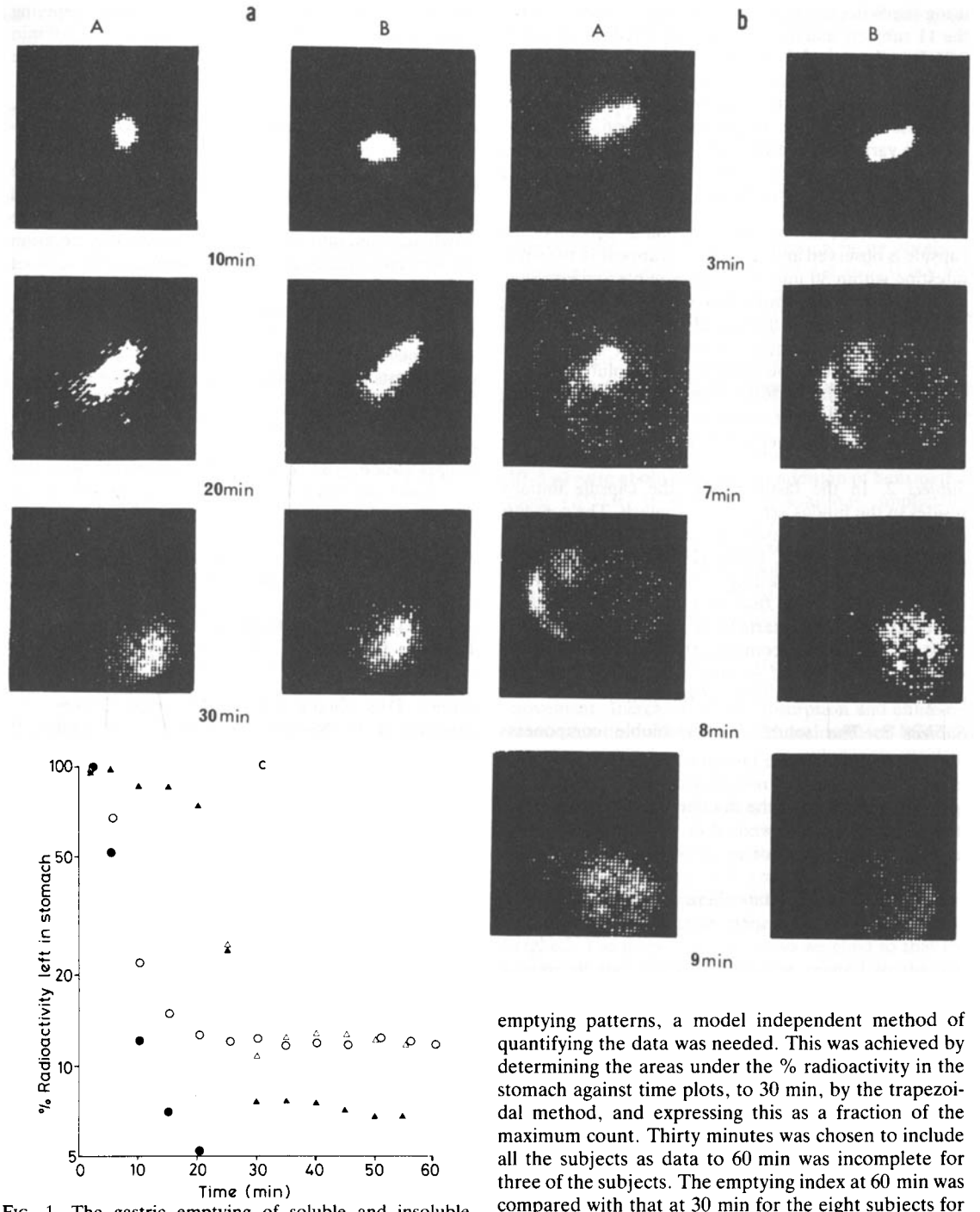


FIG. 1. The gastric emptying of soluble and insoluble components in Subject 1 as shown by scintiphotos (a, b) and plots (c) of log % radioactivity remaining in stomach against time. a: fasting, b: non-fasting, A: insoluble component, B: soluble component. ▲ = soluble component, fasting; △ = insoluble component, fasting; ● = soluble component, non-fasting; ○ = insoluble component, non-fasting.

emptying patterns, a model independent method of quantifying the data was needed. This was achieved by determining the areas under the % radioactivity in the stomach against time plots, to 30 min, by the trapezoidal method, and expressing this as a fraction of the maximum count. Thirty minutes was chosen to include all the subjects as data to 60 min was incomplete for three of the subjects. The emptying index at 60 min was compared with that at 30 min for the eight subjects for whom complete data were available, using the Wilcoxon matched-pairs signed-ranks test. The null hypothesis of no difference could not be rejected at a level of significance of 0·01 and hence 30 min is an adequate time for comparison.

Statistical analysis of the area under the curve data

using the Wilcoxon matched-pairs signed-ranks test for the 11 subjects and three degrees of freedom gave $P > 0{\cdot}01$ for all pairs of data. Hence there is no significant difference in the gastric emptying between the fasting and non-fasting conditions or between the soluble and insoluble components of the formulation. However, there is variability between the subjects, as seen from Table 1, and to illustrate this, the results from three subjects are discussed in detail.

*Subject 1.* In the fasting state, gradual dispersion of the capsule is observed and the contents appear in the small intestine within 30 min. Both the soluble and insoluble components exhibit similar behaviour. In the nonfasting state, the contents of the capsule are rapidly dispersed and are quickly emptied. Emptying is complete in 9 min. Again both the soluble and insoluble components show similar patterns of dispersion and emptying a lag time of only 1 min can be seen between the soluble and insoluble components at 7 and 8 min (Fig. 1).

*Subject 2.* In the fasting state, the capsule initially resides in the fundus area of the stomach. The contents of the capsule are released, and gastric emptying occurs as a gradual process, being virtually complete after 20 min. In the non-fasting state, emptying is much slower in contrast to that of subject 1. The capsule disperses slowly and starts to be emptied after 30 min. Most of the soluble component is seen to leave the stomach at the end of 40 min; some of the insoluble component leaves as a bolus at this point.

*Subject 3.* The soluble and insoluble components behave similarly in the fasting state. Dispersion of the contents is seen at 10 min post ingestion, and gradual gastric emptying into the duodenum and further down the intestine is observed after 20 min. Most of the capsule's contents reside in the intestine after 40 min.

In the non-fasting state there is a lag time of about 10 min between the dispersion and gastric emptying of the insoluble and soluble components. Gastric emptying occurs earlier for the soluble component at 10 min whilst dispersion is seen at 20 min for the insoluble component without much gastric emptying occurring. Most of the soluble component has emptied by 30 min, whereas 40 min is required for the insoluble component.

Two additional volunteers who took part were excluded from the results because the capsule remained in the oesophagus. On one occasion, the contents were slowly released into the stomach, on the other occasion the contents remained in the oesophagus throughout the study.

Pharmaceutical formulations often consist of mixtures of soluble and insoluble components. The current study has shown that the behaviour of two such components in the stomach is similar.

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