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The gastric emptying of hard gelatin capsules

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Summary

The gastric emptying of hard gelatin capsules has been studied by labelling the powder fill of the capsules, and visualizing externally using a gamma camera. Capsules which disperse well in vitro, disperse and empty rapidly in vivo significantly faster after a meal containing a high liquid content than on a fasting stomach ($P < 0.01$). Relatively poorly dispersing capsules, and readily soluble materials behave similarly in both fasting and non-fasting conditions. The capsules which disperse poorly in vitro do not disperse in vivo and empty into the duodenum undispersed. The readily soluble capsules dissolve and empty rapidly irrespective of the condition of the stomach.

Introduction

The absorption of most drugs is far slower from the stomach than from the small intestine (Heading et al., 1973; Levine, 1970) and hence the rate at which the drug is emptied from the stomach into the duodenum may be an important factor in determining the absorption rate of the drug. The influence of food on drug absorption has often been explained in terms of its effect on gastric emptying (Melander, 1978). Clements et al. (1978) have shown that the rate of gastric emptying could be included in a pharmacokinetic analysis of paracetamol administered orally as a solution.

Solid oral dose forms of pharmaceuticals may not empty from the stomach in a manner similar to liquids or test meals. Their dispersion in the stomach (and hence mode of emptying) will depend on such factors as the formulation of the dose form and the condition of the stomach (fasting or non-fasting). The purpose of this study is to examine the gastric emptying of a typical pharmaceutical preparation, a hard gelatin capsule filled with powder.

Methods

The behaviour of the capsules in vivo and their gastric emptying was followed by radiolabelling the powder fill of the capsules with a gamma-emitting isotope and visualizing externally using a gamma camera. Three model formulations were used, two insoluble and one soluble, 100 mg of each being filled into no. 4 hard gelatin capsules. Capsule A contained Amberlite resin [CG-400(C1)] B.D.H. Chemicals, Poole, mean particle size 25 μm, labelled with approx. 25 μCi of ^{99m}Tc. This capsule dispersed readily in water, exhibiting an in vitro disintegration time of 2 min (B.P. 1973). Capsule B was similar except that the resin was milled to give a mean particle size of 9 μm. This formulation did not disperse so readily in water, having an in vitro disintegration time of 9 min. The Amberlite resin binds the label tightly in both acid and alkaline conditions and is insoluble and not absorbed. The density of the material, 1.2 g/ml, is comparable to that of many pharmaceutical materials. Capsule C was a soluble formulation consisting of approximately 50 μCi of ^{113m}indium chloride recrystallized with sodium chloride. Indium chloride is also not absorbed.

Eleven male subjects took part in the study. In a typical experiment a subject took a capsule with 100 ml of water either after a night-long fast or after a standard breakfast of 200 ml milk, 40 g cornflakes and 6 g sugar. After administration of the 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). Data were accumulated for 60 min at 1-min intervals and stored on magnetic disc. Gastric emptying was quantified 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.

The experiments were approved by the University of Manchester Committee on the Ethics of Research into Human Beings.

Results

Plots of log % radioactivity in the stomach against time were prepared to quantify gastric emptying. The plots in general did not conform to a simple monoexponential emptying as is often observed with test meals (Sheiner, 1975), but could be classified into 5 main types, as illustrated in Fig. 1. Observation of the behaviour of the capsule in the stomach by means of the oscilloscope display of the gamma camera showed a relationship between the type of emptying pattern and the capsule's behaviour. Type 1 behaviour consisted of monoexponential emptying, sometimes preceded by a lag time. This behaviour occurred when the capsule contents became well dispersed in the stomach fluids before emptying. Type 2 behaviour was characterized by a biexponential emptying, the first phase being the faster, and signified some degree of dispersion of the capsule contents. Type 2-R behaviour was also biexponential with the first phase occurring very rapidly. This pattern was observed when the capsule contents were emptied as a whole into the duodenum without dispersion. Type 3 behaviour consisted of a biexponential type of emptying

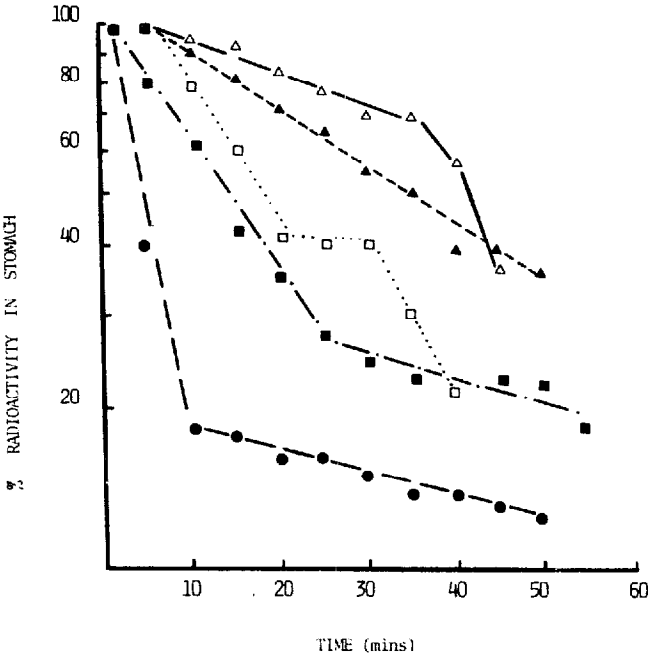

Fig. 1. The relation between log % radioactivity remaining in the stomach and time to illustrate different gastric emptying patterns.▲------▲, Type 1; ■·-·-·■, Type 2; ●— — —●, Type 2-R; △———△, Type 3; □·····□, Type 4.

with the second phase faster than the first. This was due to partial dispersion of the capsule contents giving rise to the slow first phase, followed by rapid emptying of the remainder of the contents as a whole. Type 4 emptying was a stepwise pattern and occurred when little dispersion of the capsule contents occurred. Although there was some overlap of emptying patterns, most could be classified easily into one of the aforementioned types. In some cases the capsules lodged in the oesophagus, in agreement with the findings of Evans and Roberts (1981). The results, in these cases, were not included in the analysis.

The existence of this variety of gastric-emptying patterns means the quantitation of the results cannot be undertaken by means of a simple estimate such as a half-emptying time. The gastric-emptying index of Grimes and Goddard (1977) is a more appropriate means of treating the data, and has been adopted for this study. The values of the gastric-emptying indices and the patterns of emptying are given in Table 1. There was a significantly faster emptying of Capsule A when it was administered after a meal, than on a fasting stomach ($P < 0.01$, Wilcoxon's matched-pairs signed-ranks test). No significant differences were observed between the fasting and non-fasting states for the other two capsule formulations ($P > 0.025$).

Discussion

For a drug to be absorbed, it must first be in solution. In order to maximize the rate of solution of a drug, when presented as a conventional capsule formulation,

TABLE 1

GASTRIC EMPTYING INDEX VALUES AND EMPTYING PATTERNS FOR 3 CAPSULE FORMULATIONS UNDER FASTING AND NON-FASTING CONDITIONS

Subject no.	Capsule A				Capsule B				Capsule C			
	Fasting		Non-fasting		Fasting		Non-fasting		Fasting		Non-fasting	
	Index	Pattern	Index	Pattern	Index	Pattern	Index	Pattern	Index	Pattern	Index	Pattern
1	0.022	1	0.030	1	0.055	2-R	0.007	3	0.017	2	0.001	4
2	0.017	2	0.017	4	0.026	2-R	0.005	3	0.017	1	0.025	1
3	0.008	3	0.016	1	0.028	1	0.011	1	0.015	2	0.041	1
4	E	E	0.012	2	0.025	4	0.001	N	0.008	4	0.011	1
5	0.012	1	0.022	1	0.180	2-R	0.011	3	0.086	2-R	0.014	1
6	E	E	0.021	1	0.025	1	0.095	2-R	0.014	2	0.273	2-R
7	0.018	3	0.029	1	0.058	2-R	0.061	2-R	0.032	1	0.029	1
8	0.016	3	0.124	2-R	0.002	3	0.033	2	0.055	1	0.009	2
9	0.009	2	0.008	2	0.024	4	E	E	–	–	–	–
10	0.017	4	0.052	1	0.016	3	0.012	1	–	–	–	–
11	–	–	–	–	0.019	4	0.066	3	–	–	–	–

– = no tests performed; E = capsule lodged in oesophagus; N = no distinguishable emptying pattern after 60 min.

adequate dispersion of the contents is required. This allows free access of the solvent to the drug, preventing problems of liquid penetration and wetting of the drug particles. The formulation of the powder fill of hard gelatin capsules is, in part, directed to this end. In terms of the capsules used in this study, Capsule A would represent an ideal formulation exhibiting rapid dispersion and Capsule B would be an adequate formulation, which disperses at a much slower rate. These two model formulations are insoluble, but as many drugs are only slowly soluble in gastric fluids, they are not atypical. Capsule C represents a formulation which disperses and dissolves rapidly. As most drugs are absorbed more quickly from the small intestine than the stomach, the achievement of a rapid onset of action would seem to require an adequate dispersion of the contents and rapid gastric emptying.

The lack of intermittent motion of the capsules during the studies suggests that on entering the stomach, the capsule adheres to the stomach wall. The gelatin shell will dissolve exposing the powder contents to the stomach environment. The dispersion and emptying of the capsule fill will then be dependent on the formulation and physiological condition of the stomach. Despite the good in vitro dispersion characteristics of Capsule A, dispersion in the fasting state is limited, and the capsule empties slowly from the stomach, undispersed. When taken after a meal, dispersion of the capsule contents occurs, and the emptying is significantly faster. This phenomenon may be explained on the basis of the 100 ml of water swallowed with the capsule emptying relatively rapidly (Wagner, 1971). The capsule contents can then only disperse into the mucus lining of the stomach, which will be a slow process as will be the subsequent emptying. After the meal, which as a relatively high liquid content, dispersion can take place, and emptying is faster.

A similar situation would apply for Capsule B except that the material is intrinsically less dispersible, and hence no significant difference is noticed between the fasting and non-fasting conditions, and emptying takes place for both conditions with the capsule undispersed. The rapid solubility of Capsule C gives rise to similar emptying behaviour in both the fasting and non-fasting conditions but with a predominance of the monoexponential type of emptying when the capsule was taken after the meal, indicating better dispersion in solution.

Most capsule preparations will be formulated in a manner to produce rapid in vitro dispersion as exhibited by Capsule A. To maximize the possibilities of these preparations dispersing in the stomach and emptying in a dispersed form into the intestine, they should be taken with adequate volumes of fluid.

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