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The role of gastric emptying in the absorption and metabolism of nifedipine given in a modified release pellet formulation

I.R. Wilding [a], R.A. Sparrow [b], S.S. Davis [a,c] and R.J. Horton [d]

[a] *Pharmaceutical Profiles Ltd, 2 Faraday Building, Highfields Science Park, University Boulevard, Nottingham NG7 2QP (UK),*
[b] *Department of Human Morphology, Queen's Medical Centre, Clifton Boulevard, Nottingham NG7 2UH (UK),*
[c] *Department of Pharmaceutical Sciences, Nottingham University, University Park, Nottingham NG7 2RD (UK)*
and [d] *SmithKline Beecham Pharmaceuticals, Mundells, Welwyn Garden City AL7 1EY (UK)*

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Summary

Plasma drug concentrations after a single oral administration of a modified release pellet formulation of nifedipine (20 mg) were measured in 18 healthy male volunteers after a light breakfast. The distribution of the radiolabelled pellets in the gastrointestinal tract was followed by gamma scintigraphy. The time for 50% gastric emptying ranged from 74 to 254 min (median 127 min), which is in good agreement with values reported for other multiparticulate formulations. In some subjects, periods of gastric stasis were observed, which may have been due to the inhibitory effect of nifedipine on gastric muscle contraction. Substantial spreading of the pellets occurred in both the small intestine and the colon, although in the majority of cases there was re-grouping at the ileo-caecal junction, prior to entry into the large bowel. The mean ($\pm$SD) C_{max} was 36 ± 16 ng/ml (range 8.4–70.0 ng/ml), achieved 2–12 h post-dose (median t_{max} 3 h). The pharmacokinetic data were consistent with twice daily dosage. Extended gastric residence may be an advantage for a modified release formulation. However, for nifedipine, a drug which undergoes a significant first-pass metabolism, slow gastric emptying may lead to a reduced systemic bioavailability as a result of the gradual presentation of the drug to enzymes on first pass through the intestine and liver.

Introduction

Nifedipine is a calcium channel antagonist known to be an effective and relatively well tolerated treatment for stable, variant and unstable angina, mild to severe hypertension and Raynauds phenomenon (Sorkin et al., 1985). Following intravenous administration, its pharmacokinetics can be described by a biexponential function with a terminal elimination half-life of 2 h (Foster et al., 1983). Nifedipine is extensively biotransformed to inactive metabolites, and its clearance is primarily due to hepatic and intestinal metabolism and subsequent excretion (Chung et al., 1987). Although the drug is almost completely absorbed from the gastrointestinal tract,

Correspondence: I.R. Wilding, Pharmaceutical Profiles Ltd, 2 Faraday Building, Highfields Science Park, University Boulevard, Nottingham NG7 2QP, U.K.

oral bioavailability ranges from 45 to 68% because of significant first-pass metabolism (Foster et al., 1983; Raemsch and Sommer, 1983; Kleinbloesem et al., 1984).

Conventional formulations of nifedipine must be dosed either twice daily (tablet) or three times daily (capsule). Subsequent drug absorption is rapid and this, coupled with the short elimination half-life, can result in significant fluctuations in plasma drug concentrations. This variability is considered to be associated with the transient haemodynamic side effects, such as flushing and tachycardia, observed in some patients. By controlling drug input with a modified release dosage form, plasma drug concentrations may be maintained at the desired level with minimal fluctuations. This has the potential advantage of providing a prolonged therapeutic effect and a reduced incidence of side effects (Pabst et al., 1986).

The aim of the present study was to assess the gastrointestinal transit properties of a modified release pellet formulation of nifedipine (Coracten®, based on Spansule® technology), using the technique of gamma scintigraphy, in relation to its systemic bioavailability. The non-invasive technique of gamma scintigraphy has been used to follow the in vivo performance of a variety of oral dosage forms (Davis et al., 1988; Digenis et al., 1990; Hardy et al., 1991; Wilding et al., 1991a). Such studies not only provide an insight into the in vivo behaviour of the dosage form, but also enable the distribution of the delivery system to be related to drug absorption, or other pharmacokinetic effects.

Materials and Methods

Dosage form preparation

Amberlite IR-120 beads (BDH Ltd, Poole, Dorset) were used as the model multiparticulate pellet formulation, as described previously by Hardy et al. (1985). The pellets were labelled by soaking in a solution of [^{111}In]indium chloride in 0.04 M hydrochloric acid. The cores were washed and dried in a fan oven at 60°C. The stability of the radiolabel was tested in vitro under conditions that simulated the extremes of gastrointestinal pH. No significant radioactivity was detected in the medium and the binding was considered to be stable. The labelled pellets were of the same particle size range (0.7–1.00 mm) and of similar density to the commercially available nifedipine cores (Coracten®, SmithKline Beecham Pharmaceuticals, Welwyn Garden City, U.K.).

70 mg of labelled placebo pellets were mixed with 190 mg of modified release nifedipine pellets (containing 20 mg of drug) and filled into a size 1 hard gelatin capsule. Each filled capsule had an activity of 1 MBq ^{111}In at the time of dosing.

Study design

The study was carried out in 18 male subjects (age range 19–24 years) who 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 was conducted in accordance with the Declaration of Helsinki Guidelines for Ethics in Research, and the Association of British Pharmaceutical Industry (ABPI) 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 informed consent to participate in the study. No alcohol was permitted for 24 h prior to ingestion of the test formulation nor during the 24 h study period.

Drug dosage

After an overnight fast (from midnight), the volunteers reported to the clinical unit at 07:00. A blood sample (10 ml) was taken from each volunteer as a control for the plasma nifedipine assay. The pellet formulation, labelled with ^{111}In, was administered with 150 ml of water, 30 min after a standard light breakfast. This consisted of two slices of toast, butter and preserve, 100 ml of orange juice followed by tea or coffee (1500 kJ). Lunch was provided at 4 h post-dose and dinner at 10 h post-dose. Fluids were allowed ad libitum after lunch.

Gamma scintigraphy

Anatomical markers, containing 0.05 MBq of ^{111}In, 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 every 15 min for the first 5 h of the study, every 30 min until dinner, and then every hour until the end of the study period. The gamma camera (General Electric Maxicamera II) had a 40 cm field of view and was fitted with a medium energy (300 keV) parallel-hole collimator. Images were recorded on a computer and stored on magnetic tape for analysis at a later stage.

Regions of interest were drawn around the position of the stomach. The 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 region of interest was drawn on each image away from the main area of activity. At later time points, an additional region of interest was drawn to identify arrival of the pellets at the caecum. Further manipulation of the data was carried out using a computer program which corrected for background activity and radioactive decay. In addition, the geometric mean of the counts was calculated (Tothill et al., 1978) to correct for anterior movement of the radiopharmaceutical which is a major problem in gastric emptying studies since the antrum lies more anterior than the fundus.

Blood sampling and drug assay

Blood samples were taken at 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 h post-dose through an indwelling cannula, irrigated with heparin and collected in heparinised glass tubes. The blood was centrifuged at 3000 rpm for 10 min and the plasma transferred under yellow light to labelled siliconised tubes prior to freezing at −80°C.

Plasma concentrations of nifedipine were measured by capillary gas-liquid chromatography with an electron capture detector (Tucker et al., 1985). All procedures involving the plasma samples were undertaken using precautions to prevent photo-decomposition of nifedipine. Linear calibration curves were obtained from 0 to 150 ng/ml. The lower limit of detection was 0.5 ng/ml and the lower limit of quantification was 1.0 ng/ml.

Values for C_{max} and t_{max} were obtained directly from the individual plasma drug concentration-time profiles. The area under the plasma drug concentration-time curve, up to the last measured time, AUC(0–12 h), was calculated using the linear trapezoidal rule. The measured AUC(0–12 h) represents approx. 94% of the AUC(0–∞) (Pabst et al., 1986) for this formulation and is therefore considered a good indicator of systemic bioavailability.

Results and Discussion

Gastrointestinal transit

Scintigraphic data 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 (Table 1). The overlapping of the different regions of activity, within the coiled small intestine, prevents accurate measurement in this region. Therefore, small intestinal transit was calculated by subtracting the $T_{50\%}$ for gastric emptying from the corresponding value for colon arrival. Areas under the gastric emptying curve are

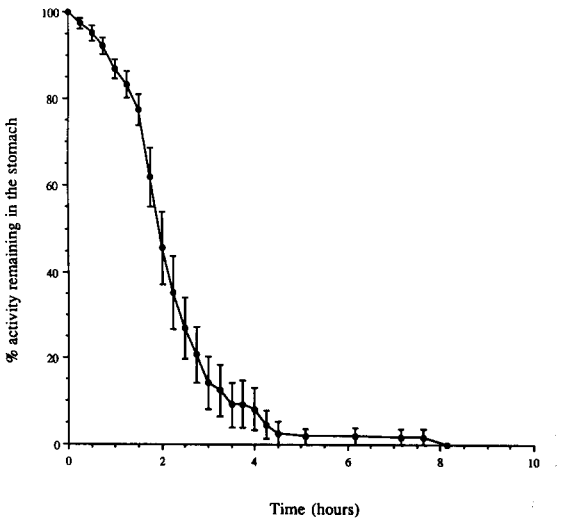

Fig. 1. Mean gastric emptying profile for the radiolabelled pellets ($n = 18$, SE).

also listed in Table 1. The mean gastric emptying profile of the pellet formulation is illustrated in Fig. 1. The gastrointestinal transit of the pellet formulation in a representative subject is indicated by a series of scintigraphic images (Fig. 2).

Multiparticulate formulations, such as Coracten®, which are composed of a myriad of pellets, have been shown to be capable of passing through the constricted pylorus leading to their gradual emptying from the stomach (Hunter et al., 1982). Such gradual emptying ensures that the subunits are well dispersed in the small intestine and minimises the opportunity for mucosal irritation (Bechgaard, 1982). However, the initial gastric dispersion of the subunits is dependent on the physiological condition of the stomach at the time of administration. The $T_{50\%}$ values (median 127 min), obtained from the gastric emptying profiles, were similar to those reported previously for pellet systems administered after a light breakfast (Davis, 1983; Davis et al., 1987).

TABLE 1

Area under the gastric emptying profile (AUC (% activity h)) and $T_{50\%}$ values for gastric emptying, small intestinal transit and colon arrival, following oral administration of a modified release pellet formulation of nifedipine

Volunteer no.	AUC (% activity h)	$T_{50\%}$ (min)		
	Gastric emptying	Gastric emptying	SI transit	Colon arrival
1	267	167	96	263
2	246	178	120	298
3	236	148	108	256
4	132	98	168	266
5	141	98	348	446
6	457	252	196	448
7	128	74	220	294
8	198	128	227	355
9	120	103	174	277
10	154	96	121	217
11	194	127	246	373
12	150	99	276	375
13	255	166	115	281
14	359	254	210	464
15	174	110	249	359
16	139	94	281	375
17	204	127	278	405
18	237	159	165	324
Mean	210	138	200	338
SD	88	52	72	73
Median	196	127	203	340

A lag phase was typically observed before the commencement of gastric emptying. This is a common occurrence and is considered to reflect a redistribution of food from the quiet fundus to the active antrum, and the conversion of solid food 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 spread throughout the stomach, presumably as the food was redistributed. In just under half of the subjects, the pellets exhibited an almost linear pattern of gastric emptying after the lag phase (Fig. 3). This is the characteristic emptying pattern of solid food (Tothill et al., 1978) and indicates that the pellets had become mixed with at least some food prior to the commencement of emptying. However, not all subjects displayed this emptying profile. In eight subjects, the pellets appeared to empty from the stomach as a series of small boluses (Fig. 4) (Hunter et al., 1982). Similar results for the gastric emptying of model pellet systems have been reported by Devereux et al. (1990) and Wilding et al. (1991b).

Two volunteers (nos 6 and 14) had periods of gastric stasis in which little or no solid material emptied from the stomach (Figs 5 and 6, respectively). The action of nifedipine on smooth muscle excitation is not specific to cardiac tissue and in vitro studies have shown that calcium channel blockers also inhibit gastric muscle contraction (Ochillo and Tsai, 1982). Nevertheless, nifedipine has been shown previously not to have an effect on the gastric emptying of solids and liquids in either normal volunteers or in patients following gastric surgery (Blackwell et al., 1981; Traube et al., 1985). Combined scintigraphic and manometric methods have also shown that nifedipine does not modify the gastric emptying of liquids or solids. However, antral motility was significantly inhibited whilst duodenal motility was increased (Santander et al., 1988). The authors suggested that these changes in gastroduodenal motility are insufficient to alter emptying.

Substantial dispersion of the pellets occurred in the small intestine and in the proximal and transverse colon at later time points (Fig. 2).

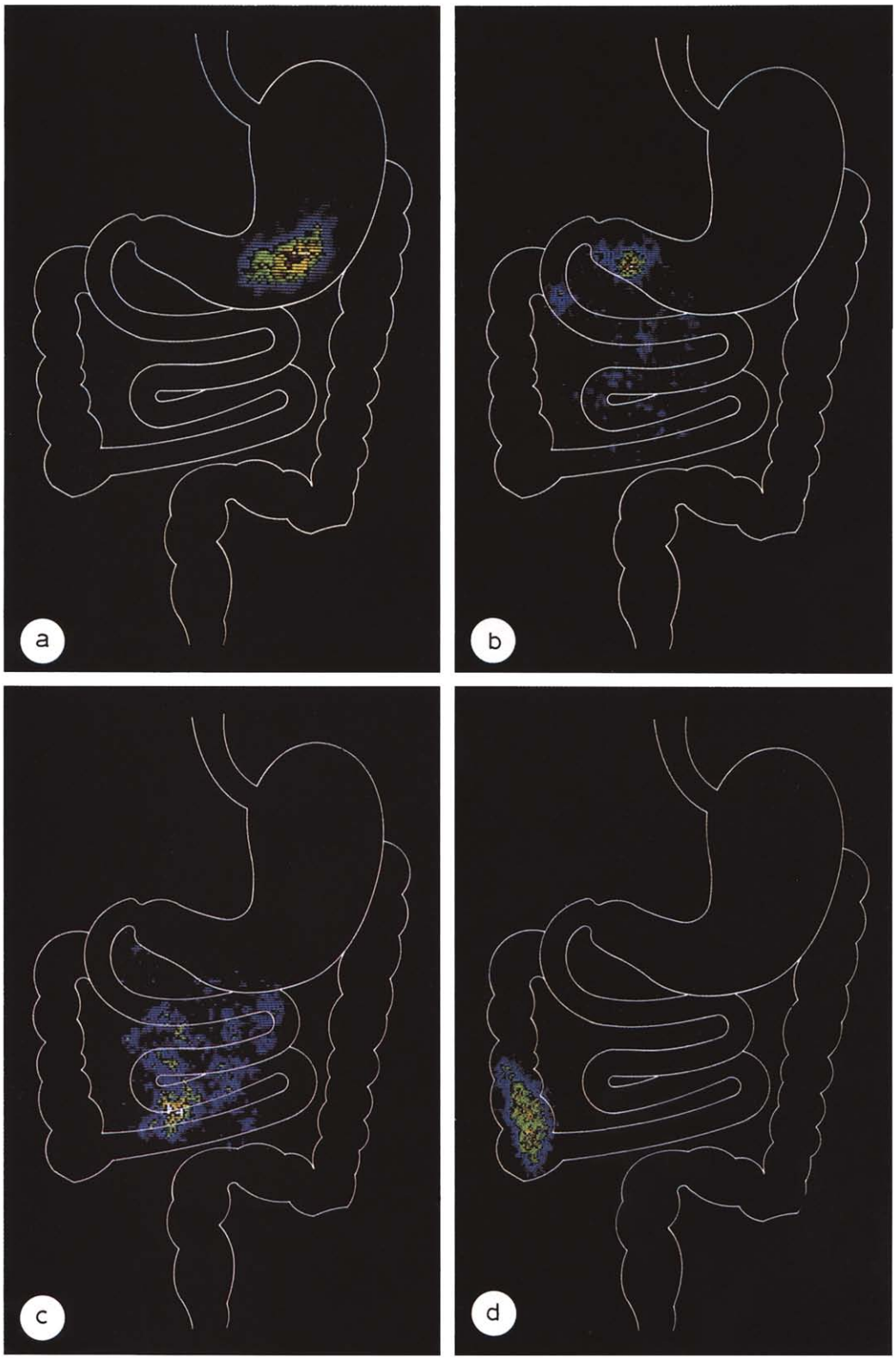

Fig. 2. Scintiphotos for subject 18 at (a) 0.75 h, (b) 2.7 h, (c) 3.25 h and (d) 7.09 h.

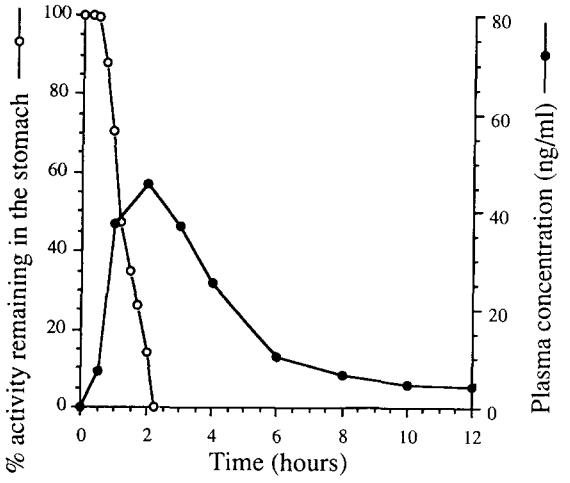

Fig. 3. Relationship between the gastric emptying curve and the plasma drug concentration-time profile for volunteer 7.

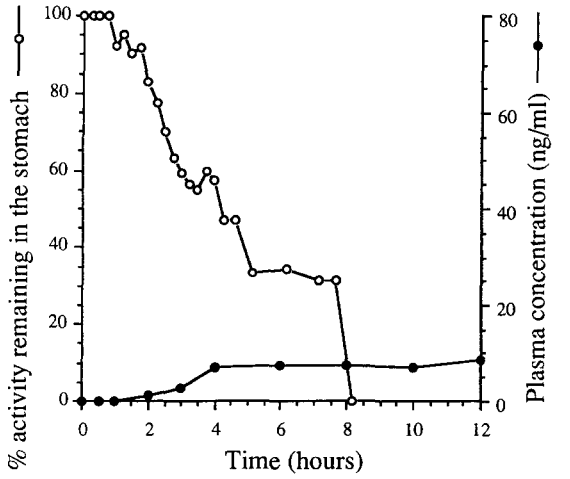

Fig. 5. Relationship between the gastric emptying curve and the plasma drug concentration-time profile for volunteer 6.

However, the pellets appeared to regroup at the ileo-caecal junction before entering the colon. Similar results have been noted previously for multiparticulate formulations (Davis et al., 1986; Wilding et al., 1991b). This stagnation effect is believed to be related to the suggested reservoir function of the terminal ileum (Spiller et al., 1987).

Pharmacokinetic assessment

Individual values for C_{max}, t_{max} and AUC(0–12 h) are listed in Table 2. A summary of the pharmacokinetic parameters is provided in Table 2. Following administration of the 20 mg nifedipine formulation, the mean C_{max} was 36.4 ± 16.3 ng/ml (range 8.44–69.95 ng/ml), achieved 2–12 h post-dose (median t_{max} 3 h). The minimal effective therapeutic plasma concentration level of

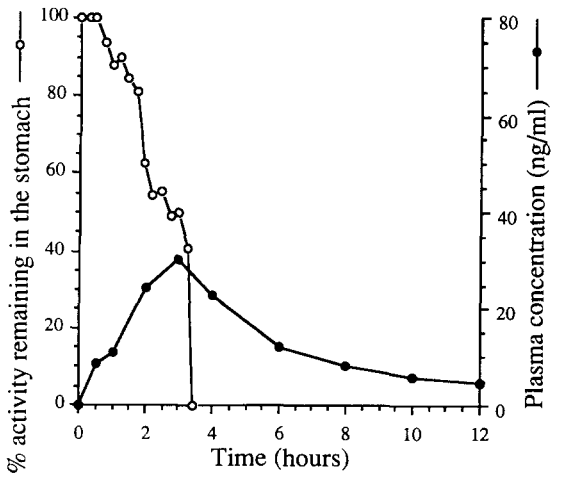

Fig. 4. Relationship between the gastric emptying curve and the plasma drug concentration-time profile for volunteer 2.

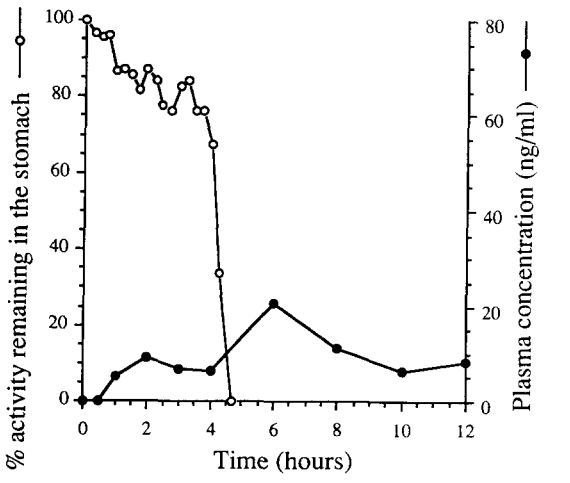

Fig. 6. Relationship between the gastric emptying curve and the plasma drug concentration-time profile for volunteer 14.

TABLE 2

Peak plasma concentrations (C_{max}), times to peak (t_{max}) and area under the plasma concentration-time curve between 0 and 12 h, AUC(0–12 h), after single oral dosing of a modified release pellet formulation of nifedipine

Volunteer no.	C_{max} (ng ml^{-1})	t_{max} (h)	AUC(0–12 h) (ng ml^{-1} h)
1	26.15	3	133.5
2	30.29	3	158.4
3	33.77	4	185.3
4	47.67	3	244.1
5	69.95	3	170.4
6	8.44	12	66.8
7	45.46	2	200.3
8	51.51	2	207.4
9	51.45	3	265.0
10	27.53	2	108.5
11	21.18	3	94.4
12	60.73	2	225.1
13	32.73	3	128.3
14	20.53	6	113.7
15	20.26	3	92.6
16	40.94	2	176.1
17	46.17	3	226.1
18	20.99	2	104.6
Mean	36.4	3.4	161.1
SD	16.3	2.4	58.8
Median	33.3	3.0	164.4

nifedipine in the management of hypertension is claimed to be between 15 and 25 ng/ml (Kleinbloesem et al., 1984). This level was achieved in all subjects, with the exception of no. 6. The pharmacokinetic data are in broad agreement with those reported previously for the same modified release nifedipine formulation (Pabst et al., 1986) and are compatible with a twice daily dosage regimen.

Theory would suggest that extended gastric residence is a significant advantage for a modified release formulation (Davis, 1985), since the drug released from the system would empty from the stomach and have the whole of the small intestine available for absorption. This expectation is the principle for the design of a number of novel formulations based upon particle density (Devereux et al., 1990), floating devices (Sheth and Toussounian et al., 1984) and bioadhesives (Park and Robinson, 1984). However, the present data question the applicability of such approaches for drugs like nifedipine. A plot of the area under the gastric emptying profile against AUC(0–12 h) suggests that extended gastric residence of the modified release pellet formulation may lead to *reduced* systemic bioavailability (Fig. 7).

In subjects with rapid gastric emptying of the pellet formulation, there was a correspondingly rapid rise in the plasma drug concentrations (Fig. 3). However, in those individuals in whom gastric emptying occurred as a series of boluses and in those showing gastric stasis, the onset of absorption was slower and systemic bioavailability was lower (Figs 4–6). The gradual presentation of the drug to enzymes on first pass through the intestine and liver may explain the lower systemic bioavailability, since nifedipine is known to be well absorbed from the entire gastrointestinal tract (Foster et al., 1983).

Two main parameters have been shown to influence the gastric emptying of modified release dosage forms, i.e., the physical size of the delivery device and whether it is administered to a fed or fasted stomach (Davis, 1987). Large modified release tablets (> 12 mm) are treated by the stomach as indigestible material and are emptied along with the phase 3 activity of the

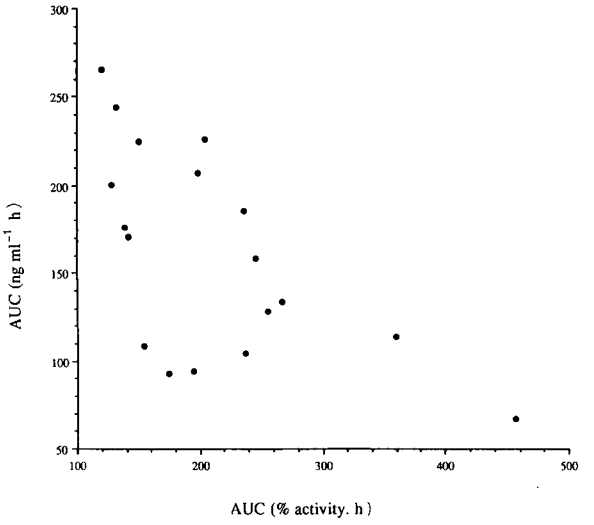

Fig. 7. Relationship between the area under the gastric emptying profile and the AUC(0–12 h).

migrating myoelectric complex (Kaus et al., 1984). If the stomach is maintained in the fed mode by a process of continuous feeding then a tablet would be retained during that time period. However, prolonged gastric retention may be a therapeutic disadvantage for drugs such as nifedipine and therefore should be considered in the design of modified release dosage forms.

In conclusion, we have demonstrated that the combination of gamma scintigraphy with pharmacokinetic assessment (pharmacoscintigraphy) can be used to examine the role of gastric emptying on the systemic bioavailability of nifedipine from a modified release pellet formulation. The results may have implications for the design of delivery systems for drugs such as nifedipine, which are subject to significant first-pass metabolism.

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