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Scintigraphic and pharmacokinetic assessment of a multiparticulate sustained release formulation of diltiazem

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Summary

The in vivo behaviour of a sustained release multiparticulate form of diltiazem (240 mg) has been evaluated by gamma scintigraphy in eight subjects under fasting or fed conditions. The gastric emptying of the pellet formulation was significantly influenced by the presence of food. Transit through the small intestine was unaffected by food and in the majority of cases, the formulation reached the caecum about 3–4 h after leaving the stomach. Post-prandial administration of the sustained release pellet formulation did not affect the bioavailability of the drug. The type of oral formulation (i.e. solution or pellets) appeared to affect the rate, but not the extent, of absorption with the relative bioavailability (pellets to solution) being greater than 90%.

Introduction

Diltiazem is an orally active calcium channel blocking agent known to be effective and well-tolerated in the prophylaxis and treatment of angina. It is typically administered three to four times daily in the form of an immediate release formulation. Recently, attempts have been made to develop sustained release (SR) preparations with extended clinical effects and a reduced dosing frequency (Barth, 1988; Geoghegan et al., 1988; Murata et al., 1989; Pool et al., 1989).

The important features for the rational design of a SR formulation of diltiazem are comparable bioavailability to the conventional dosage form, minimum peak-to-trough variation in multiple dose studies and the absence of any food effects on bioavailability. Reported half-lives for the elimination phase of diltiazem have ranged from 2 to 7 h (average about 4.5 h) (Chaffman and Brogden, 1985). Previous studies have also reported a reduced absorptive capacity for diltiazem from the distal regions of the gastrointesti-

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nal tract (Maccari, M., personal communication). Therefore, in order to achieve an optimal SR formulation of the drug, it was important to locate the best compromise between prolongation of release and subsequent bioavailability. With this in mind, a multiparticulate SR pellet formulation of diltiazem was designed with largely pH-independent release properties over an 8 h time period. Preliminary pharmacokinctic studies showed satisfactory compliance with the clinical objectives. The aims of this present study were to verify the extent of drug absorption and to assess the effect of food on the gastrointestinal transit of the pellet formulation.

The non-invasive technique of gamma scintigraphy has been routinely used to follow the gastrointestinal transit and release characteristics of a variety of oral dosage forms (Davis et al., 1986a, 1987, 1988, 1990; Digenis et al., 1990; Hardy et al., 1991; Wilding et al., 1991). Such studies not only provide an insight into the fate of the delivery system and its integrity, but also allow the relationship between in vivo performance and resultant pharmacokinetics to be examined; a subject now known as pharmacoscintigraphy. In this work we report on the scintigraphic and pharmacokinetic assessment of a multiparticulate SR formulation of diltiazem.

Materials and Methods

Preparation of placebo and diltiazem pellets

The SR multiparticulate formulation of diltiazem was manufactured using conventional nonpareil technology which involved the building up of a drug layer on sugar cores. The release properties of the system were controlled by the subsequent application of an inert polymeric film coat. Recent studies have questioned the validity of using ion-exchange resin beads as model dosage forms (Devereux, 1987) for gastrointestinal transit studies. Commercially available SR pellet formulations tend to be hydrophobic due to the presence of the film coat, whilst the ion-exchange resin beads are hydrophilic. To overcome this difficulty, we have developed a model placebo pellet formulation which mimics exactly the physical characteristics of the drug-containing units. These were manufactured under the same conditions as the diltiazem pellets except that the drug was replaced by Amberlite IR-410 resin (BDH, Poole, Dorset) ($< 90\ \mu m$).

Radiolabelling of the placebo pellets

Cores containing Amberlite IR-410 were labelled with ^{99m}Tc by soaking in a saline solution of sodium pertechnetate ($Na^{99m}TcO_4$) (CIS (U.K.) Ltd). The cores were washed and dried in a fan oven at 60 °C. The tenacious nature of the binding to resins is well documented (Theodorakis et al., 1982). A maximum of 1.8% of the radionuclide has been found to leach out over a 2 h period for Amberlite IRA-410 resin. However, strong in vitro binding does not always imply that the tracer will remain bound in vivo. ^{99m}Tc, in the form of the pertechnetate, is rapidly absorbed from the small intestine and accumulates in the thyroid and bladder of the volunteers (Early et al., 1975). Therefore, by monitoring the thyroid occasionally during imaging it was possible to confirm the integrity of the labelling procedure.

250 mg of labelled pellets were weighed out and mixed with 490 mg of drug pellets (containing 240 mg diltiazem hydrochloride) prior to filling into a size OO hard gelatin capsule. The capsules had a disintegration time of less than 5 min in 0.1 M hydrochloric acid, as measured by the standard BP test. Each filled capsule had an activity of 4 MBq ^{99m}Tc at the time of dosing.

Radiolabelling of drug solutions

60 mg of diltiazem hydrochloride was weighed out into a tared glass scintillation vial. Just prior to dosing the powder was added to 100 ml of water and the vial carefully rinsed to remove the final traces of drug.

An aqueous solution of ^{99m}Tc-labelled diethylenetriaminepentaacetic acid (DTPA) was prepared using sodium [^{99m}Tc]pertechnetate solution and a DTPA kit (CIS Biomedical Products, High Wycombe). Each drug solution was radiolabelled with a small amount of the DTPA solution to an activity of 4 MBq ^{99m}Tc at the time of dosing.

Study design

Eight volunteers (four male and four female) were recruited from the undergraduate and postgraduate populations of the university. The subjects had a mean age of 20 years (range 19–22 years), mean weight 70 kg (range 58–84 kg) and mean height 1.78 m (range 1.68–1.89 m). All the subjects were examined by a physician before the study and were judged to be in good health on the basis of medical history, physical examination, routine laboratory data and standard electrocardiogram.

The study was approved by the Ethics Committee of the University of Nottingham, and the trial was conducted in accordance with the Declaration of Helsinki Guidelines for Ethics in Research, and the Association of British Pharmaceutical Industry guidelines for medical experiments in non-patient healthy volunteers. Approval for the administration of radiolabelled formulations was obtained from the Department of Health, London.

The nature of the trial was explained both verbally and in writing to the volunteers. Each subject provided written consent to participate in the study. No alcohol was permitted for 24 h prior to ingestion of the test formulation or during the 24 h study period.

The study consisted of three administration periods of 1 day duration separated by a minimum period of 1 week. The subjects received on the different occasions one of the following treatments: (i) the SR multiparticulate diltiazem formulation (240 mg) after an overnight fast; (ii) the SR multiparticulate diltiazem formulation (240 mg) after a heavy breakfast; (iii) a solution of diltiazem (60 mg) given orally as the immediate release dosage form to obtain standard pharmacokinetic parameters. Each formulation was labelled with 4 MBq of ^{99m}Tc as described previously.

Dosing details

After an overnight fast (from 11.00 p.m.), the volunteers reported to the clinical unit at 7.30 a.m. On arrival, a blood sample (10 ml) was taken from each volunteer for baseline reference of plasma diltiazem concentration. The pellet formulation, labelled with ^{99m}Tc, was administered with 100 ml of water either after an overnight fast or a standard breakfast, in accordance with a randomised design. The cross-over part of the investigation was conducted 7 days later. On a third occasion, all the volunteers received an oral solution of the drug, labelled with ^{99m}Tc DTPA.

Each volunteer drank approx. 100 ml of orange juice 2 h post-dose. Lunch was provided at 3 h post-dose and dinner at 9 h post-dose. Details of all standard meals are provided in Table 1.

TABLE 1

Standard meals for volunteers

Breakfast
Fried egg
Two slices of bacon
Sausage
Two slices of toast
Butter and preserve
Orange juice
Tea or coffee
Lunch
Two medium filled rolls (not cheese)
Apple
Orange juice
Dinner
Orange juice
Prawn cocktail
Steak, chips and vegetables
Cheesecake
Tea or coffee

Scintigraphic details

Anatomical markers, containing 0.1 MBq ^{99m}Tc, were taped to the skin, anteriorly and posteriorly, over the liver and to the right of the stomach. Anterior and posterior scintigraphic images, each of 60 s duration, were taken at frequent intervals throughout the study period, using a gamma camera (General Electric Maxicamera, Type II) having a 40 cm field of view. The camera was fitted with a low-energy (140 keV) parallel-hole collimator. Images were recorded on a computer and stored on magnetic tape for analysis at a later stage.

Regions of interest (ROI) were drawn around the image of the stomach, using an electric cur-

sor. Stomach position for each successive view was identified by reference to both the external marker and the preceding images. To assess the background counts, a second ROI was drawn on each image away from the main area of activity. At later time points, a third ROI was drawn to identify arrival of the pellets at the caecum. The data were corrected for background activity and radioactive decay. The error due to variation in depth was minimized by the calculation of the geometric mean of the corresponding anterior and posterior views (Tothill et al., 1978).

Blood sampling and assay details

Blood samples were taken via an indwelling cannula, irrigated with heparin and collected in heparinised glass tubes. The blood was centrifuged at 3000 rpm for 15 min and the plasma transferred to labelled siliconised tubes prior to freezing at $-20\,^{\circ}$C. Plasma concentration of diltiazem and the primary metabolite, desmethyldiltiazem, were assayed, using the standard verified procedure previously described by Verghese et al. (1983).

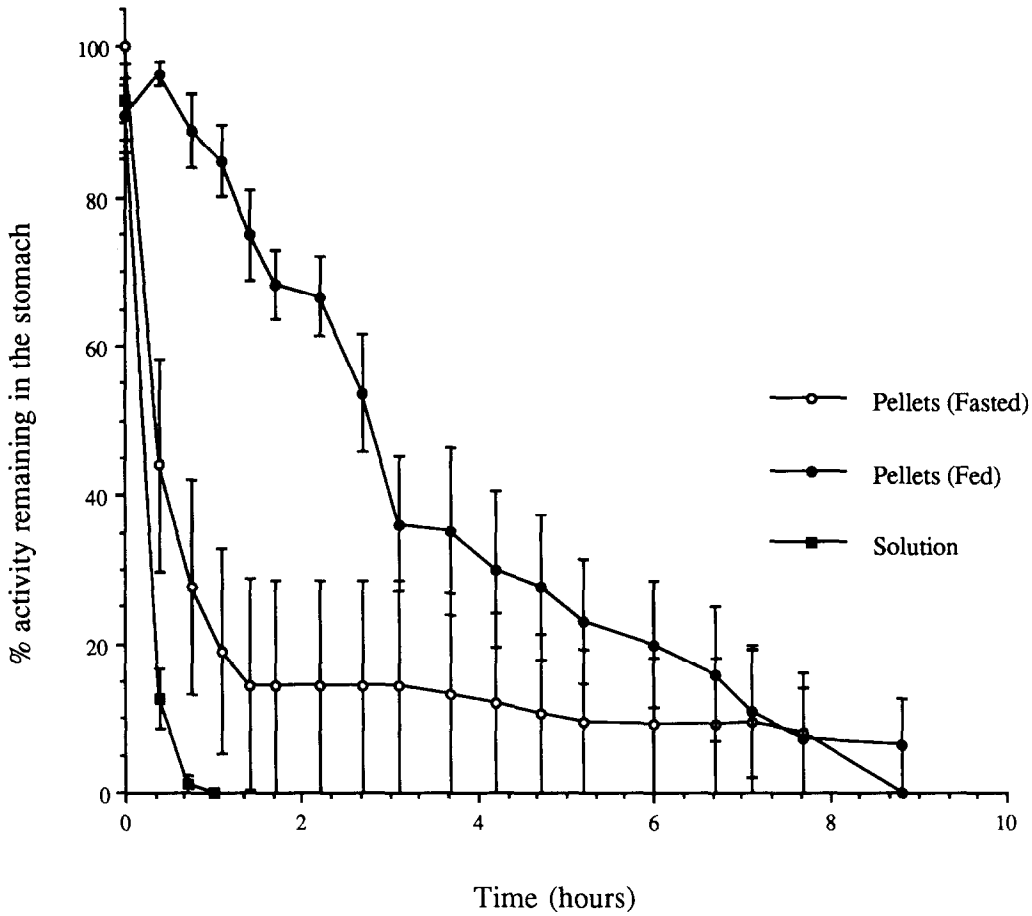

Fig. 1. Mean gastric emptying profiles following administration of the pellet and solution formulations to either fasted or fed subjects ($\pm$ SE).

TABLE 2

Gastric emptying data for the pellet formulation administered to the fasted volunteers — % activity remaining in the stomach (n = 7)

Time (h)	1	2	3	4	5 [a]	6	7	8	Mean	SE
0.0	100	100	100	100	–	100	100	100	100	0
0.4	60	24	4	39	–	81	100	0	44.0	14.4
0.75	58	9	0	0	–	27	100	0	27.7	14.5
1.1	24	8	0	0	–	32	100	0	19.1	13.9
1.4	0	0	0	0	–	1	100	0	14.5	14.3
1.7	0	0	0	0	–	0	100	0	14.3	14.3
2.2	0	0	0	0	–	0	100	0	14.3	14.3
2.7	0	0	0	0	–	0	100	0	14.3	14.3
3.1	0	0	0	0	–	0	100	0	14.3	14.3
3.7	0	0	0	0	–	0	94	0	13.4	13.4
4.2	0	0	0	0	–	0	85	0	12.1	12.1
4.7	0	0	0	0	–	0	75	0	10.7	10.7
5.2	0	0	0	0	–	0	67	0	9.6	9.6
6.0	0	0	0	0	–	0	64	0	9.1	9.1
6.7	0	0	0	0	–	0	64	0	9.1	9.1
7.1	0	0	0	0	–	0	67	0	9.6	9.6
7.7	0	0	0	0	–	0	57	0	8.1	8.1
8.8	0	0	0	0	–	0	0	0	0	0

[a] Subject 5 was unable to participate in this leg of the study due to a bout of influenza.

TABLE 3

Gastric emptying data for the pellet formulation administered to the fed volunteers — % activity remaining in the stomach (n = 7)

Time (h)	1	2	3	4	5 [a]	6	7	8	Mean	SE
0.0	67	84	100	99	84	100	86	100	90.9	4.8
0.4	90	100	100	100	100	99	93	93	96.4	1.6
0.7	100	83	63	91	87	91	100	94	88.9	4.9
1.0	97	76	63	86	84	96	82	94	84.9	4.7
1.4	89	70	55	54	82	96	79	82	75.0	6.1
1.8	82	62	60	50	70	80	79	65	68.3	4.6
2.1	80	61	55	46	70	86	74	65	66.7	5.4
3.1	68	53	25	25	68	78	66	61	53.7	7.9
3.6	59	35	18	23	69	67	51	0	36.1	9.1
4.0	69	33	26	0	37	73	45	0	35.1	11.2
4.6	60	24	13	0	33	67	47	0	30.1	10.6
5.2	63	23	9	0	30	56	43	0	27.7	9.9
6.0	56	18	9	0	33	35	43	0	23.0	8.3
6.4	60	17	0	0	40	26	37	0	20.0	8.6
7.1	61	13	0	0	29	0	37	0	15.9	9.1
7.7	63	13	0	0	0	0	0	0	10.9	8.9
8.7	50	0	0	0	0	0	0	0	7.1	7.1
9.6	45	0	0	0	0	0	0	0	6.4	6.4
10.1	40	0	0	0	0	0	0	0	5.7	5.7
11.0	46	0	0	0	0	0	0	0	6.6	6.6
12.0	50	0	0	0	0	0	0	0	7.1	7.1
12.6	43	0	0	0	0	0	0	0	6.1	6.1

[a] Data excluded from mean results.

Results and Discussion

Representation of the scintigraphic data

The data for this study are expressed as the time for 50% of the activity to leave the stomach, and the time for 50% of the activity to arrive at the caecum. The overlying of the different regions of activity, within the coiled anatomy of the small intestine (SI), prevents an accurate quantification of the units in this region. Small intestinal transit (SIT) has, therefore, been calculated by subtracting the $T_{50\%}$ for gastric emptying (GE) from the corresponding value for colon arrival.

The results are presented in Tables 2–6. Mean GE profiles for the three stages of the investigation are provided in Fig. 1.

Gastric emptying

Simple solutions have been shown to empty rapidly from the stomach in either an exponential fashion (Hunt and Macdonald, 1954) or as a linear function of the square root of the liquid volume remaining in the stomach (Hopkins, 1966). By either process liquid emptying should be rapid with a range of 5–50 min (Bechgaard, 1982). The results reported here, 9 ± 1 min, are in agreement with this suggestion.

The half-time for the GE of the pellets was affected by the size of the administered meal; the mean time was 91 ± 65 min after an overnight fast and 232 ± 47 min for the subjects after a heavy breakfast. These values were in accord with previous studies on the GE of multiparticulate formulations (Davis, 1983; Khosla and Davis, 1987; Davis et al., 1987; Khosla et al., 1989).

The emptying of the pellet formulation from the fasted stomach was very rapid and occurred in an exponential manner (Fig. 1). However, some individuals (e.g. volunteers 3 and 8) exhibited

TABLE 4

Gastric emptying values ($T_{50\%}$) for the pellet and solution formulations (min)

Subject	Pellets (fasted)	Pellets (fed)	Solution (fasted)
1	55	480	10
2	20	190	15
3	10	150	8
4	25	120	6
5 [b]	[a]	230	10
6	35	310	5
7	480	190	9
8	15	185	10
Mean	91	232	9
SE	65.0	47.0	1.2
Sample no.	7	7	7

[a] Subject 5 was unable to participate in the second part of the investigation (pellet formulation after an overnight fast) due to a bout of influenza.
[b] Data excluded from mean results.

TABLE 5

Small intestinal transit values ($T_{50\%}$) for the pellet and solution formulations (min)

Subject	Pellets (fasted)	Pellets (fed)	Solution (fasted)
1 [c]	105	[b]	145
2	340	410	365
3	300	290	192
4	245	240	184
5 [c]	[a]	[b]	180
6	115	190	190
7 [c]	140	[b]	371
8	155	175	130
Mean	231	261	212
SE	42.5	42.4	39.9
Sample no.	5	5	5

[a] Subject 5 was unable to participate in the second part of the investigation (pellet formulation after an overnight fast) due to a bout of influenza.
[b] No pellets arrived at the caecum during the imaging period.
[c] Data excluded from mean results.

TABLE 6

Colon arrival values ($T_{50\%}$) for the pellet and solution formulations (min)

Subject	Pellets (fasted)	Pellets (fed)	Solution (fasted)
1	160	> 550	155
2	360	600	380
3	310	440	200
4	270	360	190
5	[a]	> 550	190
6	150	500	195
7	620	> 550	380
8	170	360	140

[a] Subject 5 was unable to participate in the second part of the investigation (pellet formulation after an overnight fast) due to a bout of influenza.

almost a bolus emptying of the pellets and it is possible that disintegration of the hard gelatin capsule may have only occurred in the proximal SI in these cases. This rapid emptying can be ascribed to the contractions that take place during the physiological mechanism known as the migrating myoelectric complex (MMC). In the majority of the volunteers, administration of the encapsulated pellets appears to have taken place during either phase 2 or 3 of the contractions and this resulted in the very rapid emptying profile observed. However, administration during phase 1 of the MMC, when there are no contractions, presumably explains the slightly slower emptying reported for volunteer 1, with a possible lag phase during which the pellets may disperse passively in the stomach.

In the case of volunteer 7, there appeared to be almost total gastric stasis and little emptying of the pellets from the stomach after administration in the fasted state. The $T_{50\%}$ for the pellets was 480 min, much longer than that reported for the same formulation administered after a heavy breakfast (190 min). This result is not without precedent (Davis, unpublished findings) but no explanation is known. There was no reason to believe that the subject had failed to follow the fasting requirement and even if she had, one would have expected to have seen a $T_{50\%}$ close to that for the fed state.

In the fed volunteers, a lag phase was observed before the commencement of emptying of the pellets from the stomach. This is a common occurrence and is believed to reflect a redistribu-

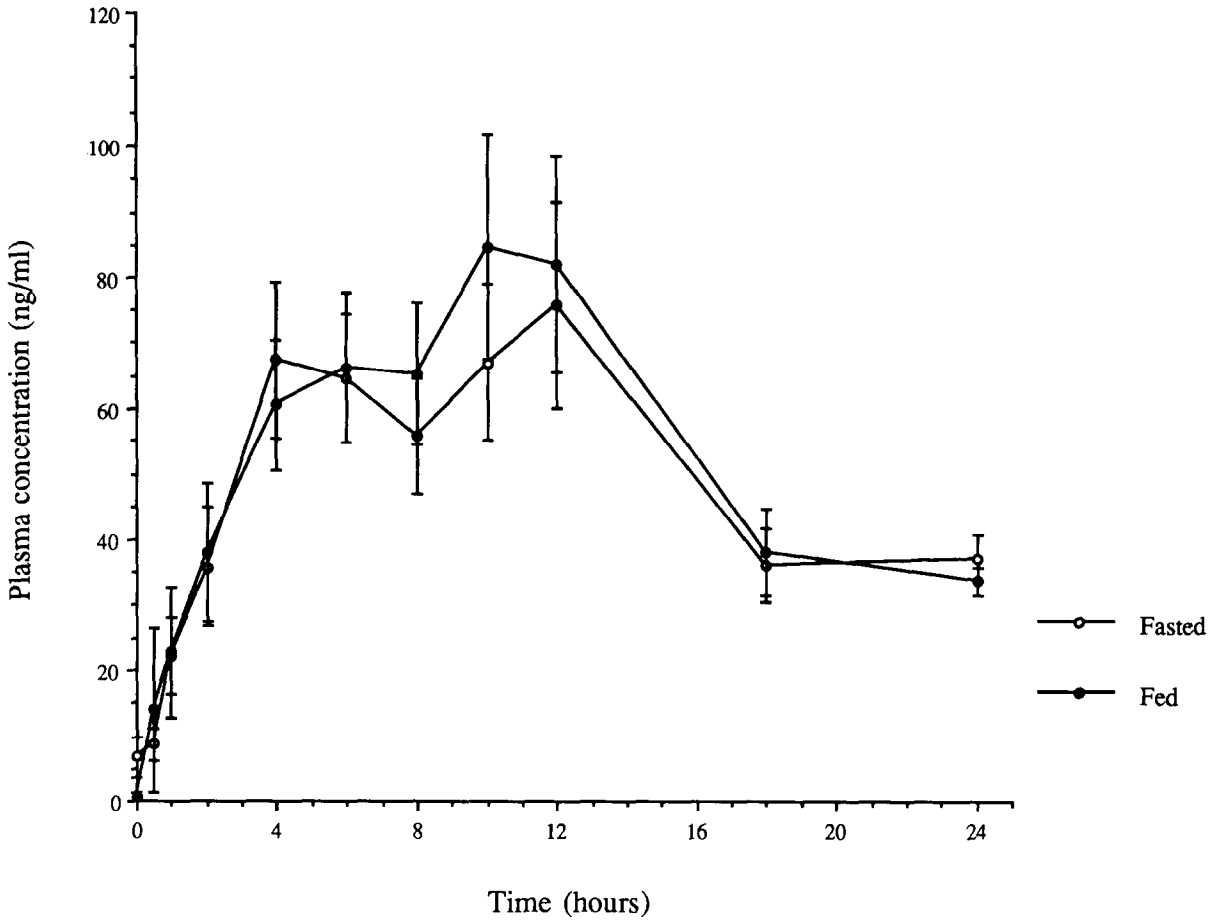

Fig. 2. The effect of food on the mean plasma concentration (±SE), following administration of a sustained release diltiazem (240 mg) pellet formulation.

tion of pellets mixed with the food from the quiet fundus to the active antrum, and the process where solid food is converted into chyme. Pellets initially remained in the upper half of the stomach, dispersed in the food (O'Reilly et al., 1987) and then tended to become spread throughout the stomach (Hunter et al., 1980), presumably as the food was redistributed. In a number of subjects, the pellets exhibited an almost linear pattern of gastric emptying after the lag phase (volunteer 2, 4 and 6). This linear profile is the characteristic emptying pattern of solid food (Tothill et al., 1978) and indicates that the pellets may have become mixed with at least some food prior to the commencement of emptying (O'Reilly et al., 1987).

It is interesting to note, however, that not all the subjects displayed the typical linear emptying profile expected in the fed state. The administration of an encapsulated pellet system, after a very heavy breakfast (5000 kJ), has been shown to be characterised by markedly enhanced gastric residence of the sub-units (Marvola et al., 1989). The authors reported that although small portions of the pellets emptied with the solid phase of the food, the majority remained in the stomach for up to 6–8 h prior to the action of the clearance process of the MMC; the 'housekeeper wave'. Such results were observed for volunteer 1 in this study, with a large proportion of the pellets remaining in the stomach for up to 6 h.

In the remaining subjects, the pellets appeared

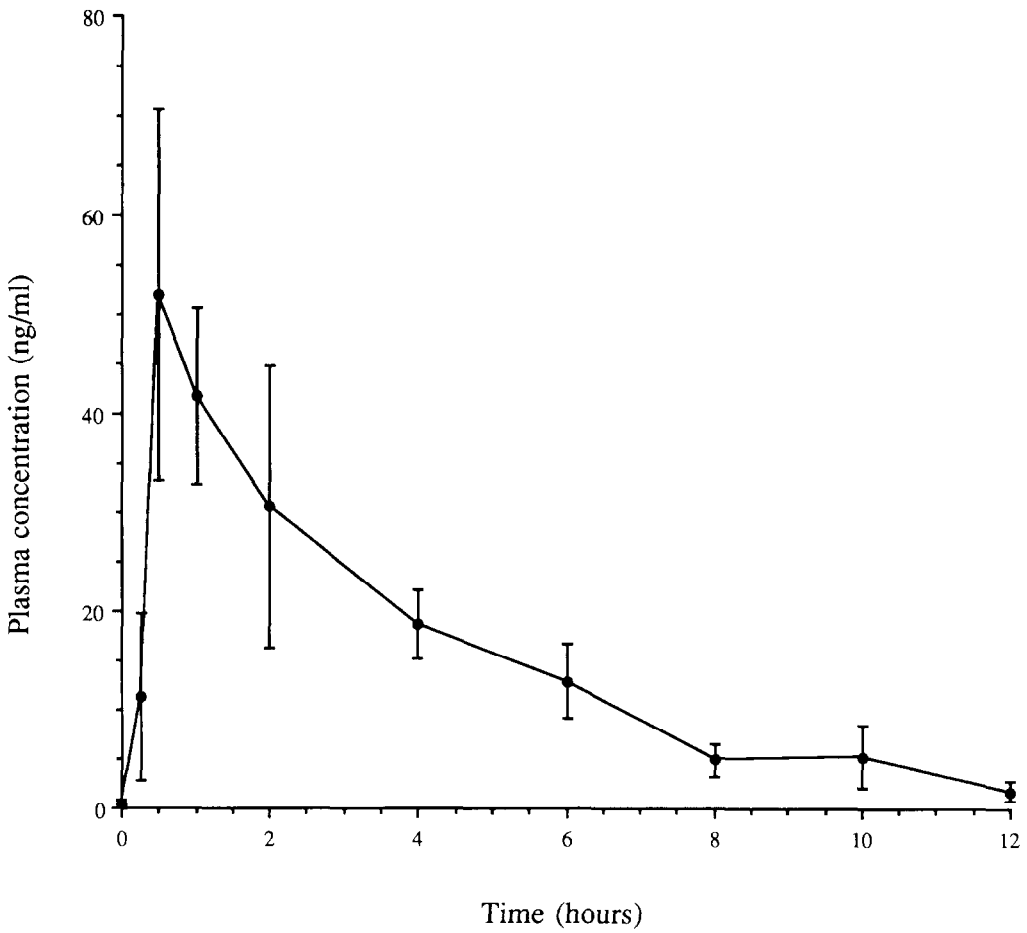

Fig. 3. Mean plasma concentration (±SE) following administration of an oral solution of diltiazem (60 mg).

TABLE 7

Pharmacokinetic parameters (mean ± SEM)

Parameter	Pellets (fasted)	Pellets (fed)	Solution
AUC (h ng ml^{-1})	1229.2 ± 183.4	1155.2 ± 233.5	219.3 ± 55.1
C_{max} (ng/ml)	82.6 ± 14.1	91.8 ± 17.9	67.9 ± 16.8
T_{max} (h)	7.4 ± 1.4	9.7 ± 1.1	0.9 ± 0.2

Student's *t*-test (paired) on pharmacokinetic parameters

	t	sig
AUC pellets fasted vs AUC pellets fed	−0.2416	0.817 (ns)
C_{max} pellets fasted vs C_{max} pellets fed	−0.4784	0.649 (ns)
T_{max} pellets fasted vs T_{max} pellets fed	−1.4292	0.203 (ns)

ns, not significant.

to empty from the stomach as a series of small discrete boluses (Hunter et al., 1982). Similar results for the GE of model pellet systems have been reported by other groups (Devereux, 1987). It would appear that pellets can leave the stomach during fed activity but not always mixed with the food as previously believed. Work is currently being performed to elucidate further the emptying mechanism of pellets from the fed stomach.

Small intestinal transit

Previous studies have indicated that the transit of different pharmaceutical dosage forms through the SI is largely independent of feeding conditions and physical properties of the system (Davis et al., 1986b). The average SI transit times in this study were approx. 3–4 h and these are in good accord with those reported previously.

The movement of dosage forms from the ileum to the caecum across the ileo-caecal junction (ICJ) is a poorly understood event. The pellets appeared to regroup at the ICJ before entering and spreading in the colon. Similar results have been noted previously for multiple unit formulations (Davis et al., 1986c; Khosla et al., 1989). This stagnation effect is believed to be related to the suggested reservoir function of the terminal ileum (Spiller et al., 1987).

Pharmacokinetic interpretation and assessment of bioavailability

The mean plasma concentration profiles are presented in Figs 2 and 3 for pellet and solution formulations, respectively. T_{max} (time of peak concentration), C_{max} (peak height concentration) and AUC (area under the plasma concentration-time curve) are reported in Table 7.

A typical blood-level time profile for the SR pellet formulation showed an initial rise in plasma concentration followed by a plateau period and then a gradual decline at later time points. A minimum plasma concentration of about 40 ng/ml (Hosada, 1978) is considered necessary for patients with angina to experience symptomatic improvement when treated with diltiazem and therefore satisfactory plasma levels were reached in about 3 h and remained for about 18 h after dosing. It is therefore possible, if the response curve matches the plasma profile, that a constant therapeutic response could be obtained with once daily delivery, which was the primary objective of the formulation.

The bioavailability of the SR formulation, as measured by AUC, appears to be independent of food (Table 7), however, there does appear to be a wide variation in the data. Previous experience has shown that diltiazem is subject to significant first-pass metabolism and therefore, large inter-subject differences in bioavailability, plasma concentrations, clearance and plasma half-life may exist due to the differing first-pass metabolic capacities (polymorphism) (Zelis and Kinney, 1982; Hermann et al., 1983). The absolute bioavailability is approx. 40% and is again affected by first-

pass effects. The type of oral formulation (i.e. solution or SR pellets) appears to affect the rate, but not the extent, of absorption with the relative bioavailability (pellets to solution) being greater than 90%.

The significance of the apparent double peak in the mean plasma profile following administration of the SR pellets is difficult to gauge. Previous work has shown a similar effect following the administration of an ibuprofen SR formulation (Wilson et al., 1989). In this case, the secondary peak was ascribed to a loss of integrity of the hydrophilic matrix after about 12–14 h, coupled with the high absorptive capacity for that drug in the ascending colon. In the present study, it is possible that disruption of the device led to the elevated peak at later time points or more likely that the drug is subject to some form of enterohepatic recirculation (Meshi et al., 1971).

The prolonged gastric residence time observed for volunteer 7 in the fasted state had no significant effect on the plasma concentration-time profile, indicating that drug release was not impaired by gastric stasis and that released drug could still be absorbed.

Conclusions

The gastric emptying of the SR pellet formulation of diltiazem was significantly influenced by the presence of food. In the fasted volunteers, the sub-units tended to empty as a single bolus from the stomach, preventing any spreading of material through the SI. In the majority of cases, the presence of food led to a gradual, more predictable emptying of pellets from the stomach and the subsequent spreading of the sub-units in the intestines. Transit through the SI was unaffected by food and in the majority of cases, the formulation reached the caecum about 3–4 h after leaving the stomach. The bioavailability of the drug from the SR pellet formulation was unaffected by food. The type of oral formulation (i.e. solution or SR pellets) appears to affect the rate, but not the extent, of absorption with the relative bioavailability (pellets to solution) being greater than 90%.

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