International Journal of Pharmaceutics, 52 (1989) 1–10
Elsevier

IJP 01741

Gastric emptying and small and large bowel transit of non-disintegrating tablets in fasted subjects

R. Khosla * and S.S. Davis

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

(Received 9 August 1988)
(Modified version received 10 October 1988)
(Accepted 28 October 1988)

Key words: Non-disintegrating tablet; Gastrointestinal transit; Colonic transit; γ-Scintigraphy

Summary

The gastrointestinal transit of non-disintegrating tablets was investigated in fasted subjects. The tablets (5 × 5 mm diameter) were administered on 3 consecutive days. Transit of the tablets was monitored using γ-scintigraphy. The tablets emptied from the stomach and traversed the small intestine as a bolus. The rate of transit through the colon showed a large inter-subject variation. However, in all cases, the tablets dispersed throughout the colon.

Introduction

It is generally accepted that, due to its small absorptive area, the colon is not a major site of drug absorption (Hofman et al., 1983). However, it has been suggested that the absorption of drugs from the colon must be greater than has been commonly believed (Davis, 1986). This is conceivable, considering that controlled release (CR) systems achieve extended absorption profiles, even when the dosage form is likely to have passed through the small intestine. The slow transit of dosage forms through the colon will prolong contact between the formulation and the absorptive surface, thereby resulting in a greater proportion of drug being absorbed than has been predicted previously. This has been illustrated in a combined bioavailability and transit studies (Davis et al., 1988). Here, the retention of a single osmotic pump system in the colon was well correlated with the bioavailability of the drug and extensive absorption of drug in the colon was indicated.

Few studies have been conducted to investigate specifically the colonic transit of oral dosage forms. Hardy et al. (1985) suggested that a relationship between particle size and transit through the colon might exist. A similar study by Davis et al. (1984) on the gastrointestinal (GI) transit of an osmotic device, also indicated that particle size was an important determinant of colonic transit. The osmotic device was found to transverse the colon ahead of the released solution.

The design of oral dosage for the selective delivery of drugs to the colon is becoming increasingly attractive. Oral formulations are not only

* Present address: Paines & Byrne, Bilton Road, Greenford, Middlesex UB6 7HG, U.K.
Correspondence: S.S. Davis, Department of Pharmaceutical Sciences, University of Nottingham, Nottingham NG7 2RD, U.K.

popular with patients, but many commonly used rectally administered preparations do not spread uniformly within the colon (Wood et al., 1985) and often fail to reach the tranverse colon (Hay, 1982). Consequently, efforts have been directed to the oral delivery of suitable drugs (e.g. corticosteroids, 5-aminosalicylic acid) to the colon; but avoiding release of drug in the small intestine (Dew et al., 1983; Levine et al., 1987). These controlled release systems have the advantage of reducing side-effects and delivery of effective concentrations of drug to the relevant site. The rational design of such formulations for selective delivery to the colon would be improved by a better understanding of the transit characteristics of the dosage form in the colon.

In the present study the gastrointestinal transit of small non-disintegrating tablets has been investigated in fasted subjects after repeated administration. Particular attention has been given to colonic transit.

The tablet formulations were dosed to healthy subjects on 3 consecutive days, so that the total transit of the tablets, and their dispersion in the colon after daily dosing, could be monitored.

Materials and Methods

Preparation of formulations

Non-disintegrating tablets (5 mm diameter) were prepared from ethylcellulose (BDH) containing a small quantity (5%) of IR120 cationic resin (BDH). The resin was first milled, and then labelled with indium-111. This radionuclide has a suitable half-life ($t_{1/2} = 2.8$ days) for the conduct of a study over a 3-day period. Labelled resin was passed through a 0.09 mm screen, and blended with ethylcellulose. The powder mix was directly compressed into tablets using a Manesty F3 single punch tablet machine. The tablets were coated with ethylcellulose to prevent leaching of the radiolabel and disintegration of the tablets. The tablets were tested for integrity in vitro under suitable conditions of temperature and pH. A more detailed description can be found elsewhere (Khosla, 1987).

In vivo study

The study was 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 Department of Health and Social Security, London.

Five, healthy male volunteers, age, height and weight ranges 20–25 years, 1.70–1.82 m, and 57–83 kg, respectively, participated with informed consent. Each subject abstained from alcohol for 24 h, and had fasted for 10 h, prior to the start of each study period. The subjects did not smoke, and were not on medication. On the morning of each day of the study, the subjects took 5 labelled tablets of 5 mm diameter (total dose of radioactivity about 1 MBq of indium-111) together with 200 ml of water labelled with [^{99m}Tc]DTPA (3 MBq). The labelled water enabled ready identification of the stomach and colon regions. The subjects remained fasted before administration of the tablets to allow for their rapid transit to the colon and also to provide data for comparison with parallel studies undertaken on fed subjects (Khosla et al., 1989). 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 medium energy (200 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, sitting or standing. The images were recorded using a Nodecrest computer system and stored on magnetic tape for subsequent analysis. Anatomical reference markers containing indium-111, 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 ham roll and 150 ml orange juice, was taken after about 4 h. An evening meal of steak, fried potatoes, peas and cheesecake was taken about 10 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). Careful examination (and if necessary, quantification) of the colon images enabled the (individual) tablets to be identified and counted. The spreading of the individual tablets often allow good identification of the various regions of the colon.

The study was repeated using the same protocol on the two subsequent days. A record of bowel habits was kept for the period of the study.

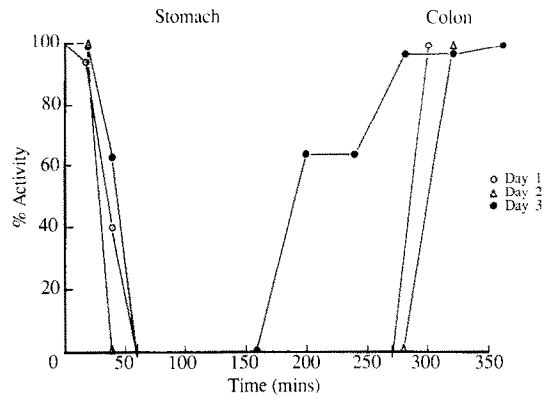

Fig. 1. Gastric emptying and colon entry of tablets for subject 3.

Results and Discussion

The data obtained in the investigation have been quantified by a number of different parameters; the times for 50% of the tablets to empty from the stomach ($St_{50\%}$) and to enter the colon ($Ct50\%$), the difference between these as an estimate of small intestine transit time (SIT), and the time for *all* tablets to move from mouth to colon (MCt) (Table 1). Representative gastric emptying profiles and colon entry curves for the subjects are shown in Figs. 1–3. The mean data are given in Fig. 4.

Scintiphotos showing the transit of the administered tablets through the gastrointestinal tract of

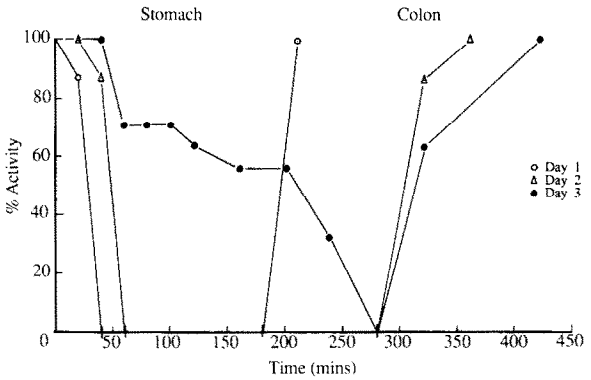

Fig. 2. Gastric emptying and colon entry of tablets for subject 5.

TABLE 1

Parameters for gastrointestinal transit

Subject	Gastric emptying $St_{50\%}$ (min)			Small intestine transit (SIT) (min)			Colon entry $Ct_{50\%}$ (min)			Mouth to colon MCt (min)		
Day:	1	2	3	1	2	3	1	2	3	1	2	3
1	35	10	43	135	210	362	170	220	405	210	240	480
2	10	30	230	252	230	173	262	260	403	320	280	> 700
3	30	30	45	255	270	145	285	300	190	320	320	360
4	20	30	100	115	70	45	135	100	145	160	120	200
5	28	50	145	167	253	167	195	303	312	200	360	420
Mean	25	30	113	185	207	178	209	237	307	242	264	432
S.E.M.	4	6	78	29	36	51	25	38	51	33	41	81
n	5	5	5	5	5	5	5	5	5	5	5	5

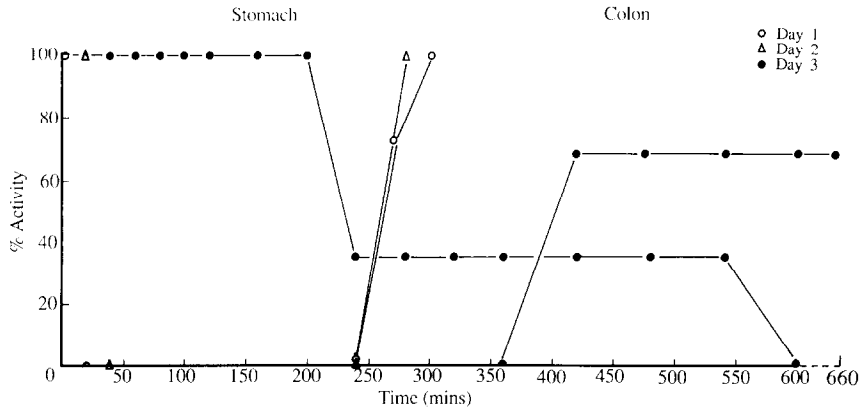

Fig. 3. Gastric emptying and colon entry of tablets for subject 2.

subject 1 on the different days of the study are shown in Fig. 5. The transit of the tablets, (often as a bolus) and grouping at the ileocaecal junction are well illustrated. Bolus emptying from the stomach can be related to the phase 2 and particularly phase 3 activity of the migrating myoelectric complex (*MMC*) that clears large undigestible objects from the fasted stomach (Code and Martlett, 1975). Previously Feely et al. (1985) have reported a similar phenomenon of bolus emptying of mini-matrix tablets in fasted subjects.

A paired Student's *t*-test on the gastric emptying ($St_{50\%}$) values obtained for the 3 separate days of the present study shows no significant difference ($P > 0.1$) between the results. The extended gastric emptying time recorded for subject 3 on day 3 is related to a lag time of about 200 min (Fig. 3) during which no gastric emptying on any of the 5 tablets was observed. Such periods of apparent stasis have been observed on other but infrequent occasions when volunteers have been dosed multiparticulates (or single units) after an overnight fast.

The small intestine transit (*SIT*) values are similar to those obtained in previous studies on the transit of tablets in fasted subjects and are in close agreement with the mean *SIT* value quoted for pharmaceutical dosage forms (Davis et al.,

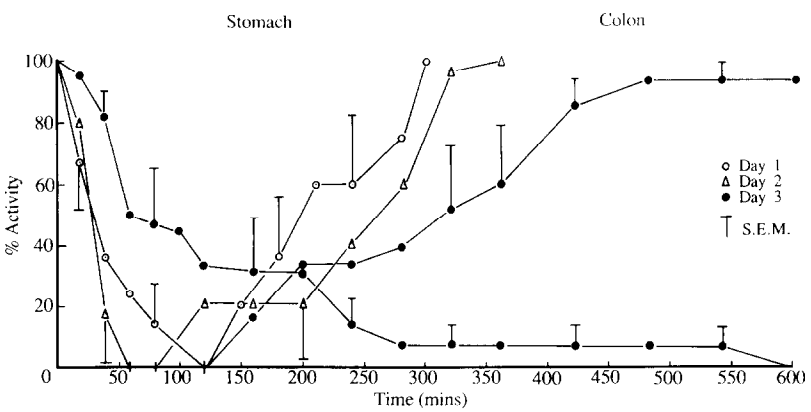

Fig. 4. Mean gastric emptying and colon entry of tablets.

1986). It was apparent from the recorded images that the tablets traversed the small intestine as a bolus. Interestingly, the values recorded for subject 4 indicate that on occasions small intestine transit can be less than 1 h in a healthy (fasted) individual.

The entry of the tablets into the caecum often occurred as a bolus (Figs. 1–3). The steep curves for filling of the caecum are indicative of clumping at the ileocaecal sphincter (ICS), followed by bolus entry into the caecum (Spiller et al., 1987). In general, the tablets did not remain at the ICS for extended periods, although for subject 1 on day 3 a long period of residence at the ICS was exhibited. The mean colon entry curves (Fig. 4) are similar to the profiles obtained when 5 mm tablets from the same batch were administered to healthy volunteers after a light breakfast (Khosla et al., 1989). The curve for day 3 suggests a less rapid rate of entry. This can be partly explained by the long gastric residence time exhibited by subject 2, which results in the curve being shifted to the right. Nevertheless, for this subject, the tablets entered the caecum as a bolus. The stagnation of the tablets at the ICS, for subject 1, as discussed above, would also tend to broaden the

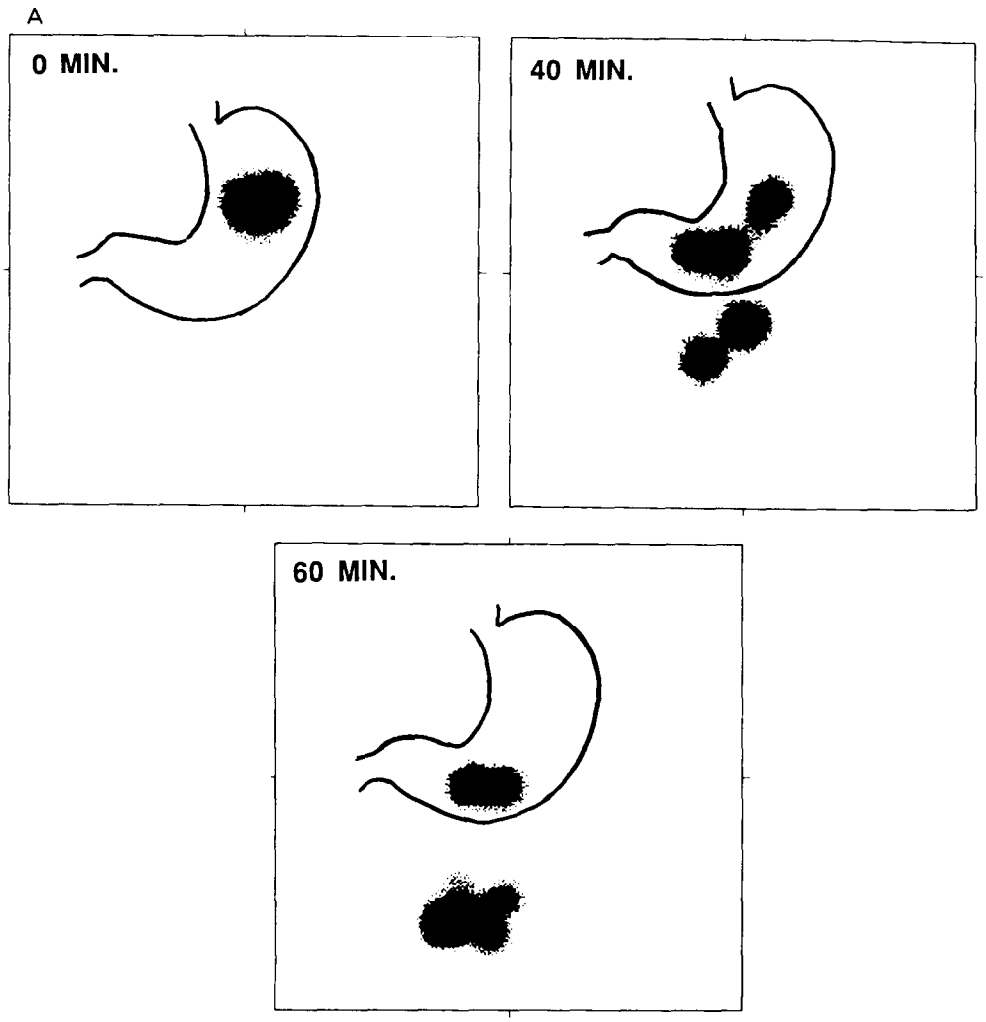

Fig. 5. Scintiphotos for subject 1. A: day 1–gastric emptying of tablets. B: day 1–colon entry of tablets. C: day 2–gastrointestinal transit. D: day 3–gastrointestinal transit.

curve for caecum entry. Future similar studies are planned in order to evaluate the frequency of extended stagnation at the ICS and to determine the general pattern of colon entry. The similarity between caecum entry curves obtained after a light breakfast (Khosla et al., 1989) and fasting (days 1 and 2) provides evidence that meal residue has little influence on transit through the ICS. It is unlikely that, the food taken for lunch on the study days would have affected colon entry, since entry usually began before or within an hour of lunch-time. Furthermore, the solid and calorific content of the meal was relatively small. There was no demonstrable relationship between the ingestion of food and either caecal filling or transit through the colon. Thus, whilst ingestion of food normally causes an increase in colonic activity, the so-called "gastrocolic" reflex (Kruis et al., 1987), this increased activity does not necessarily result in aboral movement of colonic material.

The different patterns of transit of the tablets through the colon is illustrated by the results for 3 of the subjects (Fig. 6). The tablets usually remained as a bolus in the region of the caecum, began to disperse as they progressed further through the ascending transverse and descending

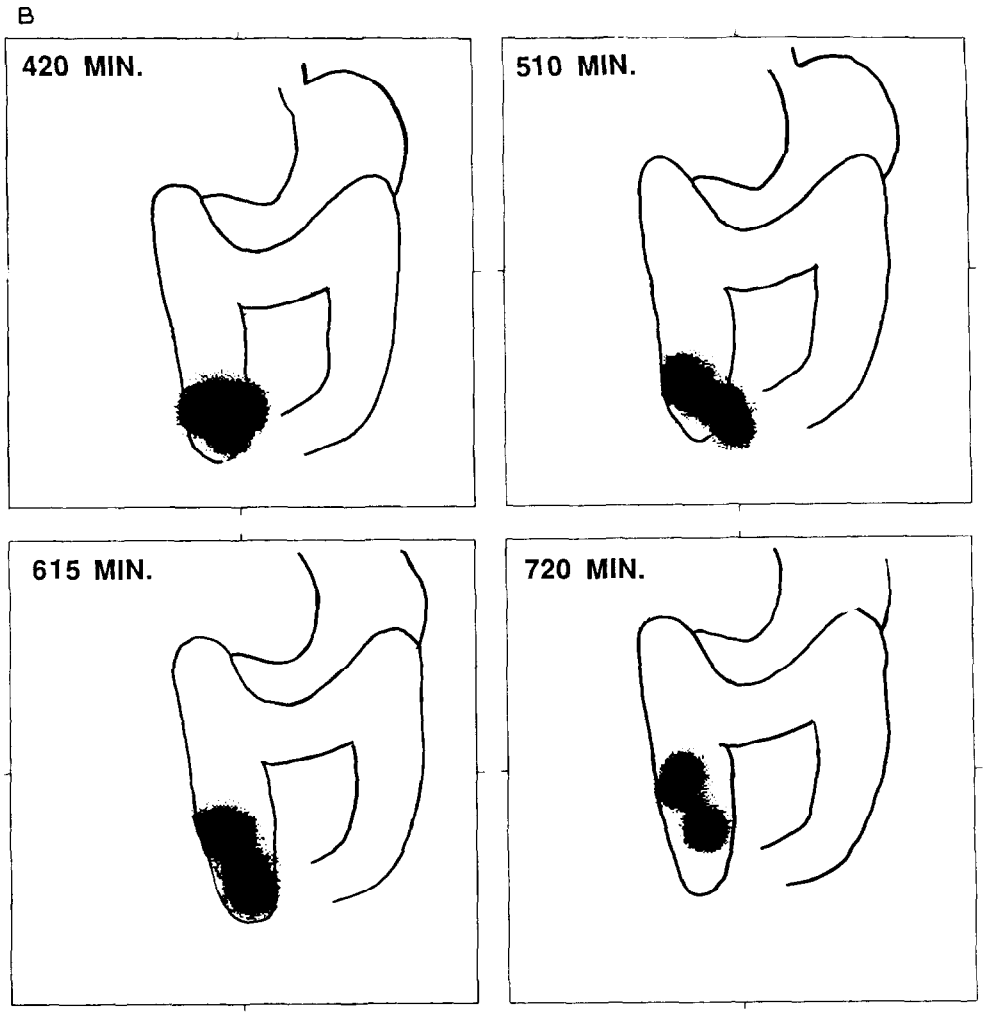

Fig. 5. (continued).

regions of the colon, before forming a grouped mass in the sigmoid colon/rectal region. Previously it has been noted that dispersive systems, such as pellets, can become widely distributed within the colon (Hardy and Perkins, 1985). A similar dispersion has also been seen for a radiolabel marker released from an osmotic device (OSMET) (Davis et al., 1984).

Subject 1 exhibited a slow transit through the colon, and all 15 administered tablets were still present in the colon at the end of day 3. These tablets were well distributed throughout the different regions of the colon. In contrast, subject 2 exhibited a much faster rate of transit. Most of the tablets given on day 2 had reached the sigmoid colon 7 h after entering the large intestine and were evacuated before the first image was taken on the morning of day 3. Subject 3 demonstrated an intermediate rate of transit. Three of the tablets given on day 1 had been evacuated by the start of day 2. It is interesting to note that, the remaining two tablets were to be found in the descending colon rather than the sigmoid colon. This suggests a mass movement of material was responsible for the evacuation of the 3 tablets. The two remaining tablets were evacuated before day 3. Subjects 4

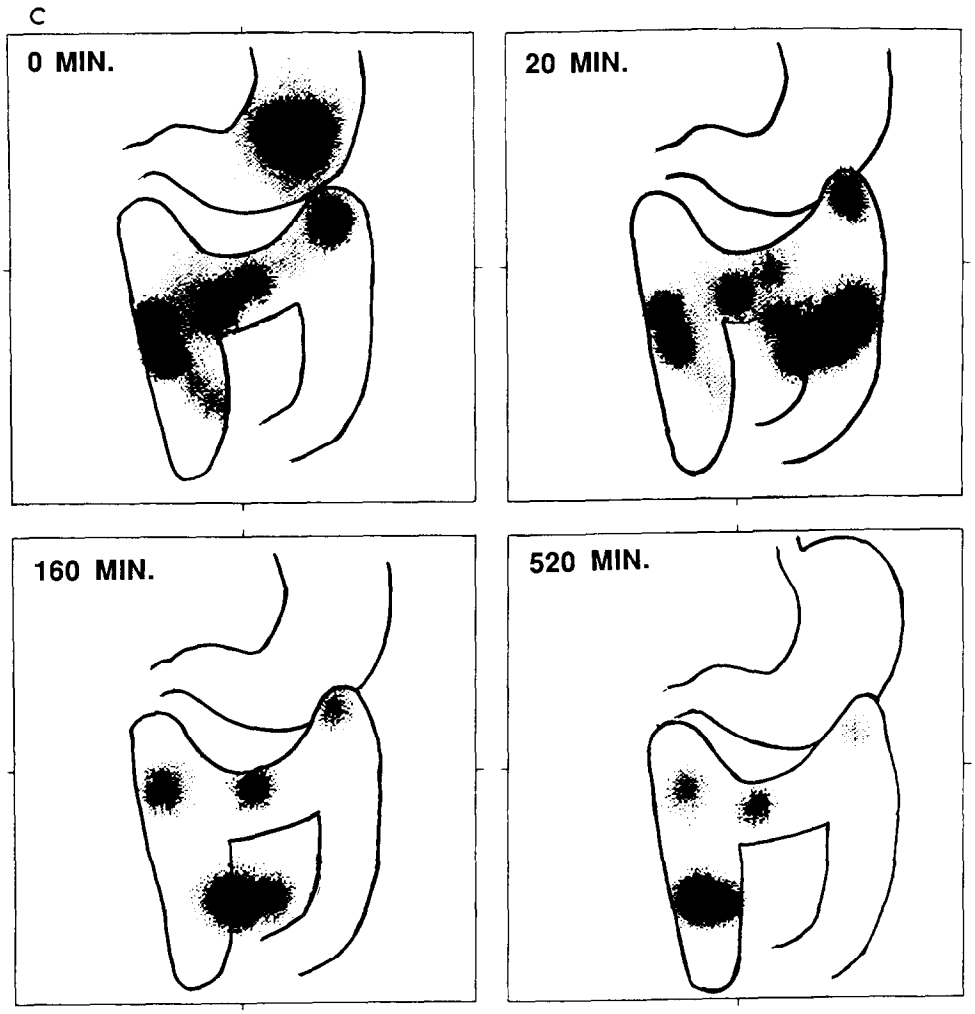

Fig. 5. (continued).

and 5 also exhibited an intermediate rate of transit. It is evident from the plots in Fig. 6 that, total transit times of the tablets (mouth to anus) ranged from about 18 h (subject 2, tablets from day 2) to more than 72 h (subject 1). Hardy et al. (1985) found total transit times of 17–72 h, for a pellet formulation given to fasted subjects, whereas John et al. (1985) reported a median mouth to evacuation time of 27.4 h, for a single unit system (OROS), in fasted subjects. However, in this latter study, individual total transit times ranged from 5.1 to 58.3 h. It has been suggested that very short transit times (less than about 6 h), may relate to a vegetarian diet (Sangekar et al., 1987). Further studies on the relation between normal diet and total transit would provide further evidence for this interesting suggestion.

Observation of the different patterns of transit indicated that the tablets did not move in a continuous manner, but had periods of little movement. Similar observations were made by Hardy et al. (1985). Defaecation did not generally result in a major progression of the tablets, except to evacuate those tablets present in the sigmoid colon and rectum. As mentioned above, a mass movement effect appears to have occurred in subject 3.

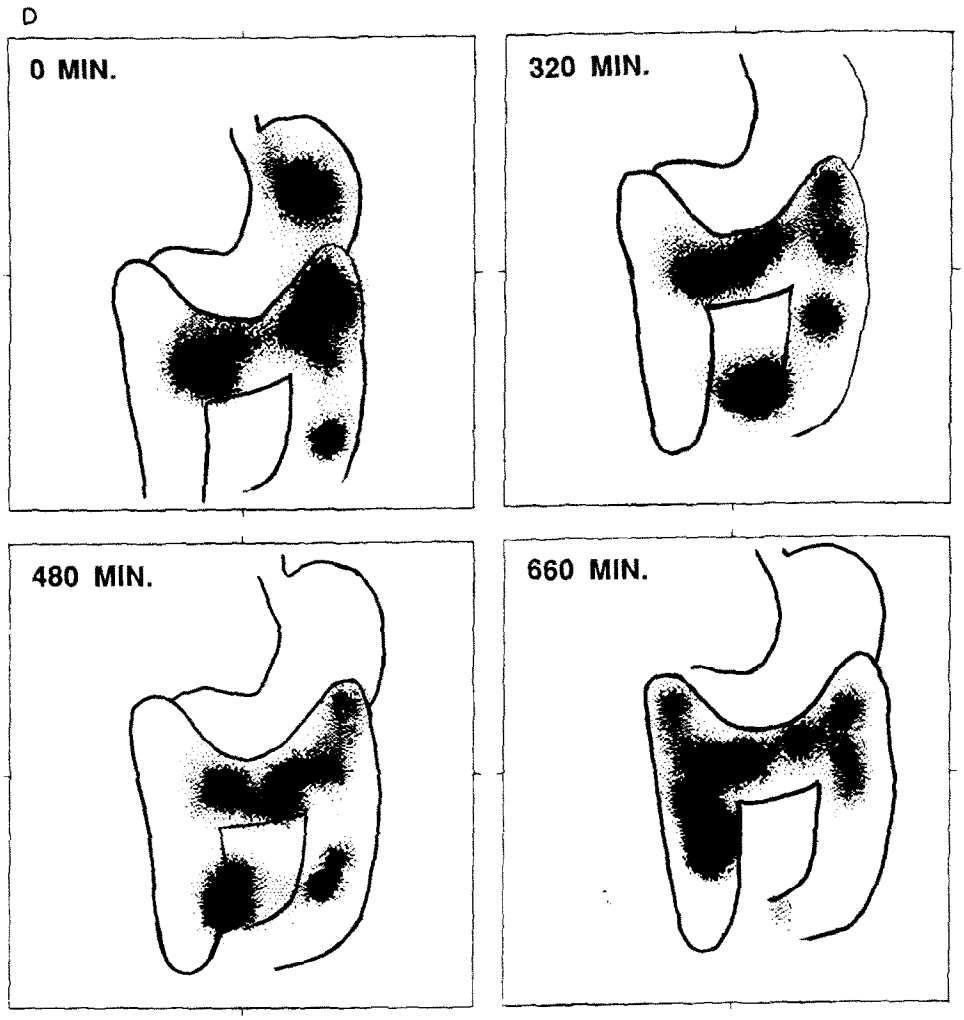

Fig. 5. (continued).

Mass movement, at the time of defaecation, is also suggested for subject 2 on day 2; where tablets progressed rapidly from the transverse colon to the sigmoid colon. Interestingly, John et al. (1985) did not find a relationship between total transit times and the frequency of bowel movements.

The present results provide substance to previous comments regarding oral controlled release systems designed for targeting drugs to the colon (Hardy et al., 1985). Our current knowledge on the GI transit of dosage forms suggests that dispersive systems should be designed to retain the drug within the formulation for 5–6 h after administration to fasted individuals. Drug released over the next few hours would distribute throughout the proximal and transverse colon. However, the effective period of drug release in vivo is restricted by the apparent inter-subject differences in colon transit times. A multiple unit system given on a once daily basis should be sufficiently dispersed in the colon to provide adequate local delivery of drug for the treatment of common colonic diseases.

The results of this study are also relevant to the design of controlled release systems in general. Total transit times of less than 24 h make once daily dosing impracticable even if a drug is well absorbed in the colon. Furthermore, it is necessary to determine the degree of drug biotransformation that can occur in the colon and more importantly, to quantify the exact extent of drug absorption that occurs in this region. Conventional bioavailability studies, combined with the technique of γ-scintigraphy are ideal for such investigations. Considerable advantage would be gained if delivery systems could be developed which had a prolonged gastric residence (Khosla et al., 1989) especially in the fasted state.

In conclusion, the transit of small tablets in the colonic region of healthy volunteers varied between individuals. However, the good dispersion of the tablets throughout the colon found for all

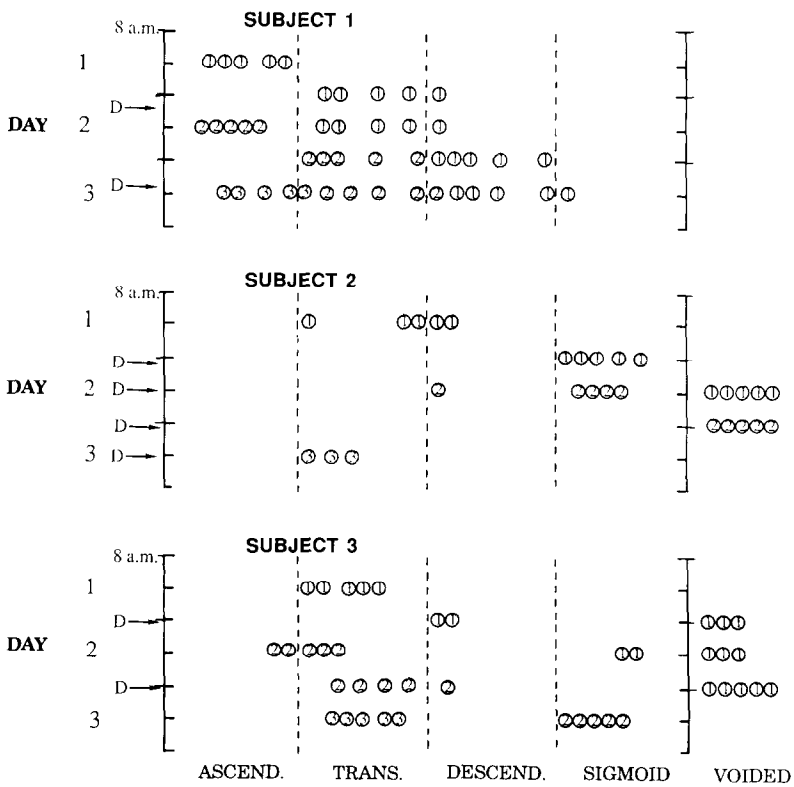

Fig. 6. Transit patterns for tablets in the colon. D = defaecation.

subjects, is relevant to the future design of oral dosage forms intended for delivery of drugs selectively to the colon for local or systemic effects. Movement of the tablets through the colon is not directly related to either the ingestion of food or bowel habits.

References

Code, C.F. and Martlett, J.A., The interdigestive myoelectric complex of the stomach and small bowel of dogs. *J. Physiol. (Lond.)*, 246 (1975) 289–309.

Davis, S.S., Studies on the gastrointestinal transit of dosage forms in human subjects using the technique of gamma scintigraphy. *STP Pharma*, 2 (1986) 1015–1022.

Davis, S.S., Hardy, J.G. and Fara, J.W., The transit of pharmaceutical dosage forms through the small intestine. *Gut*, 27 (1986) 886–892.

Davis, S.S., Hardy, J.G., Taylor, M.J., Stockwell, A., Whalley, D.R. and Wilson, C.G., The in vivo evaluation of an osmotic device (Osmet) using gamma scintigraphy, *Int. J. Pharm.*, 36 (1984) 740–742.

Davis, S.S., Washington, N., Parr, G.D., Short, A.H., John, V.A., Lloyd, P. and Walker, S.M., Relationship between the rate of appearance of Oxprenolol in the systemic circulation and the location of a 16/260 Oxprenolol Oros drug delivery system within the gastrointestinal tract as determined by scintigraphy. *Br. J. Clin. Pharmacol.*, (1988) 26 (1988) 435–443.

Dew, M.J., Ryder, R.E., Evans, N. and Rhodes, J., Colonic release of 5-ASA from an oral preparation in active ulcerative colitis. *Br. J. Clin. Pharmacol.*, 16 (1983) 185–187.

Feely, L.C., Davis, S.S. and Parr, G.D. Investigating the gastrointestinal transit of controlled release mini-matrices using gamma scintigraphy. *Proc. 12th Int. Symp. Controlled Release Bioactive Materials*, Geneva, 1985, pp. 94–95.

Hardy, J.G. and Perkins, A.C., Validity of the geometric mean correction in the quantification of whole bowel transit. *Nucl. Med. Commun.*, 6 (1985) 217–224.

Hardy, J.G., Wilson, C.G. and Wood, E., Drug delivery to the proximal colon. *J. Pharm. Pharmacol.*, 37 (1985) 874–877.

Hay, D.J., Spreading characteristics of proprietary rectal steroid preparations. In Wilson, C.G., Hardy, J.G., Frier, M. and Davis, S.S. (Eds.), *Radionuclide Imaging in Drug Research*, Croom Helm, London, 1982, pp. 171–180.

Hofman, A.F., Pressman, J.H. and Witztum, K.F., Controlled entry of orally administered drugs: physiological considerations. *Drug. Dev. Ind. Pharm.*, 9 (1983) 1077–1109.

John, V., Shotton, P., Moppert, J. and Theobald, W., Gastrointestinal transit of Oros drug delivery systems in healthy volunteers. A short report. *Br. J. Clin. Pharmacol.*, 19 (1985) 2035–2065.

Khosla, R., Feely, L.C. and Davis, S.S., The gastrointestinal transit of non-disintegrating tablets in fed subjects, *Int. J. Pharm.*, in press.

Khosla, R., *Gastrointestinal Transit of Dosage Forms*, Ph.D. Thesis, University of Nottingham, 1987.

Kruis, W., Phillips, S.F. and Zinsmeister, A., Flow across the canine ileocolonic junction: role of the ileocolonic sphincter. *Am. J. Physiol.*, 252 (1987) G13–G18.

Levine, D.S., Raisys, V. and Ainardi, V., Coating of oral beclomethasone diproprionate capsules with cellulose acetate phthalate enhances delivery of topically active anti-inflammatory drug to the terminal colon. *Gastroenterology*, 92 (1987) 1037–1044.

Sangekar, S., Vadino, W.A., Chaudry, I., Parr, A., Beihn, G. and Digenis, G., Evaluation of the effect of food and specific gravity of tablets on gastric retention time. *Int. J. Pharm.*, 35 (1987) 187–191.

Spiller, R.C., Brown, M.L. and Phillips, S.F., Emptying of the terminal ileum in intact humans. *Gastroenterology*, 92 (1987) 724–729.

Tothill, P., Mcloughlin, G.P. and Heading, R.C., Techniques and errors in scintigraphic measurement of gastric emptying. *J. Nucl. Med.*, 19 (1978) 256–261.

Wood, E., Wilson, C.G. and Hardy, J.G., The spreading of foam and solution enemas. *Int. J. Pharm.*, 25 (1985) 191–197.