*International Journal of Pharmaceutics*, 53 (1989) 107–117
Elsevier



IJP 01792

# Gastrointestinal transit of non-disintegrating tablets in fed subjects

R. Khosla *, L.C. Feely ** and S.S. Davis

*Department of Pharmaceutical Sciences, University of Nottingham, Nottingham (U.K.)*

(Received 10 October 1988)
(Modified version received 6 January 1989)
(Accepted 12 January 1989)

*Key words*: Gastric emptying; Tablet size; γ-Scintigraphy; Gastrointestinal transit

## Summary

The gastrointestinal transit of non-disintegrating tablets of different sizes (3–7 mm diameter) was monitored in fed subjects. Transit of the tablets was followed using the technique of γ-scintigraphy. Neither the gastric emptying nor small intestine transit of the tablets was affected by their size. However, the nature of the meal consumed had a marked effect on gastric emptying. The nature of the meal also appeared to influence the transit through the ileocaecal sphincter.

## Introduction

Oral drug administration has been historically the predominant route for drug delivery. However, it is only recently that the need to control the gastrointestinal (GI) transit of oral dosage forms, especially controlled release systems, has become apparent (Davis, 1985). Furthermore, it has been suggested that control over gastric emptying (GE) is the preferred option (Khosla and Davis, 1986). A number of strategies have been proposed for this purpose. These have included particle density (Bechgaard and Ladefoged, 1978), floating tablets (Sheth and Tossounian, 1984) and bioadhesives (Park and Robinson, 1984). However, only limited success has been achieved using these approaches. One further proposal is the use of particle size (Meyer et al., 1985).

Several studies in dogs, have suggested that the size of the administered particles can be a major determinant of the GE of solids during the digestive state (Hinder and Kelly, 1977). Digestible solids can empty from the stomach of the dog only after they have been reduced to a size of about 2 mm (Kelly, 1981). Small indigestible particles will be able to empty in a similar fashion. Larger indigestible solids are retained in the fed stomach and are only emptied by contractions associated with the migrating myoelectric complex (MMC) of the fasted stomach. More recent studies conducted in dogs have attempted to specifically address the relationship between the particle size of indigestible solids and GE. Meyer et al. (1985) reported a progressively faster rate of emp-

* *Present address:* Paines & Byrne, Bilton Road, Greenford, Middlesex UB6 7HG, U.K.
** *Present address:* Reckitt & Colman, Dansom Lane, Kingston-Upon-Hull HU8 7DS, U.K.
*Correspondence:* S.S. Davis, Department of Pharmaceutical Sciences, University of Nottingham, Nottingham NG7 2RD, U.K.

tying as sphere diameter was reduced from 5 mm to 1 mm. Spheres of 0.015 mm, however, had a rate of emptying similar to 1 mm spheres.

Published studies on the gastrointestinal transit of dosage forms in man provide little evidence to support or refute the findings of the canine studies. For example, Park et al. (1984) found no effect of either size or shape on the rate of GE of enteric coated tablets, albeit in fasted subjects. Feely et al. (1985) observed that small tablets (3 mm diameter) emptied gradually from the fed stomach of healthy volunteers but as a bolus in fasted subjects. Jian et al. (1983) reported that pellets (4 mm in diameter) when taken with food, had a linear pattern of emptying. This was similar to the behaviour of digestible solids, but the rate of emptying was slower for the pellets than for the co-administered food (Jian et al., 1983). The results of these various studies suggest the much discussed 2 mm cut-off size for the GE of indigestible solids during the digestive phase is not applicable to man. Indeed, it is probable that there will be no exact cut-off size per se, but a gradation of size over which predictable emptying from the fed stomach becomes uncertain and highly variable.

The transit of dosage forms from the terminal ileum to the caecum through the ileocaecal sphincter (ICS) is much less well understood than for the corresponding situation of GE. The actual role of the ICS in regulating entry of material into the colon is relatively unknown. Quigley and Phillips (1983) have conducted several studies which have indicated that the ICS controls the passage of chyme into the colon. Feely et al. (1985) have suggested that sub-units of a multiple unit system (which have spread in the small intestine, due to their variable GE), can re-group at the ICS before entering the colon. Here also objective information relating particle size and transit across the ICS, would prove most beneficial in the design of dosage forms for site specific delivery to the different regions of the colon.

The present study had the objective of following the gastrointestinal transit of non-disintegrating tablets in fed subjects and to ascertain the relationship between tablet size and gastric emptying and transit across the ICS.

## Materials and Methods

*Study design*

The study was conducted as two separate but related parts. The first part investigated the gastrointestinal transit of 3, 4 and 5 mm tablets, administered in groups of 10 taken after either a light or heavy breakfast. The second study examined the transit of 5, 6 and 7 mm tablets, taken in groups of 10 after a medium-sized breakfast. The second study was conducted according to a cross-over design. A cross-over design was not possible in the first study because of restrictions in giving radiolabelled formulations to human volunteers on consecutive occasions.

*Preparation on formulations*

Non-disintegrating tablets were prepared from ethylcellulose (BDH) and Amberlite IRA410 resin (BDH). The resin was first milled, and then labelled with technetium-99m using pertechnetate from a generator. Labelled resins were passed through a 0.09 mm screen and blended with ethylcellulose powder. The powder mix was directly compressed into tablets using a Manesty F3 single-punch tablet machine. Details of the tablets are described in Table 1.

The tablets were coated to prevent leaching of the radiolabel and to stop the tablets from disintegrating. The tablets were tested in vitro for the integrity of the radiolabel under appropriate conditions of temperature and pH. A more detailed description of the preparation can be found elsewhere (Khosla, 1987).

TABLE 1

*Formulation details*

| Diameter (mm) | Shape of punch | Mean uncoated tablet weight (mg) |
|---|---|---|
| 3.1 | Normal curvature | 20 |
| 4.0 | Flat-faced | 35 |
| 5.0 | Flat-faced | 55 |
| 6.2 | Flat-faced | 75 |
| 7.1 | Concave | 81 |

*In vivo studies*

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.

*(i) Study 1.* Six, healthy male volunteers, age range 19–25 years, height range 1.69–1.87 m, weight range 65–76 kg, 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, 3 subjects consumed a light breakfast (1500 kJ):

1 bowl cereal with milk
1 slice toast, butter, marmalade
1 glass orange juice

and the other 3 subjects took a heavy breakfast (3500 kJ):

1 egg
1 rasher bacon
1 sausage
tomatoes
1 slice toast, butter, marmalade
1 glass orange juice

Immediately after breakfast, the subjects took either ten 3 mm, 4 mm or 5 mm tablets together with 200 ml water. Each dose of 10 tablets had an activity of about 3 MBq. Anterior and posterior images, each of 60 s duration, were taken at regular intervals, using a γ-camera (General Electric Maxicamera, Type II) having a 40 cm field of view and fitted with a low energy (160 keV) parallel hole collimator. The subjects stood in front of the camera for imaging and were asked to keep body movements to a minimum. During the study, the subjects remained in an upright position either sitting or standing. The images were recorded, and stored on computer (Nodecrest). Anatomical reference markers containing technetium-99m, were taped to the skin, anteriorly and posteriorly, over the liver to the right of the stomach. At about 2.5 h after dosing the subjects were given a drink of orange juice. A standard light lunch consisting of one cheese roll, one ham roll and 150 ml orange juice, was taken after about 4 h. An evening meal of steak, chips, peas, and cheesecake was taken about 9.5 h after dosing.

The recorded images were analysed by drawing regions of interest around the position of the stomach and colon. The activity in these regions was quantified, and then corrected for background activity and radioactive decay. The error due to the variation in depth of radionuclide in the stomach and colon, was minimized by calculating the geometric mean of corresponding anterior and posterior views (Tothill et al., 1978).

The study was repeated using the same protocol on two further occasions, such that each subject received each size of tablets, after eating the same breakfast they had consumed on the first day.

*(ii) Study 2.* A further 6, healthy male volunteers, age range 19–25 years, height range 1.72–1.90 m, weight range 59–83 kg, participated with informed consent. The study used the same protocol as Study 1, except a medium-sized breakfast (2300 kJ) was consumed by all 6 subjects:

1 bowl cereal
2 slices toast, butter, marmalade
1 glass orange juice

Immediately after breakfast, the subjects took either ten 5 mm, 6 mm or 7 mm tablets together with 200 ml water. Each dose of 10 tablets had an activity of about 3 MBq. The study was repeated using the same protocol on two further occasions, such that each subject received each size of tablets.

## Results and Discussion

The data for the investigation are expressed in a number of different ways. The time for 50% of the tablets to empty from the stomach ($St_{50\%}$) (and observed lag time), and to enter the colon ($Ct_{50\%}$), as well as the small intestine transit (SIT) are presented in Tables 2 and 3. Gastric emptying profiles and colon entry curves for grouped subjects are shown in Figs. 1–3. Representative scintiphotos, which illustrate the various phases of transit are presented in Fig. 4. The observed spreading of tablets from the stomach, followed by subsequent regrouping at the ICS was a typical

TABLE 2

*Gastrointestinal transit data for Study 1 light and heavy breakfasts*

| Subject | 3 mm | | | | 4 mm | | | | 5 mm | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Gastric emptying | | Small intestine transit SIT (min) | Colon entry $Ct_{50\%}$ (min) | Gastric emptying | | Small intestine transit SIT (min) | Colon entry $Ct_{50\%}$ (min) | Gastric emptying | | Small intestine transit SIT (min) | Colon entry $Ct_{50\%}$ (min) |
| | Lag (min) | $St_{50\%}$ | | | Lag (min) | $St_{50\%}$ | | | Lag (min) | $St_{50\%}$ | | |
| *Light* | | | | | | | | | | | | |
| 1 | 15 | 85 | 175 | 260 | 5 | 95 | 178 | 273 | 15 | 70 | 252 | 267 |
| 2 | 90 | 113 | 164 | 277 | 5 | 35 | 118 | 153 | 30 | 73 | 167 | 240 |
| 3 | 60 | 143 | 77 | 220 | 30 | 67 | 188 | 255 | 20 | 83 | 242 | 325 |
| Mean | 52 | 114 | 139 | 252 | 13 | 66 | 161 | 277 | 22 | 75 | 220 | 277 |
| S.E.M. | 20 | 14 | 25 | 14 | 7 | 14 | 18 | 31 | 4 | 3 | 22 | 20 |
| *Heavy* | | | | | | | | | | | | |
| 4 | 45 | 250 | 205 | 455 | 5 | 23 | 300 | 323 | 45 | 235 | 158 | 393 |
| 5 | 105 | 207 | 183 | 390 | 35 | 275 | 100 | 375 | 105 | 243 | 102 | 345 |
| 6 | 90 | 123 | 197 | 320 | 75 | 167 | 110 | 277 | 15 | 157 | 136 | 293 |
| Mean | 80 | 193 | 195 | 388 | 38 | 155 | 170 | 325 | 55 | 212 | 132 | 344 |
| S.E.M. | 15 | 30 | 5 | 32 | 17 | 60 | 53 | 23 | 22 | 22 | 13 | 24 |

phenomenon. In a number of cases, the individual tablets could all be distinguished and were spread in the different regions of the colon. A representative histogram plot also demonstrates these spreading/grouping effects (Fig. 5).

*Study 1*

In the light breakfast group, the tablets emptied quite rapidly from the stomach, with no appreciable lag phase (Fig. 1). The linear pattern of emptying exhibited by all 3 tablet sizes, is typical for digestible solids (Tothill et al., 1978) and indicates the tablets had become dispersed with, and emptied together with the food (O'Reilly et al., 1987). A lag phase was more evident with the heavy breakfast, although the 4 mm tablets showed a rapid initial emptying (Fig. 2), and possibly a biphasic pattern. The difference in emptying pat-

TABLE 3

*Gastrointestinal transit data for Study 2 – medium breakfast*

| Subject | 5 mm | | | | 6 mm | | | | 7 mm | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Gastric emptying | | Small intestine transit SIT (min) | Colon entry $Ct_{50\%}$ (min) | Gastric emptying | | Small intestine transit SIT (min) | Colon entry $Ct_{50\%}$ (min) | Gastric emptying | | Small intestine transit SIT (min) | Colon entry $Ct_{50\%}$ (min) |
| | Lag (min) | $St_{50\%}$ | | | Lag (min) | $St_{50\%}$ | | | Lag (min) | $St_{50\%}$ | | |
| Subject | | | | | | | | | | | | |
| 1 | 10 | 90 | 190 | 280 | 65 | 105 | 153 | 258 | 20 | 53 | 247 | 300 |
| 2 | 35 | 143 | 292 | 435 | 125 | 225 | 292 | 517 | 95 | 213 | 272 | 485 |
| 3 | 35 | 147 | 300 | 335 | 10 | 88 | 155 | 243 | 10 | 123 | 104 | 227 |
| 4 | 10 | 157 | 113 | 270 | 20 | 237 | 206 | 443 | 10 | 33 | 77 | 110 |
| 5 | 20 | 225 | 60 | 285 | 50 | 140 | 115 | 255 | 125 | 265 | 128 | 393 |
| 6 | 125 | 165 | 145 | 310 | 155 | 178 | 135 | 313 | 35 | 60 | 200 | 260 |
| Mean | 39 | 155 | 183 | 319 | 71 | 162 | 176 | 338 | 49 | 125 | 171 | 296 |
| S.E.M. | 16 | 16 | 36 | 23 | 22 | 23 | 24 | 43 | 18 | 35 | 30 | 49 |

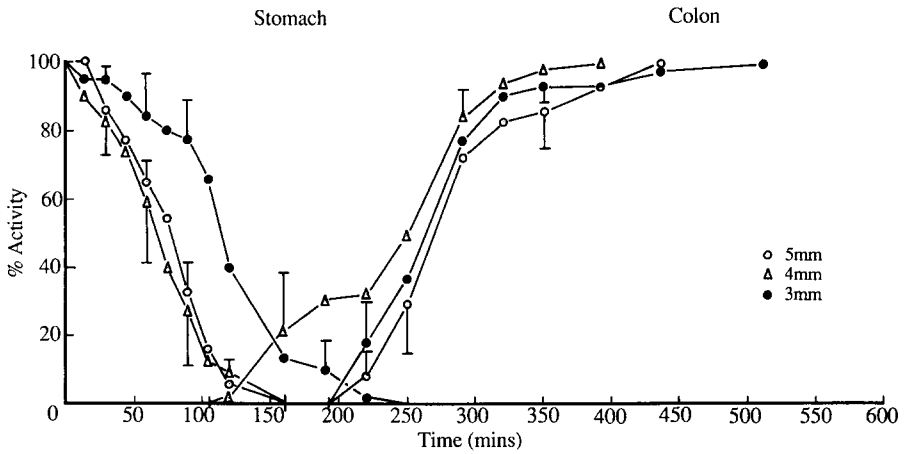


Fig. 1. Mean gastric emptying and colonic entry of tablets — light breakfast ($n = 6$).

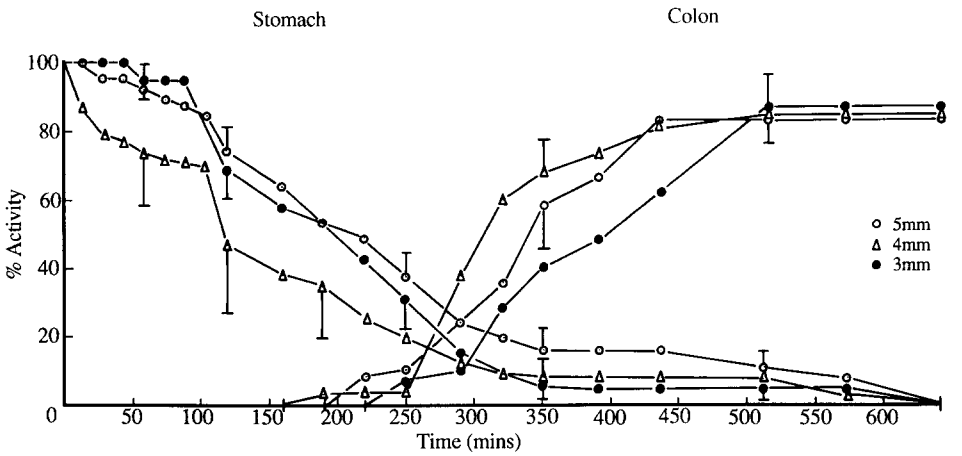


Fig. 2. Mean gastric emptying and colonic entry of tablets – heavy breakfast ($n = 6$).

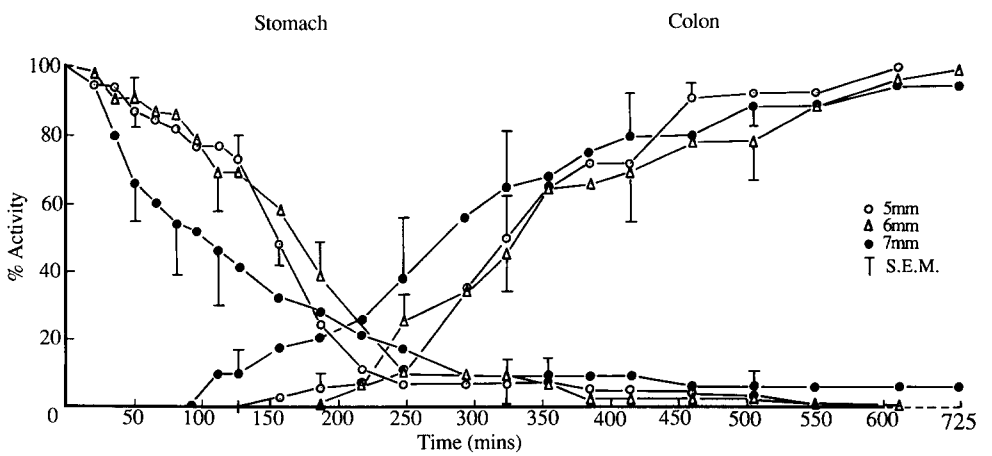


Fig. 3. Mean gastric emptying and colonic entry of tablets – medium breakfast.

terns between the light and heavy breakfast, suggests that the nature of the meal is the major determinant ($P < 0.005$) in the gastric emptying of small tablets and that gastric emptying is not significantly influenced by tablet size ($P > 0.1$).

The $St_{50\%}$ values for the tablets are similar to

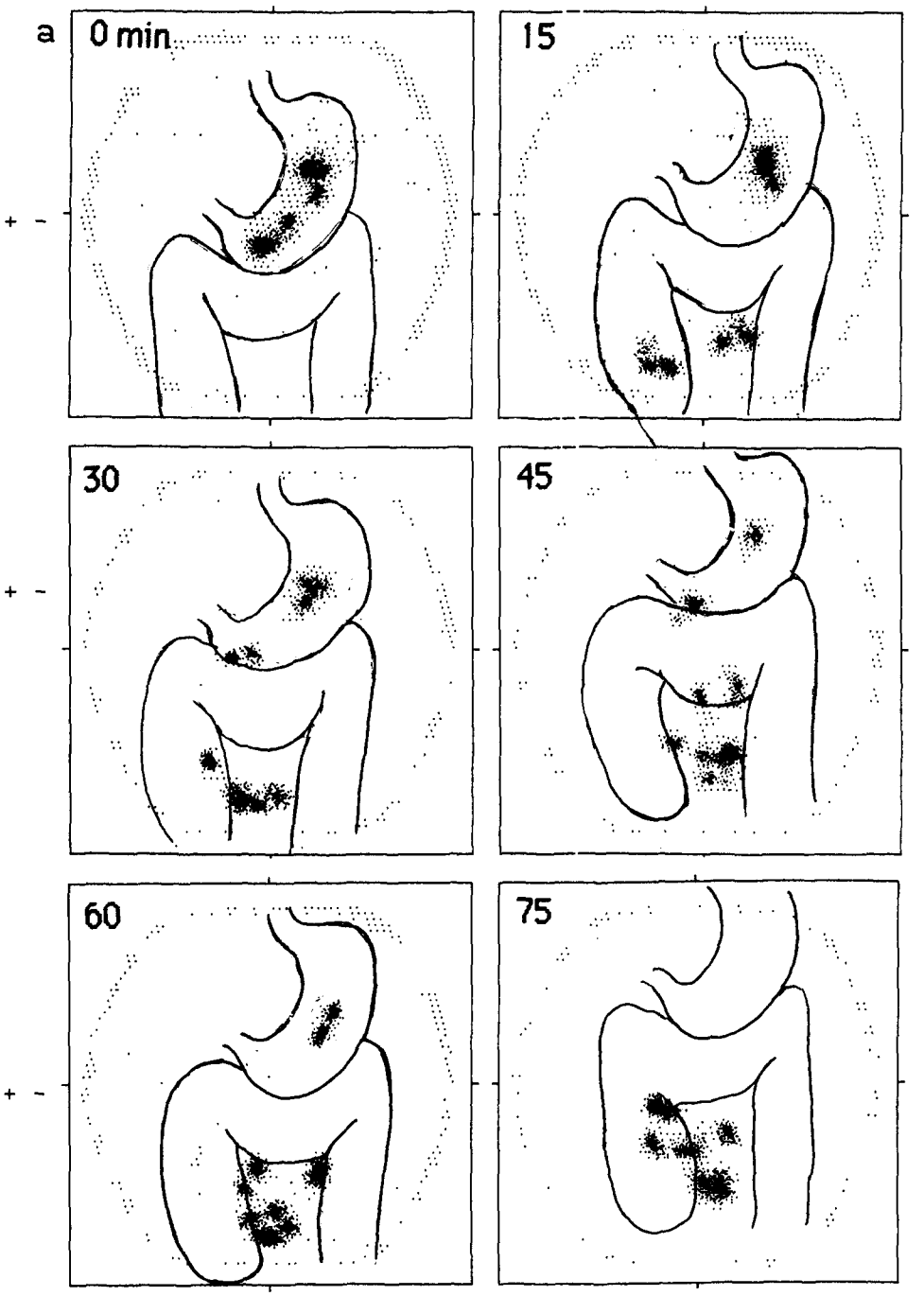


Fig. 4. Gastrointestinal transit of 4 mm tablets; Subject 3, light breakfast.

those reported previously for man using labelled pellets (0.5–1.0 mm): 77 min after a light breakfast and 170 min after a heavy breakfast (Davis et al., 1987). Similarly, minimatrices (3 mm in diameter) had a mean $St_{50\%}$ of 130 min after a medium-sized breakfast (Feely et al., 1985). The

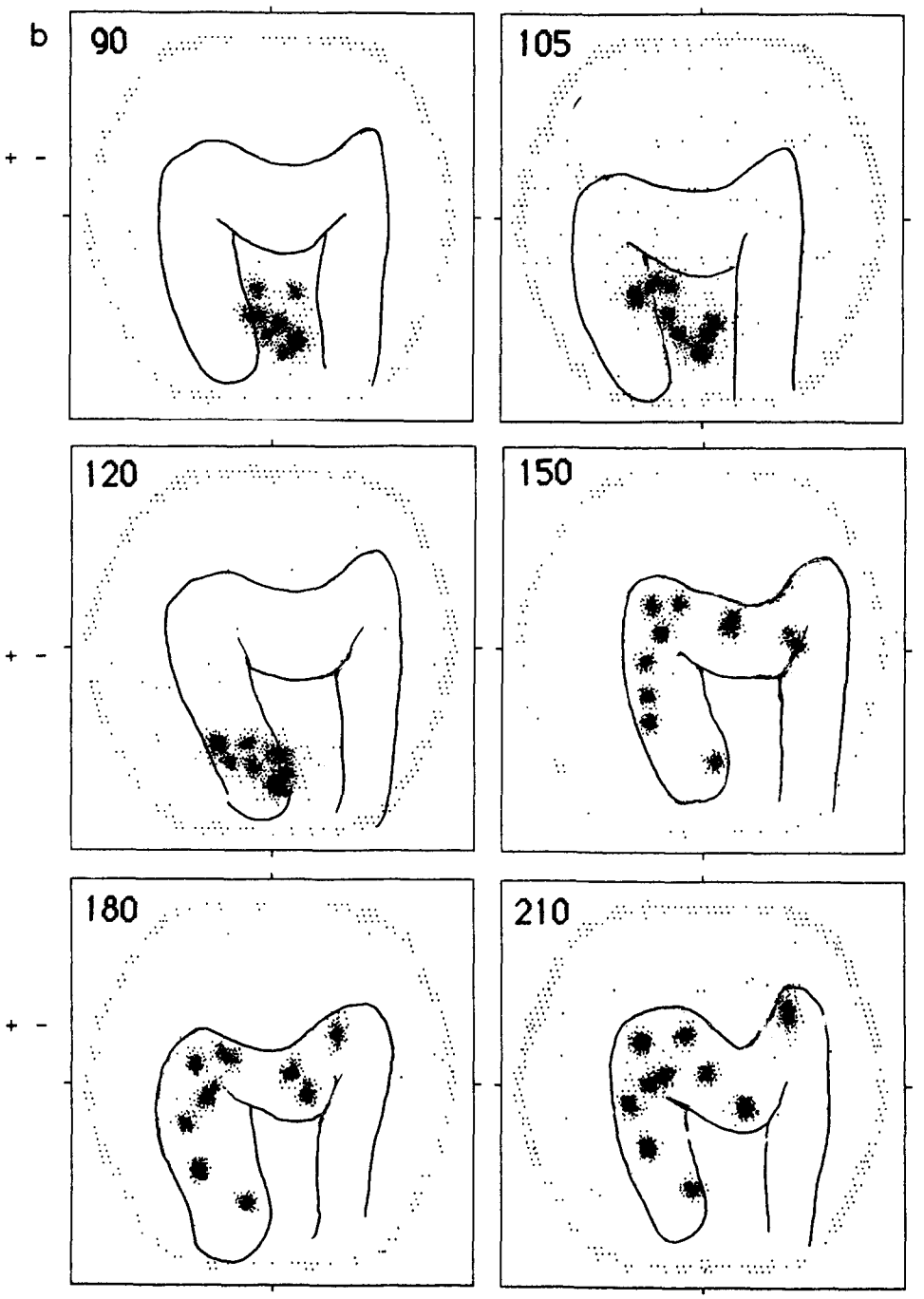


Fig. 4 (continued).

present results are in contrast to similar studies conducted in fed dogs (Meyer et al., 1985; Itoh et al., 1986) where particles greater than 5 mm in size were mainly retained in the stomach for 6 h or longer. Digestible liver particles of the same size had $St_{50\%}$ values of about 2 h. Prolonged periods of gastric residence (> 7 h) have also been seen for 4.1 mm diameter tablets given to rabbits (Takahashi et al., 1985). Thus we can conclude that data obtained in the fed dog or rabbit should be extrapolated to man with great care. The generally accepted cut-off size of 2 mm (obtained with dogs) is (not surprisingly) of little or no relevance to man.

The transit time of the tablets through the small intestine (SIT) was unaffected by either meal or tablet size. Indeed, the observed SIT values are in good agreement with the commonly observed value of 3 h (±1 h S.D.) for oral dosage forms (Davis et al., 1984, 1986a).

The data for the entry of the tablets into the colon are similar to those previously reported for pellets; mean $Ct_{50\%}$ values of 253 min after a light breakfast and 420 min after a heavy breakfast (Davis et al., 1987). This significant difference ($P < 0.001$) between the light and heavy breakfast groups, irrespective of tablet size, simply reflects the difference in the gastric emptying for the two groups. Colon entry did not reach 100% with all 3 tablet sizes in the heavy breakfast group during the study period of 11 h.

*Study 2*

The pattern of gastric emptying was generally similar for all 3 tablet sizes ($P > 0.1$) (Fig. 3). The gastric emptying curves are similar in shape to those of Study 1 and confirm that indigestible solids, up to at least 7 mm diameter can empty from the fed stomach together with food. The mean $St_{50\%}$ values, as well as the mean SIT and $Ct_{50\%}$ values, are in good agreement with the literature values quoted above. Once again, the present values do not support the generally accepted data from animals. However, it should be noted that on occasions, tablets remained in the stomach 10 h after ingestion (e.g. subject 5, 7 mm diameter tablets).

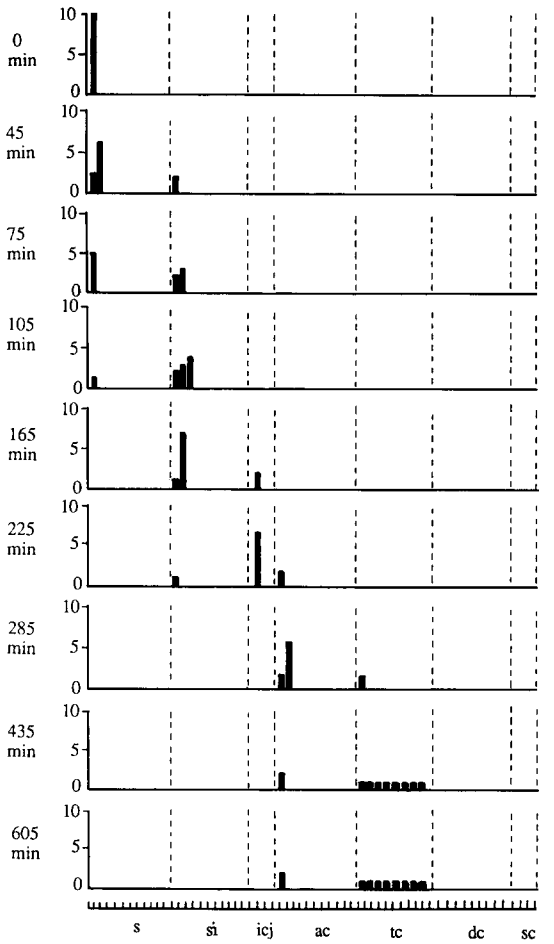


Fig. 5. Histogram plots showing the distribution of tablets in different regions of the gastrointestinal tract after a light breakfast. Legend: s = stomach; si = small intestine; icj = ileocaecal sphincter; ac = ascending colon; tc = transverse colon; dc = descending colon; sc = sigmoid colon.

The general pattern of transit and spreading was similar to that in Study 1. Tablets spread in the small intestine, as a consequence of their gastric emptying, but regrouped at the ICS, before entering the colon and spreading again.

*Gastric emptying and the effect of tablet size and food*

The data obtained for both studies suggest that indigestible solids, up to 7 mm in diameter, can empty from the fed stomach of man. This is in contrast to current literature, where a critical size

of about 2 mm is proposed (Kelly, 1981) from work largely conducted in dogs. A simple difference in relative physiology may account for the discrepancy between human and canine data; for example, the mean resting pyloric diameter in man is 12.8 ± 7 mm (Munk et al., 1978).

Gastric emptying does not depend solely on pyloric diameter but also on the pressure gradient between the antrum and duodenum. Dozois et al. (1971) noticed that plastic spheres subject to contractions in canine stomach were normally swept into, and then retropelled from the terminal antrum. Occasionally, a sphere became "trapped" in the terminal antrum, and on the next contraction, the trapped sphere could pass through the partially occluded pylorus into the duodenum. This process will be random but facilitated by the pressure gradient between the antrum and duodenum generated by the approaching contraction. Blythe et al. (1959) made a similar observation when studying radio-opaque enteric coated tablets.

Thus, 10 tablets given to one subject will essentially empty in a random fashion from the stomach, but over a given period the emptying appears to be regular. Thus it can be envisaged that both the diameter of the human pylorus and fortuitous emptying are responsible for the present results.

The variability in the recorded data (expressed as S.E.M.) increases with the size of the tablet (for example, the S.E.M. values for $St_{50\%}$ are 16, 23 and 35 for 5, 6 and 7 mm tablets, respectively). This is as expected since the pattern of emptying should become more unpredictable as the size of the administered dosage form approaches a critical value. Thus, gastric emptying becomes less predictable as tablet diameter increases and eventually large tablets (i.e. greater than 10 nm) will be retained because of their size (Jonsson et al., 1983; Smith and Feldman, 1986).

The original rationale for conducting the present studies was to determine the size of tablet that would *not* empty from the fed stomach, and then to design novel multiparticulate controlled release dosage forms. Unfortunately, there will now be obvious practical problems with this approach.

The far more important effect of food on the gastric emptying of small tablets is well illustrated by the data obtained in both studies. The greater the energy content of the meal, the longer the duration of emptying. Taking the available mean data for 5 mm tablets under a given condition of feeding, it is possible to summarize the observations (Fig. 6). Other workers have reached similar conclusions concerning the importance of food intake on gastric emptying (Smith and Feldman, 1986; Davis et al., 1986b and c; Mojaverian et al., 1985; Sangekar et al., 1987).

The entry of the various tablets into the colon was determined by the time for gastric emptying, and not by the time for transit in the small intestine. This result reinforces the observation that transit through the small intestine is relatively

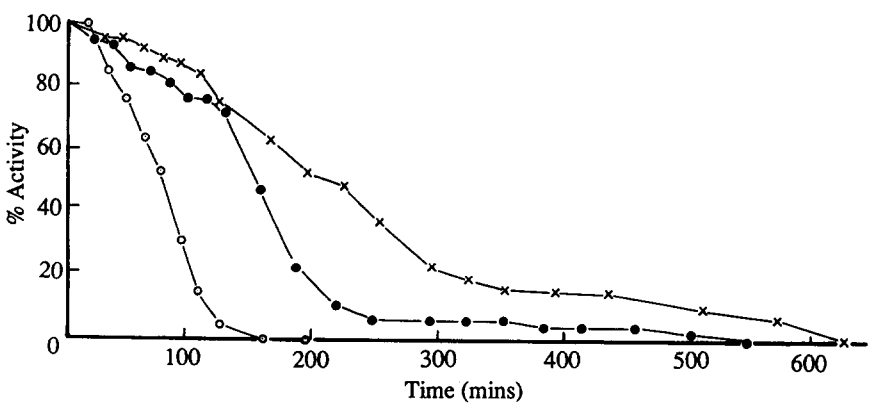


Fig. 6. The effect of meal size on the gastric emptying of tablets of 5 mm size. ○, light breakfast ($n = 3$); ×, heavy breakfast ($n = 3$); ●, medium breakfast ($n = 6$).

constant and is unaffected by the energy content of administered food (Davis, 1986) and the physical nature of the dosage form (Davis et al., 1986a).

*Transit through the ileocaecal sphincter*

The tablets that had spread in the small intestine were observed to re-group at the ICS, before entering the caecum. This (stagnation) effect is no doubt related to the suggested reservoir function of the terminal ileum (Spiller et al., 1987) and has been observed previously by us for both multiple (Feely et al., 1985) and single unit (Davis, 1986) controlled release systems. No obvious relation could be found between tablet size and transit through the ICS nor with subsequent feeding. Spiller et al. (1986) have concluded that the gastroileal reflex is of minor importance to ileocaecal transit.

In some cases, entry into the caecum was as a bolus, but no obvious pattern emerged that related tablet size to bolus entry. Kruis et al. (1987) suggest that 30–50% of ileocolonic transit occurred as a bolus with the remainder occurring as a steady trickle. Bowel movement was considered a likely factor of importance, and consequently this was monitored carefully in Study 2. The times at which the subjects defaecated during the study were recorded. However, there was no observable connection with entry of tablets into the colon.

Spiller and others have suggested that the shape of colon entry curves and $Ct_{50\%}$ values are useful parameters when measuring ICS transit (Spiller et al., 1987). A comparison of the $Ct_{50\%}$ values for the various tablets of different sizes, for each type of breakfast, shows no significant difference between the values ($P > 0.1$). It is interesting to note that a detailed examination of the grouped colon entry curves indicates that administration of a light breakfast yields steeper entry curves than those for the medium and heavy breakfasts. A similar examination of the curves for the individual subjects also shows this rapid entry after the light breakfast. These steep curves reflect the bolus entry of material into the colon, after remaining immobile in the terminal ileum (Spiller et al., 1987). The longer plateau, seen with the medium and heavy breakfast curves, is indicative of episodic colonic inflow. This difference in the rates of entry, may relate to the solid content of the meal, since high residue meals are known to have a slower rate of colonic filling than low residue meals (Spiller et al., 1987). Further studies are required, that take greater consideration of bowel habits and diet, before a complete understanding of the ileocaecal transit or pharmaceutical dosage forms can emerge.

## Conclusion

Tablets up to 7 mm in diameter, can empty from the fed stomach in an apparently linear fashion. There is an increase in variability of emptying as tablet size increases in the range 5–7 mm diameter but no significant difference in gastric emptying due to the size of the tablets can be found. In contrast, the nature of the meal consumed has a very significant effect on gastric emptying and may even influence ileocaecal transit.

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