International Journal of Pharmaceutics, 21 (1984) 331–340
Elsevier

IJP 00739

The effect of food on the gastrointestinal transit of pellets and an osmotic device (Osmet)

S.S. Davis [1], J.G. Hardy [2], M.J. Taylor [1,*], D.R. Whalley [2] and C.G. Wilson [3]

[1] *Dept. of Pharmacy, University of Nottingham, Nottingham NG7 2RD;* [2] *Dept. of Medical Physics, Queen's Medical Centre, University of Nottingham, Nottingham NG7 2UH; and* [3] *Dept. of Physiology and Pharmacology, Queen's Medical Centre, University of Nottingham, Nottingham NG7 2RD (U.K.)*

(Received May 2nd, 1984)
(Accepted June 14th, 1984)

Summary

The gastrointestinal transit of a pellet formulation and an osmotic pump device (Osmet) has been evaluated in 6 subjects using the technique of gamma scintigraphy. The two formulations were labelled with different radionuclides so that they could be monitored concurrently. The transit from the stomach through the small intestine to the colon was influenced by the nature of the meal taken shortly before dosing. On a light breakfast the pellets and osmotic devices were emptied quite rapidly. However, following a heavy breakfast the pellets were emptied more slowly while the osmotic devices were retained in the stomach for approximately 10 h. Transit behaviour is discussed in terms of the known physiological determinants of gastrointestinal motility and the concept of the 'reserve length' for drug absorption.

Introduction

The biological availability of a drug will be influenced by a variety of pathological, physiological and pharmaceutical factors (Mayersohn, 1979). Important among the physiological factors are gastric residence time and intestinal transit. Indeed recently Ho and others (1977) and Higuchi and others (1979) have introduced the

* *Present address*: School of Pharmacy, Leicester Polytechnic, Leicester, U.K.
Correspondence: S.S. Davis, Dept. of Pharmacy, University of Nottingham, Nottingham NG7 2RD, U.K.

concept of the 'reserve length' for absorption (defined as the anatomical length over which absorption could occur, less the length at which absorption is complete) and the dependence on factors such as bulk flow rate, the spreading of the dose in the intestines and the permeability coefficient of the drug. They stressed that proper dosage form design should take into account the reserve length concept and observed that since few drugs were absorbed significantly from the stomach or the colon, this length would have a maximum value of about 300 cm in man (the length of the small intestines). Efficient absorption would give a large reserve length while spreading of the dose would tend to increase the length at which absorption would be complete and thereby decrease the reserve length. Methods for calculating the optimum particle size of a drug suspension to give release (dissolution) and drug absorption within the reserve length have been described (Higuchi et al., 1979). However, in order to apply such a concept properly it is important to have experimental data from man on gastrointestinal transit times and the spreading of administered dosages.

The gastrointestinal transit of a pharmaceutical dosage form will depend not only upon the size, shape and nature of the system (single unit, or multiparticulate) but also upon physiological factors, the most important being the presence or absence of food in the stomach (Bechgaard, 1982; Davis et al., 1984a). The stomach is able to empty different materials at different rates even though they might have been taken simultaneously. Liquids are emptied quite rapidly but digestible materials need to be broken down to a size of about 1 mm or less before they are allowed to pass into the duodenum. Thus pharmaceutical dosage forms of a size greater than 2 mm taken with or shortly after a meal would be expected to be retained in the stomach throughout the postprandial period and to be emptied only when the stomach was empty of food (Kelly, 1981). In contrast, a solid dosage form administered to a fasted stomach or following a light meal may be emptied rapidly from the stomach and pass quickly through the small intestines to the colon (Hunter et al., 1981).

A special mechanism called the interdigestive myoelectric complex or 'housekeeper wave' can produce powerful contractions in the gastrointestinal tract that will sweep indigestible material from an empty stomach past the pylorus into the duodenum. Later waves of the complex will move the material rapidly down the small intestine into the colon (Szurszewski, 1969). Indeed it is possible to deliver a radiolabelled solution from mouth to the caecum in an average time of 80 ± 7 min ($n = 14$) (Caride et al., 1982). When meals of different energy content are ingested the rate of gastric emptying is such that the number of calories delivered to the duodenum tends to be constant with time (Hunt and Stubbs, 1975; Kelly, 1981). That is a heavy meal will be emptied over a much longer period of time than a light meal (Christian et al., 1980). In addition certain foodstuffs, in particular fats are believed to have an inhibitory effect on gastric emptying (Kelly, 1981).

The transit of material through the intestines is less well defined (Weisbrodt, 1981) although mixing of contents can occur both in the small intestine and the large intestine (Halls, 1965). A change in intestinal motility can be brought about by eating and hormones released by the presence of different foods has been proposed (Weisbrodt, 1981).

In the past X-ray methods using radio-opaque dosage forms (usually made with barium sulphate) have been popular as a means of exploring the gastrointestinal transit of pharmaceutical systems (Wagner et al., 1958; Galeone et al., 1981). However, this method suffers from a number of disadvantages (Christensen et al., 1984a) and more recently the technique of gamma scintigraphy has become a popular alternative (Hunter et al., 1981, 1982; Digenis, 1982; Bechgaard, 1982; Wilson et al., 1984; Christensen et al., 1984a and b; Davis, 1983; Davis et al., 1984a and b).

In the present study the gastrointestinal transit of a pellet system and a single unit osmotic pump (Osmet) (Eckenhoff and Yum, 1981) have been followed. The two formulations were labelled with different radionuclides and dosed concurrently following standard light and heavy breakfasts. The use of gamma scintigraphy to follow the release of a radiolabelled marker from the osmotic pump has been described elsewhere (Davis et al., 1984b).

Materials and Methods

Pellets

Amberlite ion-exchange resin (IRA 410) from British Drug Houses, density 1.2 g/cm^3 was used as a model pellet system as described by Hunter et al. (1982). The material was sieved to provide particles in the size range 0.7–1.2 mm and labelled by mixing 1 g with [^{99m}Tc]sodium pertechnetate (50 MBq) obtained from a generator (CIS (U.K.), London). The integrity of the labelled pellets was evaluated in vitro and in vivo as discussed by Davis et al. (1984a). The transit behaviour of the pellets has also been compared with technetium-99m labelled coated pellet systems (described by Christensen (1984)) using 3 human volunteers. Both pellet systems had very similar transit characteristics (Davis, 1983).

The labelled pellets were filled into size 3 capsules to give a fill weight of 140 mg, comprising about 280 pellets, of total activity 2 MBq of technetium-99m.

Osmotic pumps

Osmet 12-hour systems were obtained from Alza, Palo Alto, CA. These were made from a styrene–butadiene copolymer and had a nominal fill volume of 200 μl. The pumps were filled, using a blunt type 25-gauge filling tube attached to a syringe, with a solution of indium-111-labelled diethylenetriaminepentaacetic acid (DTPA) to give a radionuclide activity of approximately 4 MBq per unit (Davis et al., 1984b). DTPA was chosen since this chelates indium very strongly (Kelly, 1982) and the material is not absorbed from the gastrointestinal tract.

In vivo studies

Six healthy volunteers (age 19–21 years, height 1.63–1.82 m, weight 70–81 kg) participated in the study on two occasions with informed consent. The indium-111-labelled osmotic pumps and technetium-99m-labelled pellets were administered following a standard light or heavy breakfast (Table 1). The osmotic pumps were

TABLE 1

Standard breakfasts

Light breakfast (calorific value = 1500 kJ)
Two toasted slices of white bread lightly buttered and with a scrape of marmalade.
1 glass orange juice.

Heavy breakfast (calorific value = 3600 kJ)
2 sausages
1 rasher of bacon
1 fried egg
1 fried tomato
1 piece of fried bread
Coffee with milk (and sugar if desired)

administered a few minutes before the pellets in order to obtain a scatter down correction factor (see below). The position of the osmotic pumps and pellets within the different regions of the gastrointestinal tract was followed using simultaneous dual radionuclide imaging by standing the subjects in front of a gamma camera having a 40 cm diameter field of view fitted with a medium energy (300 keV maximum) parallel hole collimator (Davis et al., 1984a).

An external marker made from adhevise tape labelled with approximately 1 MBq [^{99m}Tc]sodium pertechnetate was attached to the skin overlying the liver to the right of the stomach. Anterior and posterior images of 60 s duration were taken at suitable intervals over a period of 24 h. The data were recorded by computer for subsequent analysis. Regions of interest were defined around the images of the stomach and colon (ascending and transverse). The activity in these regions was quantified and corrected for background activity. The imaging of two radionuclides simultaneously requires that a correction be made for the 'scatter down' of the activity of the higher energy nuclide (indium-111) into the energy window of the lower energy tracer. This correction factor was estimated by administering the indium-111-labelled osmotic pumps before the technetium-labelled pellets and imaging in both energy windows with indium-111 alone. The corrected technetium counts, and the indium counts, were then further corrected for radioactive decay. The geometric mean of the anterior and posterior counts was calculated to give a result that was approximately independent of the depth of the activity in the body (Tothill et al., 1978). The volunteers were allowed to drink and eat normally during the course of the study.

Results and Discussion

The transit of the pellets and the osmotic pumps through the different regions of the gastrointestinal tracts of the volunteers was followed using gamma camera imaging. The radionuclide images obtained were similar to those presented and described by Daly et al. (1982), Wilson et al. (1984), Christensen et al. (1984a), and Davis et al. (1984a and b). The emptying of the osmotic pump from the stomach and

its arrival in the caecum represents a random stochastic process and the approximate times for each of the volunteers are given in Table 1. The difference in the gastric emptying time and caecum arrival time allows the estimation of a small intestine transit time for 5 out of 6 of the subjects following the light breakfast. The pronounced effect of food intake is very evident. When the subjects were given the heavy breakfast all of them retained the osmotic pump in the stomach for approximately 10 h. For 2 subjects, gastric emptying occurred between 9 and 11 h, while for the remainder, emptying took place at times greater than 11 h. All pumps used were found in the colon (usually transverse and descending colon) at 24 h. These results have implications for the design of controlled release formulations and the reserve length concept. For a fasted individual or one receiving a light meal, a prolongation of drug delivery may be of no avail if the dosage form is emptied rapidly from the stomach and passes the sites for absorption before the major proportion of the drug has been released.

The data for the transit of pellets have been expressed as the time for 50% to leave the stomach and for 50% to arrive at the caecum. The difference between these two values is taken as an estimate of transit in the small intestine. This is only an approximate figure, especially for the subjects receiving a heavy breakfast, since not all the activity had left the stomach before some of the pellets reached the colon. Complex deconvolution techniques requiring more frequent imaging would be necessary in this case to provide better estimates of intestinal transit. As with the osmotic pumps, the effect of food on transit is clear. The pellets emptied much more slowly when the subjects were given a heavy breakfast; times for 50% gastric emptying were 119 ± 15 and 285 ± 45 min, respectively. The pooled data have been plotted in Figs. 1 and 2 as mean ± S.E.M. for the 6 subjects.

The degree of spreading of the pellets can be quantified by measuring the gradient of the emptying curve at 50% activity (Davis et al., 1984a). The spreading

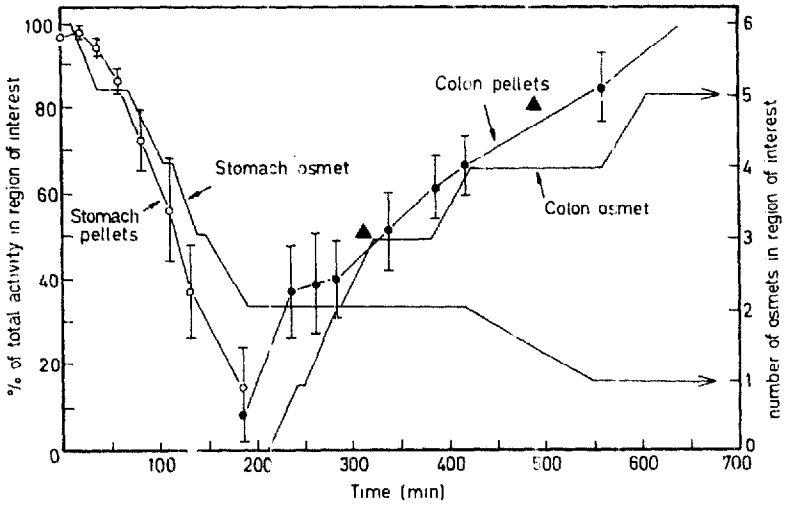

Fig. 1. The gastrointestinal transit of pellets and osmotic devices following a light breakfast. ▲, data from Dew et al. (1982). (Pellet data, mean ± S.E.M., n = 6).

factors for the pooled data for the transit of pellets following a light and heavy breakfast (Figs. 1 and 2) are 130 and 500, respectively. In a previous publication, Davis et al. (1984a) have reported a spreading factor as low as 50 min for similar pellets administered to a fasted subject.

The gastric emptying and colonic arrival patterns for the osmotic pumps are also shown on Figs. 1 and 2 for comparative purposes. Here the data for the 6 subjects have been pooled to give a total of 6 units for a given region of the gastrointestinal tract.

The data for the pellet systems are in good agreement with previous investigations that have employed gamma scintigraphy to follow gastrointestinal transit (Christensen et al., 1984a; Davis et al., 1984a). For instance, in a preliminary study on the use of gamma scintigraphy to follow the gastrointestinal transit of pharmaceutical formulations, Christensen et al. (1984a) reported a $t_{50\%}$ gastric emptying of 99 ± 7 min and colonic arrival of 304 ± 28 min ($n = 8$) for the pellets given to subjects who had taken a light breakfast. The corresponding transit time for the small intestines was 204 ± 31 min. The present study shows that presence of a large quantity of digestible food in the stomach increases the mean gastric emptying time for pellets (and as a consequence the time for colonic arrival). However, the time for transit though the small intestine is unaffected (Table 2). This is in line with the recent observation of Read et al. (1982) who failed to show any correlation between gastric emptying and transit through the small intestine. Further evidence for the independent nature of transit through the small intestine can be found in the work of Christensen et al. (1984a) who have reported a stomach to colon transit time of 244 ± 28 min ($n = 5$) for a simple solution formulation and Davis et al. (1984a) who reported mean values of 227 ± 82 ($n = 5$) and 188 ± 23 ($n = 5$) for the transit of pellets and tablets, respectively, in subjects who had received breakfasts of different calorific values.

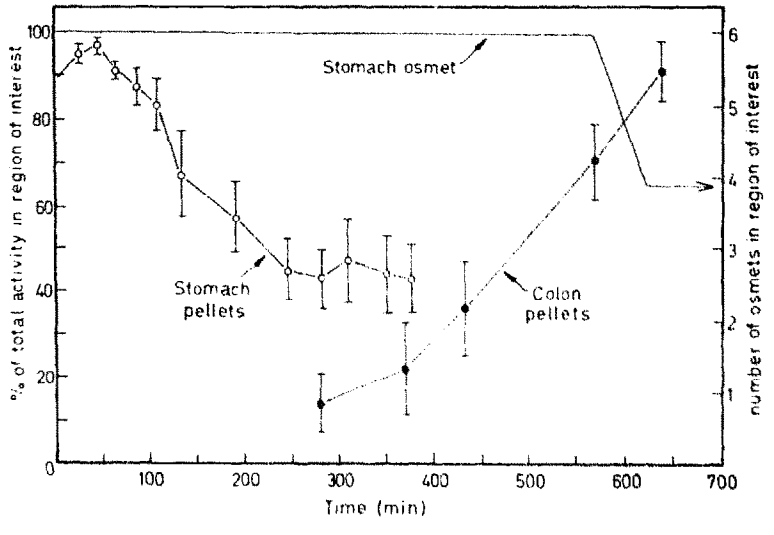

Fig. 2. The gastrointestinal transit of pellets and osmotic devices following a heavy breakfast. (Pellet data, mean + S.E.M., n = 6).

TABLE 2

GASTROINTESTINAL TRANSIT OF PELLETS AND OSMOTIC PUMPS

Volunteer	Light breakfast						Heavy breakfast					
	Pellets ($t_{50\%}$ min)			Osmotic pumps (approx. times—min)			Pellets ($t_{50\%}$ min)			Osmotic pumps (approx. times—min)		
	Gastric emptying	Arrival at caecum	Small intestine transit	Gastric emptying	Arrival at caecum	Small intestine transit	Gastric emptying	Arrival at caecum	Small intestine transit	Gastric emptying	Arrival at caecum	Small intestine transit
1	100	225	125	105	270	165	375	480	105	> 660	> 660	< 1400
2	190	420	230	600	> 660	–	420	580	160	> 660	> 660	< 1400
3	80	260	240	30	220	190	330	500	170	> 550	> 660	< 1400
4	100	245	145	480	600	120	250	525	275	> 550	> 660	< 1400
5	120	230	110	150	360	210	170	300	230	> 660	> 660	< 1400
6	125	400	275	150	420	270	150	425	275	> 660	> 660	< 1400
Mean	119	296	188	183	374	191	285	468	202	> 550	> 660	
± S.E.M.	15	36	28	77	66	24	45	39	28	< 1400	< 1400	
n	6	6	6	5	5	5	6	6	6			
Median between	120–125	245–260	145–230	150	360–420	190	250–330	480–500	170–230	> 550	> 660	< 1400

The gastric emptying and intestinal transit of solid dosage forms has been considered by Bechgaard (1982) and Sjogren and Bogentoft (1982). The range has been from 30 min to more than 24 hours for gastric emptying, depending on dietary intake. A study by Sjogren and Bogentoft (1982) using external scanning has given gastric emptying times ranging from 0.5 to 4.5 h (median 2 h) in the fasting state and from 2 to 4.5 h (median 4 h) for the fed state.

Dew et al. (1982) examined the gastrointestinal transit of tablets using X-ray methods. Each of 6 volunteers was given 6 tablets and the data for the group were pooled. 50% of the tablets were found in the colon after 5 h and 81% after 8 h. These data points have been included in Fig. 2 and fit well with the patterns for both the pellets and osmotic pumps.

The derived data can also be examined in terms of the distribution of activity within the various regions of the gastrointestinal tract with the reserve length concept in mind. An example is shown in Fig. 3 for volunteer 3, who received the heavy breakfast. The histograms represent the amount of activity in the 3 designated regions (stomach, small intestine and colon). The activity within the osmotic device and the released activity (Davis et al., 1984b) have been shown separately. The movement and distribution of the pellets, the released solution from the osmotic device (and the device itself) from the stomach to the small intestine and thence to the colon are demonstrated. The osmotic device remains in the stomach for an extended period of time as already discussed. However, the released solution is distributed in the gastrointestinal tract in a similar manner to the pellet system. This approach to the analysis of scintigraphic data for gastrointestinal transit will be examined in further detail elsewhere.

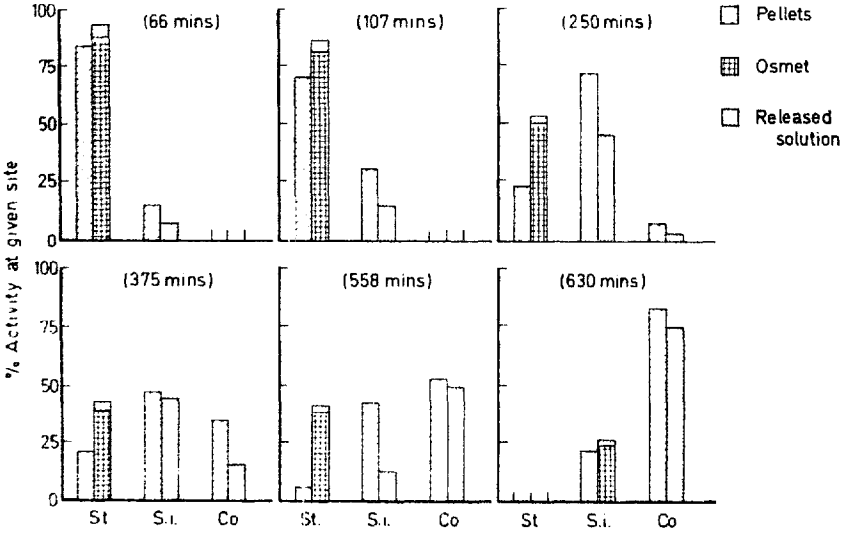

Fig. 3. Distribution of pellets, osmotic device and released solution in different regions of the gastrointestinal tract (data for volunteer 3). St = stomach; si = small intestine; co = colon.

Conclusions

The results of the present study demonstrate clearly the importance of food in controlling the gastrointestinal transit of pellet and single unit formulations in man. Following a light breakfast pellets and osmotic pump systems are emptied quite rapidly and move through the small intestine in about 200 min. After a heavy breakfast the pellets empty more slowly from the stomach and as a consequence are distributed more widely in the intestines. However, the average transit time in the small intestine is still of the order of 200 min. In contrast the single unit osmotic pumps are retained in the stomach after a heavy breakfast for at least 9 h but the released solution is well distributed to the small intestines and the colon.

Acknowledgements

The authors wish to thank Dr. M.L. Wastie, Department of Radiology, Queen's Medical Centre, Nottingham, for advice and helpful discussions.

References

Bechgaard, H., Critical factors influencing gastro-intestinal absorption—what is the role of pellets? Acta Pharmac. Technol., 28 (1982) 149–157.

Caride. V.J., Prokop, E.K., McCallum, R., Troncale, F.J., Buddoura, W. and Winchenbach, K., Scintigraphic evaluation of gastrointestinal transit time. Comparison with hydrogen breath test. Nuclear Medicine and Biology, Proceedings of the Third World Congress of Nuclear Medicine and Biology, Paris, 1982, pp. 2427–2429.

Christensen, F.N., European Patent Application 83302304.7.

Christensen, F.N., Davis, S.S., Hardy, J.G., Taylor, M.J., Whalley, D.R. and Wilson, C.G., The use of gamma scintigraphy to follow the gastrointestinal transit of pharmaceutical formulations. J. Pharm. Pharmacol., (1984a) in press.

Christensen, F.N., Bechgaard, H., Davis, S.S., Hardy, J.G., Taylor, M.J., Whalley, D.R. and Wilson, C.G., The gastrointestinal transit of pellets in normal subjects. J. Pharm. Pharmacol., (1984b) submitted.

Christian, P.E., Moore, J.G., Sorenson, J.A., Coleman, R.E. and Welch, D.M., Effects of meal size and correction technique on gastric emptying time: studies with two tracers and opposed detectors. J. Nucl. Med., 21 (1980) 833–885.

Daly, P.B., Davis, S.S., Frier, M., Hardy, J.G., Kennerley, J.W. and Wilson, C.G., Scintigraphic assessment of the in vivo dissolution rate of a sustained release tablet. Int. J. Pharm., 10 (1982) 17–24.

Davis, S.S. The use of scintigraphic methods for the evaluation of dosage forms in the gastrointestinal tract. In Breimer, D.D. and Speiser, P. (Eds.), Topics in Pharmaceutical Sciences, Elsevier Biomedical, Amsterdam, 1983, pp. 205–215.

Davis, S.S., Hardy, J.G., Taylor, M.J., Whalley, D.R. and Wilson, C.G., A comparative study of the gastrointestinal transit of a pellet and tablet formulation. Int. J. Pharm. (1984a) in press.

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. J. Pharm. Pharmacol., (1984b) in press.

Dew, M.J., Hughes, P.J., Lee, M.G., Evans, B.K. and Rhodes, J., An oral preparation to release drugs in the human colon. J. Clin. Pharmacol., 14 (1982) 405–408.

Digenis, G.A., The utilisation of short lived radio-nuclides in the assessment of formulation and in vivo

deposition of drugs. In Wilson, C.G., Hardy, J.G., Frier, M. and Davis, S.S. (Eds.), Radionuclide Imaging in Drug Research, Croom Helm, London, 1982, pp. 103–143.

Eckenhoff, B. and Yum, S.I., The osmotic pump: novel research tool for optimising drug regimens. Biomaterials, 2 (1981) 89–97.

Galeone, M., Nizzola, L., Cacioli, D. and Moise, G., In vivo demonstration of delivery mechanisms from sustained release pellets. Current Ther., Res., 29 (1981) 217–234.

Halls, J., Bowel content shift during normal defaecation. Proc. Roy. Soc. Med., 58 (1965) 859–860.

Higuchi, W.I., Ho, N.F.H., Park, J.Y. and Komiya, I., Rate-limiting steps and factors in drug absorption. In Prescott, L.F. and Nimmo, W.S., (Eds.), Drug Absorption, MTP Press, Lancaster, 1979, pp. 35–60.

Ho, N.F.H., Park, J.Y., Morozowich, W. and Higuchi, W.I., Physical model approach to the design of drugs with improved intestinal absorption. In E.B. Roche (Ed.), Design of Biopharmaceutical Properties through Prodrugs and Analogs, Am. Pharm. Ass., Washington, 1977, pp. 136–227.

Hunt, J.N. and Stubbs, D.F., The volume and energy content of meals as determinants of gastric emptying. J. Physiol. (Lond.), 215 (1975) 209–225.

Hunter, E., Fell, J.T., Calvert, R.T. and Sharma, H., In vivo disintegration of hard gelatin capsules in fasting and nonfasting subjects, Int. J. Pharm. 4 (1980) 175–183.

Hunter, E., Fell, J.T. and Sharma, H., A comparison of the behaviour of tablet and capsule formulations in vivo. J. Pharm. Pharmacol., 33 (1981) 617–618.

Hunter, E., Fell, J.T. anad Sharma, H., The gastric emptying of pellets contained in hard gelatin capsules. Drug Develop. Ind. Pharm., 8 (1982) 751–757.

Kelly, K.A., Motility of the stomach and gastroduodenal junction. In L.R. Johnson (Ed.), Physiology of the Gastrointestinal Tract, Vol. 1, Raven Press, New York, 1981, pp. 393–410.

Kelly, J.D., Choice of radionuclides for scintigraphy. In Wilson, C.G., Hardy, J.G., Frier, M. and Davis, S.S. (Eds.), Radionuclide Imaging in Drug Research, Croom Helm, London, 1982, pp. 39–59.

Mayersohn, M., Physiological factors that modify systemic drug availability and pharmacologic response in clinical practice. In Blanchard, J., Sawchuk, R.J. and Brodie, B.B. (Eds.), Principles and Perspectives in Drug Bioavailability, Karger, Basel, 1979, pp. 211–273.

Read, N.W., Cammack, J., Edwards, C., Holgate, A.M., Cann, P.A. and Brown, C., Is the transit time of a meal through the small intestine related to the rate at which it leaves the stomach? Gut, 23 (1982) 824–828.

Sjogren, J. and Bogentoft, C., How useful is enteric coating to improve drug delivery? In Bundgaard, H., Hansen, A.B. and Kofod, H. (Eds.), Optimisation of Drug Delivery, Munksgaard, Copenhagen, 1982, pp. 53–62.

Szurszewski, J.H., A migrating electric complex of the canine small intestine. Am. J. Physiol., 217 (1969) 1757–1763.

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

Wagner, J.G., Veldkamp, W. and Long, S., Correlation of in vivo with in vitro disintegration times of enteric coated tablets. J. Am. Pharm. Ass. (Sci. Edn), 47 (1958) 681–685.

Weisbrodt, N.W., Motility of the small intestine. In L.R. Johnson (Ed.), Physiology of the Gastrointestinal Tract, Vol. 1, Raven Press, New York, 1981, pp. 411–443.

Wilson, C.G., Parr, G.D., Kennerley, J.W., Taylor, M.J., Davis, S.S., Hardy, J.G. and Rees, J., Scintigraphic and pharmacokinetic studies on a sustained release aspirin product (Zorprin). Int. J. Pharm., 18 (1984) 1–8.