DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 8(5), 751-757 (1982)

THE GASTRIC EMPTYING OF PELLETS CONTAINED IN HARD GELATIN CAPSULES

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ABSTRACT

The gastric emptying of pellets analogous to those used in sustained release preparations has been studied *in vivo*, using gamma scintigraphy. The results show that under certain conditions, the pellets may not necessarily empty from the stomach in a randomized manner.

INTRODUCTION

Controlled release dosage forms may be conveniently divided into two types; the single-unit dose, and the multiple-units dose (1). The single-unit dose is exemplified by matrix tablets which release the drug during their passage through the gastrointestinal tract, but do not disintegrate. The multiple-units dose consists of many coated pellets or crystals contained in a tablet or capsule, designed to disintegrate upon ingestion.

One advantage of the multiple-units type of formulation is said to be its independence of the variable effect of gastric emptying. The pellets are said to be small enough to pass through the pylorus when closed (1), behaving as though a solution had been administered (2).

Recently, a technique has been described that allows the visualization of dosage forms *in vivo* (2) (4). It was noted (4) that capsules that disintegrate rapidly *in vitro*, do not necessarily disperse well in the stomach. The work reported in this paper examines the influence of fasting and non-fasting conditions and patient posture on the *in vivo* behaviour of capsules containing pellets analogous to those used in multiple-units dosages.

MATERIALS AND METHODS

Amberlite resin (IRA-410 B.D.H. Ltd, Poole, England), was sieved to give a size fraction of 690-850 μm. The density of the material was 1.18 g/cc (Air Comparison Pycnometer, Beckmann Ltd). This material was labelled with ^{99m}Tc as described earlier (4). Samples of 0.1 g of the labelled resin were packed, by hand, into No 4. hard gelatin capsules. The disintegration times of the capsules (B.P. 1980) was approx 2 min.

Two male subjects were used for the study. The capsules were administered with 100 ml of water after an overnight fast, or immediately after a breakfast consisting of 40 g cornflakes, 200 ml milk and 6 g sugar. The subjects were placed either supine, or seated in such a manner as to allow the abdomen to

be scanned with a gamma camera (Med II, Nuclear Data Inc). Data were collected for 60 min at 1 min intervals and stored on a magnetic disc. Gastric emptying was determined by plotting log % radioactivity remaining in the stomach against time, correcting for isotopic decay. First order rate constants for gastric emptying were determined by regression analysis.

RESULTS AND DISCUSSIONS

Typical gastric emptying curves are shown in Figure 1 showing a lag time before emptying occurs. The lag times and first order emptying constants are given in Table 1.

For subject 1, after an overnight fast and in the supine position, the capsule contents were emptied rapidly, as a whole, into the duodenum. This could be seen to be due to active pyloric contractions. After the meal, the capsule contents dispersed, and emptied at a slower rate. When subject 1 was in an upright position no gastric emptying occurred in the 60 min period when the capsule was taken after the meal, although the capsule contents dispersed, but on a fasting stomach, emptying occurred after a lagtime of 35 min.

Subject 2 showed slower emptying rates than subject 1. In the upright position no gastric emptying was observed in the 60 min period of study.

A comparison of the emptying rates of both subjects in the supine position (TABLE 1) shows that for subject 1, the rate was greater in the fasting condition whereas for subject 2 the reverse was true. This is believed to be due to differences in

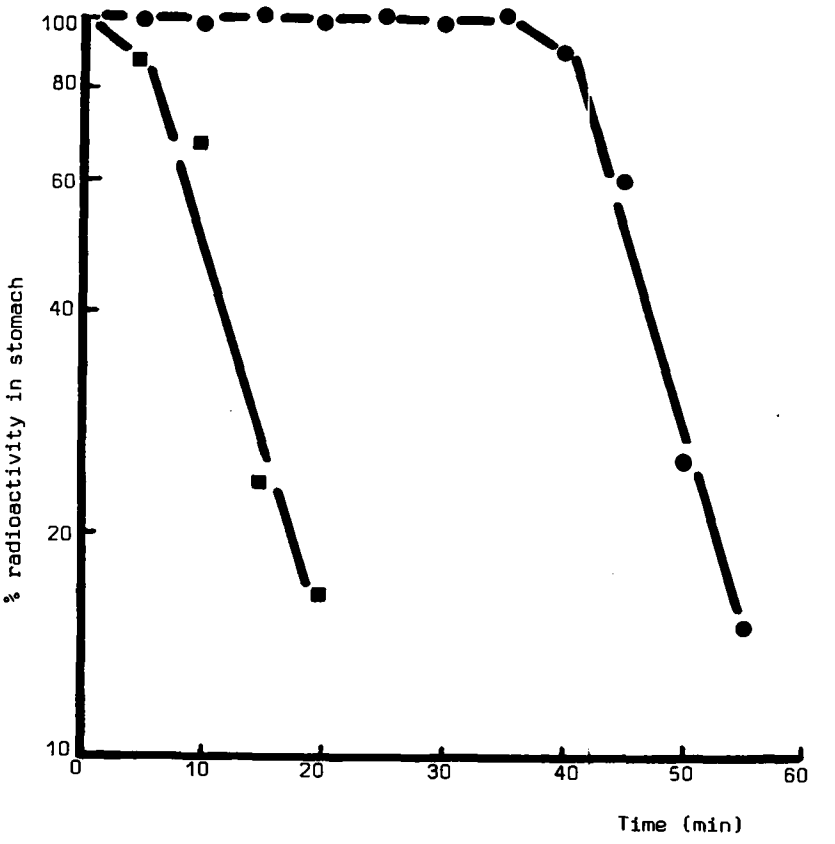

FIGURE 1.

Typical Gastric Emptying Curves, log% radioactivity in stomach vs Time (Subject 1).
● = Subject upright, fasting.
■ = Subject supine, fasting.

stomach mobility between the subjects. When the stomach is fasted the dosage preparation lodges between the rugal folds of the stomach (5) and remains stationary (3). Dispersion is then limited to the surrounding mucus. The emptying of the preparation is now dependent upon the pyloric contractions of the stomach,

Table 1. VALUES OBTAINED FOR GASTRIC EMPTYING RATE CONSTANTS AND LAG TIMES

Subject	Stomach Condition	Kg(min^{-1})		Lagtime(min)	
		Supine	Upright	Supine	Upright
1	Fasting	0.095	0.077	0	35
1	After meal	0.007	-	0	-
2	Fasting	0.001	-	0	-
2	After meal	0.20	-	15	-

Kg = first order gastric emptying rate constant

\- = no emptying during the 60 min study period

which bring about clearance of the mucus into the duodenum. If these contractions are rapid as in the case of subject 1, there is a greater chance that the dosage form will be emptied rapidly as a whole. If, as in subject 2, they are less active, then gastric emptying will be more dependent upon the dispersion of the dosage form contents. Since the liquid of the meal provides a greater dispersion medium, gastric emptying in this subject, in the supine position, was more rapid after the meal. For both subjects however, the dispersion of the dosage form within the stomach was aided by the presence of the meal.

Bead like preparations such as those employed in the current study are utilized in controlled release preparations to randomize emptying from the stomach. The results discussed above indicate that this will not be the case if the preparation is

given to a fasting subject who exhibits rapid pyloric contractions. Under such conditions, a high percentage of the pellets would be emptied together. Although gastric emptying is a variable process, even within a single subject; this rapid emptying is similar to that reported for other capsule formulations (3, 6) and is therefore likely to be a frequent occurrence. To maximise the possibility of randomized emptying, an adequate volume of liquid should be given along with the dosage form.

Placing the subject in an upright position had in all cases an inhibitory effect on gastric emptying. It is a generally held view that the presence of a meal invariably inhibits the gastric emptying of a dosage form (7). Although this would obviously depend on the type of meal, this study suggests that body position may make an important contribution to this effect.

These studies provide an insight into the behaviour of a dosage form in the human stomach. They suggest that research needs to be directed not only to improving the formulation of dosage forms, but also to methods of optimizing their behaviour in the stomach by the control of physiological conditions.

ACKNOWLEDGEMENTS

We wish to thank The Science Research Council for a CASE award to E.H., Professor B. Pullan for providing facilities and Anne-Marie McNeilly for excellent technical assistance.

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