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The effect of tablet size on the gastric emptying of non-disintegrating tablets

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Summary

The gastrointestinal transit of non-disintegrating tablets of different sizes (7–13 mm diameter) was investigated in fed subjects using the technique of gamma scintigraphy. The 13 mm tablets took longer to empty from the stomach, with less variation between the individual data, than the smaller tablets.

The need to control the gastrointestinal transit of oral dosage forms has recently become apparent (Davis, 1985). This could be achieved by delaying the gastric emptying of dosage forms, using methods such as particle density (Bechgaard and Ladefoged, 1978), and particle size (Meyer et al., 1985). Studies in dogs, have suggested that particle size controls the gastric emptying of solids during the digestive state (Kelly, 1981). Solids can empty from the stomach only if they are about 2 mm in diameter, whilst larger digestible particles are reduced to this size by the digestive contractions of the stomach. Larger indigestible solids are retained in the stomach, and emptied by the contractions of the migrating myoelectric complex (MMC) of the fasted stomach. Meyer et al. (1985) suggest there is a gradation in the size effect rather than a precise 'cut-off' value. In their study, indigestible spheres of 5 mm had a slower rate of gastric emptying than 1 mm spheres.

Recently, studies have been conducted in man, to address specifically the relationship between gastric emptying and particle size (Khosla et al., 1989). Neither gastric emptying nor small intestine transit was affected by the size of tablets (in the range 3–7 mm diameter), which indicates that the 2 mm cut-off size is not applicable to man, and that non-disintegrating tablets, up to an undetermined critical size, can empty from the fed stomach.

The current study had the objective of determining the size of tablet which does not empty from the fed stomach.

Non-disintegrating tablets (7, 11 and 13 mm diameters) were prepared from ethylcellulose (BDH) and Amberlite IR120 cationic resin (BDH) labelled with indium-111. The tablets were coated to prevent leaching of the radiolabel, and disintegration of the tablets. A more detailed descrip-

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tion of the preparation of similar tablets can be found elsewhere (Khosla, 1987).

The studies were approved by the Ethical Committee of the University of Nottingham, and conducted in accordance with the declaration of Helsinki Guidelines for Ethics in Research. Approval to administer radiopharmaceuticals was obtained from the DHSS.

Five, healthy male volunteers (age, height and weight ranges 19–25 years, 1.74–1.85 m and 61–86 kg, respectively) participated with informed consent. Each subject abstained from alcohol for 24 h, and had fasted for 10 h prior to each study day. The subjects did not smoke and were not on any medication. On the morning of each study day each subject consumed a light breakfast (1500 kJ). Immediately after breakfast, the subjects took either two 7 mm, 11 mm or 13 mm tablets together with 200 ml technetium-99m DTPA labelled water. The labelled water enabled ready identification of the stomach and colon regions. Anterior and posterior images were taken at regular intervals, using a gamma-camera (General Electric Maxicamera, Type II) having a 40 cm field of view and fitted with a medium-energy (200 keV) parallel hole collimator. A standard light lunch was taken after about 4 h, and the study was terminated about 9 h after dosing. The recorded images were analysed by noting the time of the image in which one or both tablets had emptied from the stomach.

The study was repeated using the same protocol on two further occasions, such that each subject received each size of tablet.

The mean gastric emptying data (Table 1) of 116, 128, and 171 min for the 7, 11 and 13 mm tablets, respectively, are similar to those found previously for man: 130 min for 3 mm minimatrices after a medium breakfast (Feely et al., 1985); 125 min for 7 mm tablets after a medium breakfast (Khosla et al., 1989); and 170 min for pellets after a heavy breakfast (Davis et al., 1987). In all subjects, the 13 mm tablets emptied as a bolus, whereas this was not always the case for the smaller sized tablets.

Individual gastric emptying times of less than 1 h for the 7 mm tablets add further evidence to the observation that indigestible solids of this size can empty from the fed stomach of man (Khosla et al., 1989). Moreover, the gastric emptying data for the 11 mm tablets suggest that even indigestible solids of this diameter can empty from the fed human stomach. This is in marked contrast to the often accepted but erroneous critical value of 2 mm obtained from work in dogs (Kelly, 1981). The data for the 13 mm tablets, suggest that indigestible particles of this diameter are less likely to empty from the fed stomach. In the present study it was difficult to determine when the fed state ended, and the activity of the MMC began. It is likely however, that the fed state for a meal of 1500 kJ will last for at least 1 h.

TABLE 1

Gastric emptying time (min) of tablets

Subject	Tablet size		
	7 mm	11 mm	13 mm
1	150	120	150
2	(i) 30, (ii) 60	150	105
3	180	150	210
4	120	180	180
5	(i) 15, (ii) 150	(i) 15, (ii) 60	210
Mean	116	128	171
S.E.	19	17	13
n [a]	10	10	10

[a] Number of single units.

In the present study, bolus emptying, and gastric emptying times in excess of 2 h (which occurred for all three tablet sizes) indicate that emptying occurred sometime during the actions of the MMC. Bolus emptying from the stomach of large indigestible solids has been attributed to the phase 2 and particularly phase 3 activity of the MMC (Code and Martlett, 1975). It can be envisaged that large tablets (i.e. > 13 mm) will be retained and emptied only during the powerful phase 3 contractions, whilst smaller tablets could be emptied earlier by phase 2 contractions. The data in the present study also show that the 13 mm sized tablets were retained for a longer period of time and had a smaller variability in gastric emptying time than did the 7 mm and 11 mm tablets.

It has been proposed (Khosla et al., 1989) that the gastric emptying of non-disintegrating tablets, during the fed state, is a random event determined

by the diameter of the human pylorus and facilitated by the pressure gradient between the antrum and duodenum. Tablets may become trapped in the terminal antrum, and at the start of the next contraction pass through the partially occluded pylorus. Small indigestible particles empty by virtue of their small size, and exhibit a uniform pattern of emptying. Slightly larger particles would be subject to so called fortuitous emptying, which would become more irregular as the particle size approached the critical value. However, over a given period of time, multiparticulate systems composed of such larger sized units would apparently exhibit a regular pattern of emptying.

Tablets larger than the critical value will be retained in the stomach and will be emptied by the more powerful contractions of the MMC (Smith and Feldman, 1986). We suggest here that the critical value will probably be similar in diameter to the aperture of the resting pylorus, 12.8 + 7 mm (Munk et al., 1978). This is the state of the pylorus just before each digestive contraction takes place. In conclusion, non-disintegrating tablets of up to 11 mm in diameter can empty from the fed stomach, whereas tablets with a diameter greater than 11 mm are more likely to empty only during the contractions of the MMC.

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