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Research Papers

'IN VIVO' DISINTEGRATION OF HARD GELATIN CAPSULES IN FASTING AND NON-FASTING SUBJECTS

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SUMMARY

The dispersion of hard gelatin capsules in the stomach has been followed using a model formulation consisting of an ion exchange resin labelled with a gamma-emitting isotope and monitoring externally with a gamma camera. Capsule formulations were prepared giving both slow and fast in vitro disintegration times. Little dispersion of the capsule contents occurred in fasting subjects, whereas after food, the dispersion was more in keeping with the in vitro disintegration times. Gastric emptying curves could be related to the behaviour of the capsule in the stomach. In one case, the capsule lodged in the oesophagus and gradually emptied its contents into the stomach.

INTRODUCTION

The absorption of a drug is known to be dependant on physical characteristics such as particle size (Fincher, 1968) and also on its presentation to the site of absorption, which for the majority of drugs is the small intestine. The passage of a dosage form along the gastro-intestinal tract can influence the absorption of a drug, and in particular, the rate of gastric emptying can be a controlling factor in the onset of absorption (Heading et al., 1973). Studies on dosage forms to assess their release and absorption characteristics involve 'in vitro' tests such as disintegration times, and dissolution rate, and 'in vivo' measurements of plasma or urinary drug levels. These studies do not, however, give an insight into the behaviour of the dosage form within the gastro-intestinal tract itself.

Various direct methods of studying the 'in vivo' behaviour of solid dosage forms have been published and have been reviewed by Wagner (1971). These methods suffer from the major drawback that the preparations cannot be monitored on a continuous basis. The

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recent developments of scintiscanning and gamma camera techniques for following formulations labelled with a gamma-emitting isotope overcomes the earlier problems, and have the added advantage of allowing a quantitative estimation of gastric emptying to be made (Digenis et al., 1976, Alpsten et al., 1976). In this study, a gamma camera has been used to follow the 'in vivo' behaviour of labelled capsule formulations in fasting and non-fasting human subjects.

MATERIALS AND METHODS

Materials

An ion exchange resin was chosen as a model material as the label, ^{99m}Tc, was bound tightly both in acid and alkali, and the material was insoluble and not absorbed. Amberlite resin CG-400(C1) (chromatographic grade, B.D.H. Chemicals, Poole) is available in a range of particle sizes. A grade exhibiting a mean particle size of 25 μm (Fisher Sub Sieve Sizer) was used as received (A), and also milled (Gem. T. Helme Products, N.J., U.S.A.) to give a mean particle size of 9 μm (Fisher Sub Sieve Sizer) (B). A further grade was sieved to give a size fraction of 150–210 μm (C). The density of the material, 1.2 g/ml (Air Comparison Pycnometer) is similar to many pharmaceutical materials.

Labelling and capsule filling

Of the ion exchange resin 0.5 g was stirred into 30 ml of distilled water. Approximately 300 μCi of $[^{99m}Tc]O_4^-$ were eluted from a generator with 0.9 N saline. This was mixed with the ion exchange resin suspension and stirred. The labelled resin was then recovered from the suspension by centrifugation at 3000 rpm, decanting the supernatant, followed by drying. Samples of 0.1 g were packed by hand into No. 4 hard gelatin capsules.

Disintegration times

These were measured by the B.P. (1978) method, using single capsules, with distilled water as the test fluid. The results are the means of 5 determinations.

In vivo experiments

Three male subjects were used for the study. In a typical experiment, a subject took a capsule with 100 ml of water after a night-long fast or immediately after a standard breakfast of 200 ml milk, 40 g cornflakes and 6 g sugar. One week was allowed to elapse between experiments. After administration of a capsule, the subject was placed in a supine position on a stretcher to allow the upper abdominal region to be viewed by a gamma camera linked to an on-line computer (MED II Nuclear Data Inc.). Data were accumulated for 60 min at 1-min intervals and stored on a magnetic disc. Throughout each study, scintiphotos were taken from the oscilloscope display at 10-min intervals. Gastric emptying curves were obtained by counting the total radioactivity (adjusted for decay) in the stomach in each 1-min period as a percentage of the initial 1 min count.

RESULTS AND DISCUSSION

The process of labelling the resin involves the addition of an aqueous fluid and causes approximately a 40% increase in the mean particle size of the powders. After this initial wetting, drying and then rewetting did not cause the particle size to alter. The disintegration times of the capsules are given in Table 1. Capsules A and C behave as 'ideal pharmaceuticals' with very short disintegration times, whereas the capsule containing the milled resin exhibited a prolonged disintegration time. Although this could simply be a function of the particle size reduction, the milled resin did appear to be more hydrophobic in character, although its binding properties for the label were not altered.

As some intersubject variation existed, the results from the 'in vivo' studies are discussed for each subject.

Subject 1

Gastric emptying curves plotted as log per cent radioactivity remaining in the stomach with time are shown for capsules A and B in Fig. 1. It is generally thought that food delays the gastric emptying of pharmaceutical dosage forms (Bates and Gibaldi, 1970) but for capsule A, emptying is more rapid after food than in the fasting state. This may be a function of the high liquid content of the test meal.

The scintiphotos for capsule A in this subject in the fasting and non-fasting state, taken at 10-min intervals up to 40 min are shown in Fig. 2. This capsule exhibited rapid disintegration in vitro. After a meal, the contents of the capsule appear to be released and disperse well in the stomach, and from 20 min onwards the capsule contents can be seen in the duodenum. In the fasting state, it can be seen that very little dispersion of the capsule contents takes place, despite the in vitro disintegration time being short. It is considered that the capsule, on entering the stomach, adheres to the mucus lining. The volume of water administered with the capsule is small, and will be cleared rapidly from the stomach. The capsule contents can thus only disperse into the mucus lining which, being viscous, will retard this process. Emptying of the capsule contents from the stomach will be governed by a normal mucus clearance into the duodenum. Hence the gastric emptying plots show a change of slope when the bulk of the contents are discharged from the stomach.

TABLE 1

"IN VITRO" DISINTEGRATION TIMES OF THE HARD GELATIN CAPSULES

Formulation	Approximate particle size (μm)	Disintegration time (min)
A	25	2
B	9	9
C	180	2

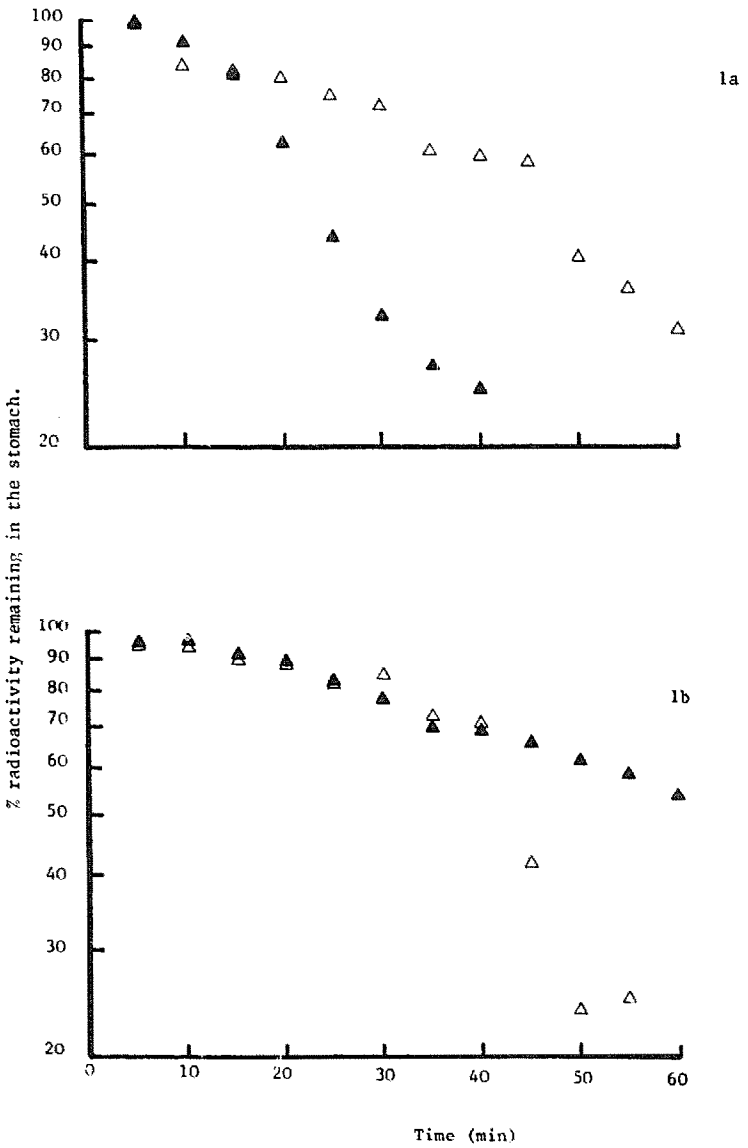

Fig. 1. a: gastric emptying curves for capsule A in subject 1. Ordinate: log % radioactivity remaining in the stomach; abscissa: time (min). △, fasting; ▲, non-fasting. b: gastric emptying curves for capsule B in subject 1. Ordinate: log % radioactivity remaining in the stomach; abscissa: time (min). △, fasting; ▲, non-fasting.

The scintiphotos for capsule B are shown in Fig. 3. This capsule exhibited slow in vitro disintegration times and showed little dispersion in the stomach. Emptying from the stomach will presumably take place via the mucus and the majority of the capsule contents will leave the stomach together. This can be seen as a rapid decrease in the radioactivity in the stomach in Fig. 1b in the fasting case, the final scintiphoto in Fig. 3 showing the

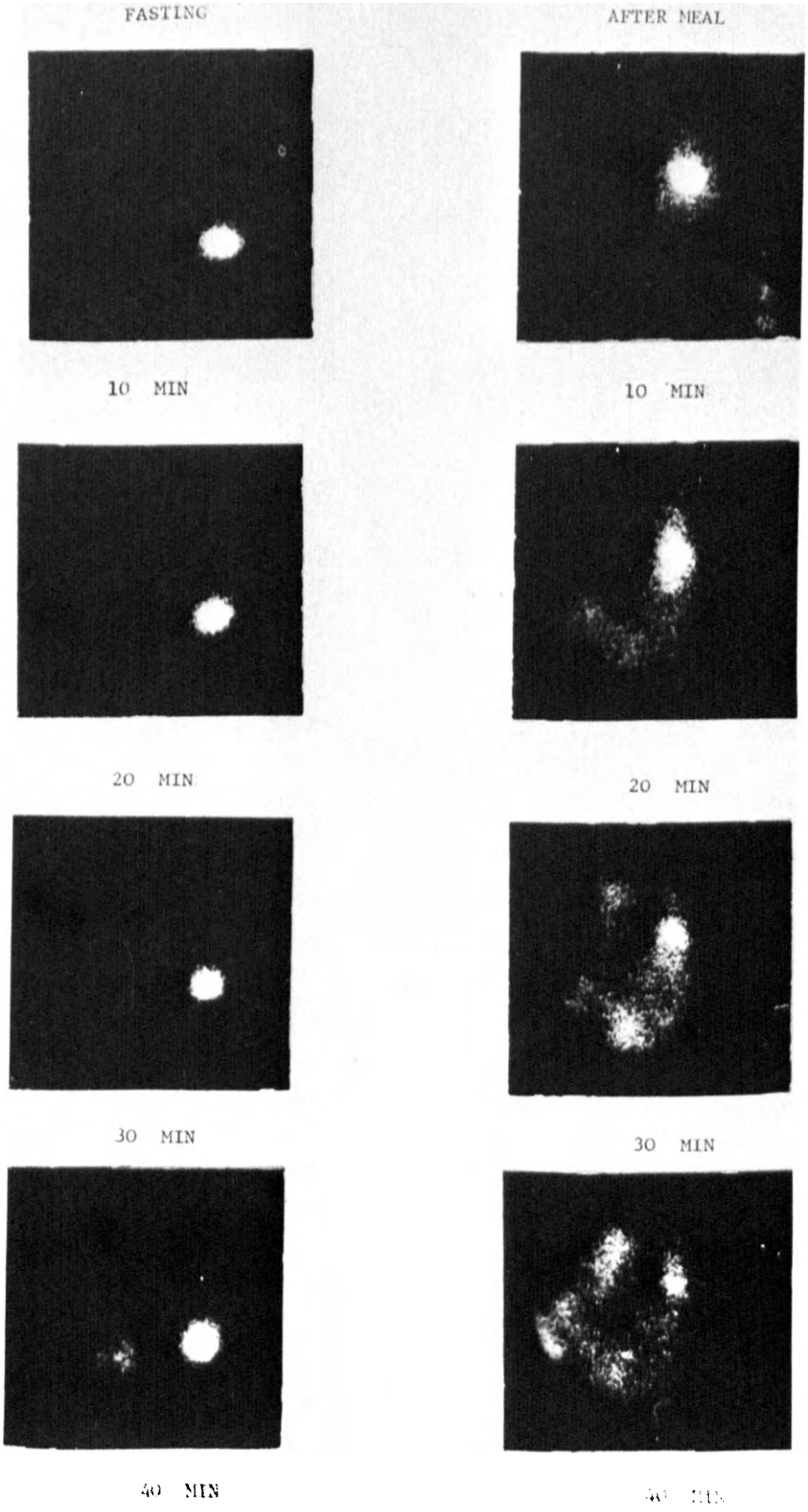

Fig. 2. Scintiphotos of capsule A in subject 1 in fasting and non-fasting states.

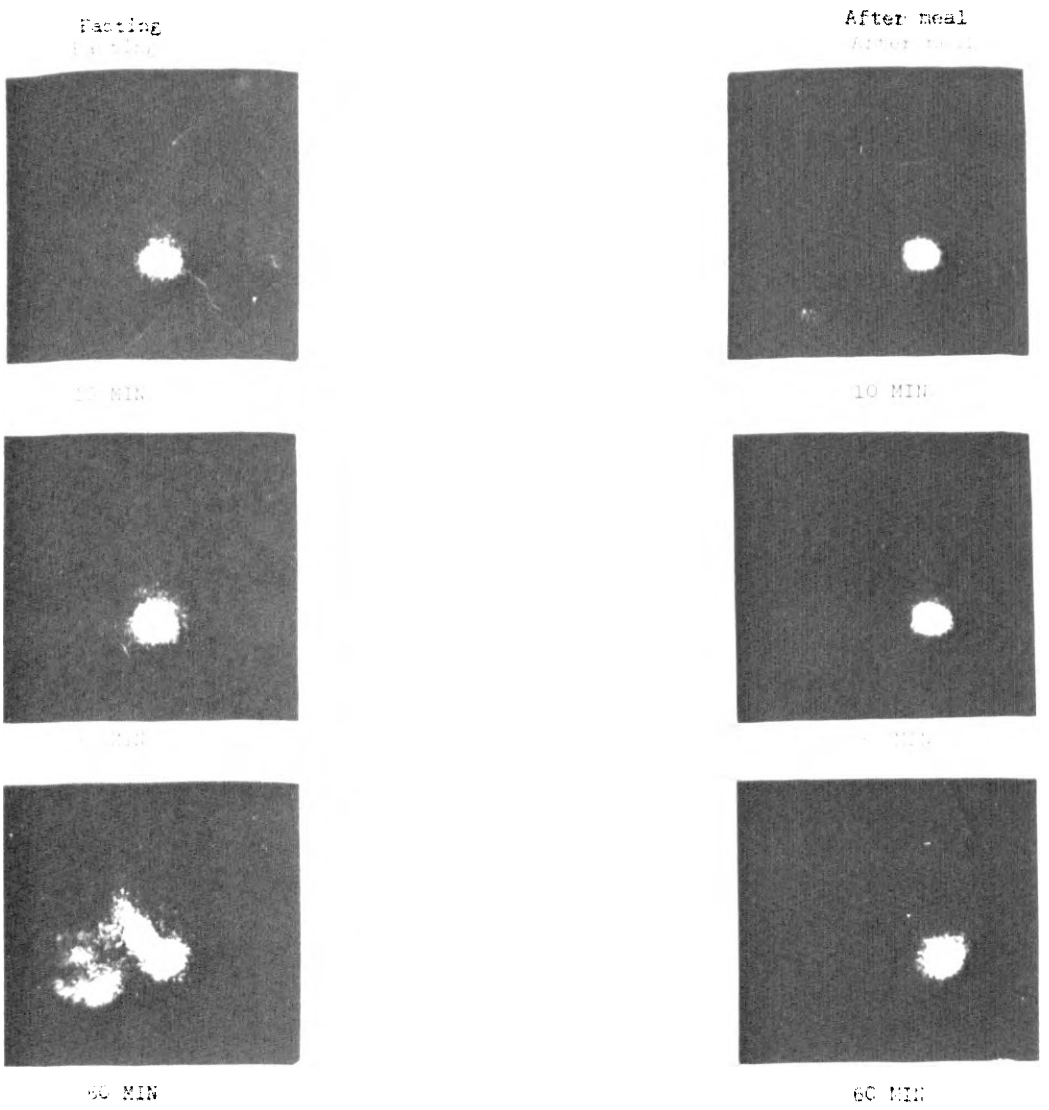

Fig. 3. Scintiphotos of capsule B in subject 1 in fasting and non-fasting states.

material in the duodenum. After food, little emptying has taken place in the one hour experimental period. This could be due to the capsule lodging in the mucus lining higher in the stomach in the presence of a meal, and therefore having further to travel to the sphincter.

Capsule C containing the larger particles behaved qualitatively the same as capsule A, except a greater degree of dispersion was noted in the fasting case.

Subject 2

The behaviour of the capsules was qualitatively similar to that in subject 1 except for capsule A taken after food. In this case, the scintiphotos showed the capsule to be lodged

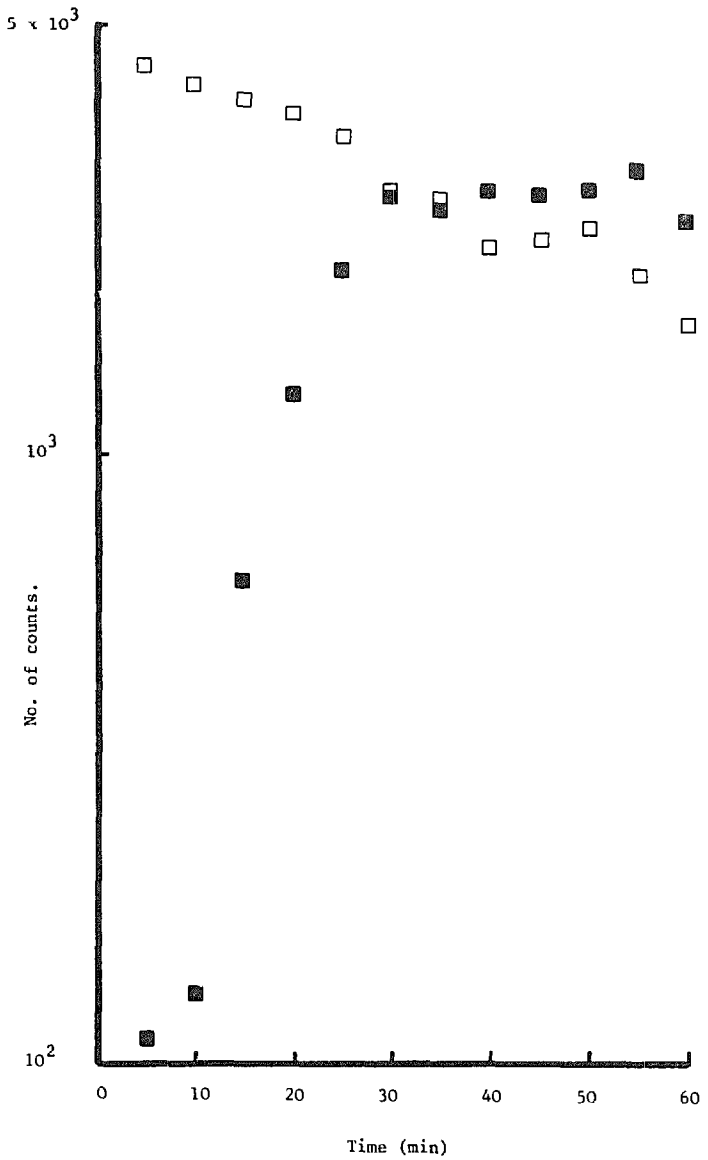

Fig. 4. The release of capsule contents into the stomach after lodgement of the capsule in the oesophagus. Ordinate: number of counts; abscissa: time (min). ■, stomach; □, oesophagus.

in the lower oesophagus, gradually releasing its contents into the stomach. This is shown graphically in Fig. 4. The subject was not aware of the capsule in the oesophagus. This phenomenon was also noted during preliminary studies in these laboratories, and with barium sulphate tablets and capsules (Evans and Roberts, 1976). The powder formulation in the capsule is presumably not significant in this phenomenon, but whenever the effect was noted, it was always after food.

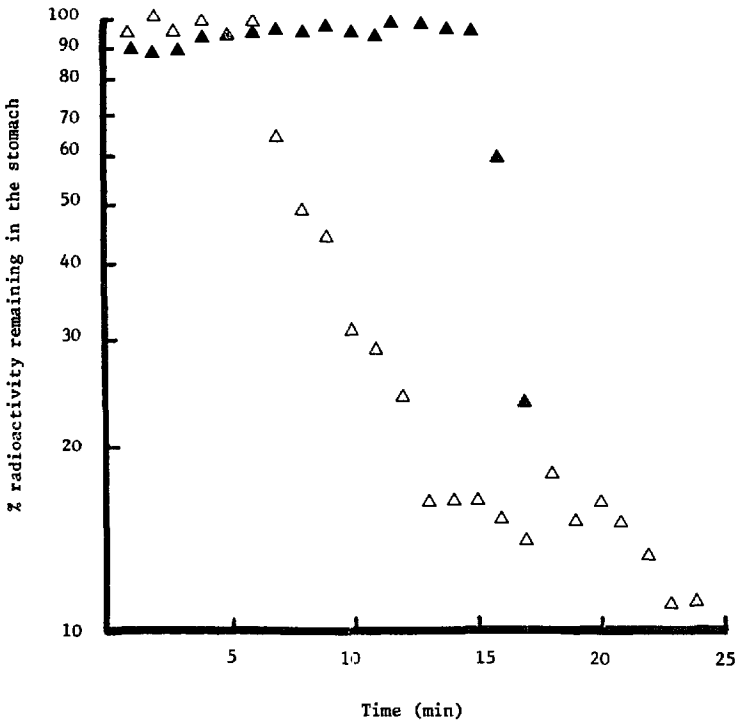

Fig. 5. Gastric emptying curves for capsule A in subject 3. Ordinate: log % radioactivity remaining in the stomach; abscissa: time (min). △, fasting; ▲, non-fasting.

Subject 3

In this subject, gastric emptying was very rapid in all cases giving little time for any dispersion of the capsule contents to occur. The presence of food slowed down the emptying, but in all cases it appeared that the stomach contents were emptied as a whole, giving rise to the type gastric emptying curves shown in Fig. 5.

In a limited study such as this where there is a degree of intersubject variation, general conclusions cannot be drawn. However it is worthy of note that rapidly disintegrating hard gelatin capsules when administered with a small amount of liquid to fasting subjects did not disperse in the stomach, and this may have a bearing on bioavailability and the design of bioavailability studies.

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