Absorption, Gastrointestinal Transit, and Tablet Erosion of Felodipine Extended-Release (ER) Tablets

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The gastrointestinal transit and tablet erosion of felodipine extended release (ER) tablets 10 mg were studied by gamma scintigraphy in eight healthy young males after administration under fasting and nonfasting conditions. Plasma concentrations of felodipine were also measured. Gastric emptying after administration together with food (mean, 3.2 hr) was slower in all subjects compared to emptying under fasting conditions (mean, 0.6 hr). The mean small intestinal transit times for the two study conditions did not differ significantly (5.1 and 4.7 hr, respectively). Tablets did not leave the colon in any subject within 14 hr after administration. Felodipine was shown to be absorbed in the colon, although the major part of the dose was absorbed in the small intestine. The absorption rate of felodipine was related to erosion of the hydrophilic matrix tablet. Tablet erosion and hence drug absorption were slower in the more distal parts of the gastrointestinal tract. Administration together with food did not significantly affect tablet erosion.

KEY WORDS: felodipine extended-release tablet; plasma concentration; gastrointestinal transit; tablet erosion.

INTRODUCTION

Felodipine is a vasoselective calcium antagonist of the dihydropyridine type, specially developed for the treatment of hypertension (1). The effect on blood pressure correlates with the plasma concentration of felodipine (2,3). Felodipine is marketed as an ER tablet. The formulation, based on the hydrophilic matrix principle, has a nearly constant release rate over several hours both *in vitro* and *in vivo* (4). The resulting plasma profiles are smooth without excessive plasma peak levels, which seem to be associated with adverse experiences (5). Effective drug levels are attained over the entire dosing interval after once-daily administration, while a twice-daily regimen is required for conventional felodipine tablets (6).

Felodipine is completely absorbed from the gastrointestinal (GI) tract after administration of a solution. The absolute extent of bioavailability is reduced to 15% because of presystemic elimination (5). For a dosage form releasing its content over an extended period of time, such as felodipine ER tablets, transit times in the GI tract can affect drug absorption. Various sites in the GI tract differ in absorption of drug molecules. The distal part, colon, has been assumed to be an unsuitable region for drug absorption. This is certainly true in some cases but data confirming colonic absorption have been reported for several drugs (7). The extent of bioavailability for felodipine ER tablets is not reduced compared to an oral solution or conventional tablets, which indicates acceptable distal absorption (6). However, more elucidative studies of the site of drug absorption for felodipine ER tablets have not been performed.

Another factor in drug absorption is changes in the release rate from the dosage form. For ER dosage forms, the varying physicochemical characteristics and contractile intensity along the GI tract are potential sources of altered drug release. The *in vitro* release of felodipine from the ER tablet is controlled mainly by erosion of the hydrophilic matrix. A limited number of *in vivo* studies of tablet erosion as a mechanism for the control of drug release has been published (8–10).

To study transit and erosion of a tablet *in vivo*, one can label the formulation with suitable radioisotopes for external measurements of the emitted radiation by gamma scintigraphy. In this study, felodipine ER tablets were labeled with the radionuclides ^{51}Cr and ^{59}Fe, which also have been used in previous studies (11). By combining gamma scintigraphy with measurements of drug concentration in plasma, it was also possible to relate drug absorption with the behavior of the dosage form in the GI tract.

The objectives of the present study were to study felodipine ER tablets after administration during fasting and nonfasting conditions with respect to GI transit, absorption of felodipine in relation to the localization, and erosion of the tablet.

MATERIALS AND METHODS

Study Formulation

Felodipine ER tablets, 10 mg, manufactured with laboratory-scale equipment were used in this study. Felodipine ER is a circular biconvex, hydrophilic matrix tablet based mainly on hydroxypropyl methylcellulose (HPMC). ^{59}Fe was introduced in the center of the tablet in a single pellet to ascertain the position of the tablet whereas ^{51}Cr was homogeneously dispersed in the tablet matrix as a marker for erosion. Both radionuclides were used as nonsoluble forms coated with an inert material (paraffin) in order to prevent dissolution and absorption of the markers. ^{59} Fe was used as $^{59}Fe_2O_3$, which is one of the least biologically available compounds of iron (12), and ^{51}Cr was given as $Ba^{51}CrO_4$. The total weight of the labeling material was 2% of the tablet weight. The radioactivity of ^{59}Fe and ^{51}Cr in each tablet did not exceed 0.2 and 3 MBq, respectively, at the start of the study.

In Vitro Tests

The dissolution of felodipine, ^{51}Cr, ^{59}Fe, and tablet erosion were measured in 500 mL phosphate buffer, pH 6.5, containing 1% sodium laurylsulfate, 37°C, using USP Dissolution Apparatus II (paddle) modified with a stationary basket. The paddle stirring rate was 50 rpm. In addition, the

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dissolution of the radioactive markers was also determined at pH 1.2 (HCl) and pH 2.0 (phosphate buffer). Felodipine was detected by UV-spectrophotometry and the radionuclides were detected by a gamma counter (Compugamma LKB-1282). Tablet erosion was measured by detection with an ion-chamber detector (Capintec CRC-120) of the ^{51}Cr remaining in the tablet after different times in the dissolution apparatus and by dissolution of the gel-forming agent, HPMC. The dissolution of HPMC was determined by gel-filtration chromatography (Toyo Soda TSK gel G2000SW, 10 μm) with refractive index detection (ERC-7512).

In Vivo Study

The study was approved by the Swedish Medical Product Agency, the Ethics Committee of the Medical Faculty of the University of Gothenburg, and the Isotope Committee of Sahlgren's Hospital, Gothenburg. Written informed consent was obtained from all volunteers before the study.

The study was a two-way, randomized crossover study with a washout period of at least 6 days. The study included eight healthy male volunteers aged 22–32 years, weighing 67–83 kg, and with a height of 180–190 cm. The subjects abstained from food and fluids since 10 PM the day before drug intake. The use of tobacco, alcohol, prescription, and over-the-counter drugs were not permitted prior to and during the study. In randomized order each subject took a single dose of the study drug in the morning immediately after a light breakfast (~1900 kJ) on one occasion and during fasting conditions on the other treatment period. The breakfast consisted of 2 slices of bread, 30 g of cheese, 0.15 L of orange juice, 0.15 L of milk, and 20 g of cereal. The tablet was swallowed together with 100 mL of tap water. Standardized meals were served at 4 hr (lunch), 7 hr (snack), 10 hr (dinner), and 12 hr (snack) after tablet administration. Gamma scintigraphic images and plasma samples were collected frequently over 14 hr after intake and again after 24 hr.

Gamma scintigraphic measurements were performed mainly with a gamma camera system but also with a scanning system (11). The latter equipment was used occasionally for simultaneous measurements of ^{51}Cr and ^{59}Fe when ambiguous images were obtained by the gamma cameras. The gamma camera system consisted of two opposite cameras allowing simultaneous posterior and anterior images. The cameras had a 40-cm field of view and were fitted with high-energy, parallel-hole collimators. Images of 60-sec duration were taken with the subjects sitting in a standardized position between the cameras. In addition, a determination of the remaining activity in the subjects was performed about 1 week after the last study day using a whole-body counter (11).

Gastric emptying (GE), small intestinal transit (SIT), and time for colon arrival (CA) were determined for the tablet. In order to estimate tablet erosion, the size of the tablet was estimated from the number of counts within a region of interest (ROI) of predefined size. The geometric mean for the anterior and posterior images was calculated after correction for background radiation and for scattered radiation from ^{59}Fe. Data were excluded from the analysis when (a) congruity between the tablet positions determined from the anterior and posterior images was not obtained, (b) the tablet was located at the edge of the field of vision for the gamma cameras, and (c) a movement of the tablet during the 60-sec pulse collecting time was apparent from the images. All individual erosion-time data were plotted, and erosion rates were determined by linear regression analysis.

The plasma samples were assayed for felodipine by gas chromatography with electron capture detection (13). The area under the felodipine plasma concentration–time curve between 0 and 24 hr (AUC_{0-24}) was calculated according to the trapezoidal rule. The *in vivo* dissolution at different times was determined by numerical deconvolution (14) on the mean plasma concentration–time data using mean plasma concentrations from previous studies with felodipine oral solutions, 10 mg, as a weighting function in the deconvolution procedure.

In order to evaluate differences between the administrations with and those without food with respect to transit times and tablet erosion, Student's t test was used, with $P < 0.05$ statistically significant.

RESULTS

In Vitro Evaluations

The dissolution of the radionuclides was low. No ^{51}Cr or ^{59}Fe was detectable in dissolved form at pH 6.5. The mean ($n = 3$) dissolutions obtained after 10 hr at pH 1.2 and pH 2.0 were 6 and 2% for ^{51}Cr, respectively, and <1 and 4% for ^{59}Fe, respectively. This implied that the radionuclides did not diffuse through the hydrated tablet matrix and thus were suitable markers for determination of position and tablet erosion.

The plots of ^{51}Cr eroded from the tablet at different times and the dissolution–time profile for the hydrophilic matrix were similar (Fig. 1a). The tablet erosion rate was 9.0 and 10.7%/hr as determined by linear regression for the ^{51}Cr data and HPMC dissolution, respectively, indicating that the measurements of ^{51}Cr mirrored the tablet erosion.

The *in vitro* dissolution rate of felodipine was almost constant with time and unaffected by the inclusion of markers (Fig. 1b). The *in vitro* dissolution rate was 8.3 and 8.5%/hr as determined by linear regression for labeled and unlabeled tablets, respectively. The release profile for the labeled tablets resembled that of tablets manufactured in production scale.

Gamma Scintigraphy

The GI transit times after administration with and without food are given in Table I. In all subjects the tablets were emptied from the stomach within 1.1 hr after administration under fasting conditions. Gastric emptying after administration with food (average, 3.2 hr) was slower in all subjects and somewhat more variable compared to the fasting conditions. The gastric emptying was prolonged by 1.5–4.2 hr by the concomitant intake of breakfast as determined from individual data. The small intestinal transit times, on average 5.1 and 4.7 hr with and without food, respectively, were not significantly different. The mean time for colon arrival of the tablet was 5.3 hr for fasting subjects and the corresponding value for nonfasting subjects was 8.3 hr. The slower transit of the tablet to colon after administration with food was

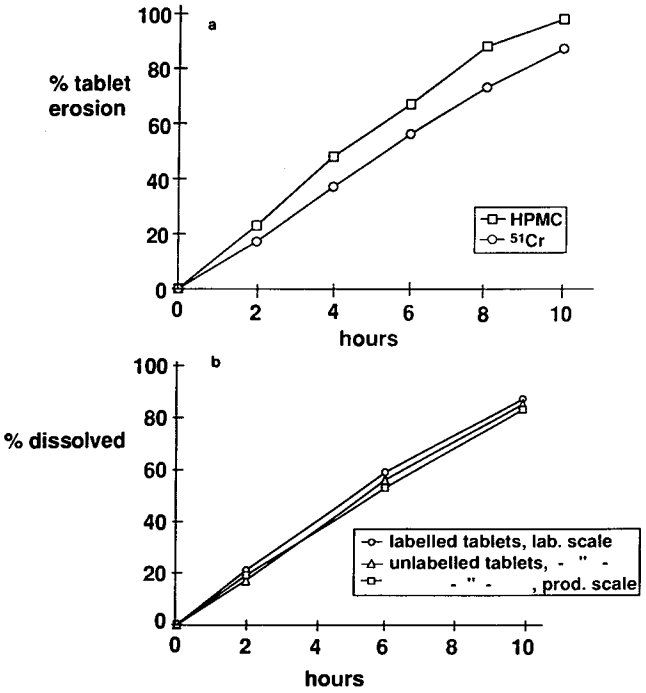

Fig. 1. *In vitro* evaluations. (a) Mean *in vitro* tablet erosion determined as ^{51}Cr remaining in the tablet (n = 2) and dissolution of the gel-forming ingredient, HPMC (n = 2), for labeled felodipine ER tablets. (b) Mean *in vitro* dissolution of felodipine from a production batch (n = 6) and a labeled (n = 3) and an unlabeled experimental batch (n = 6) of felodipine ER tablets.

solely related to the difference in gastric emptying. The tablet appeared to move more slowly in the colon than in the small intestine. Fourteen hours after intake, no tablet had been transported beyond the hepatic flexure in all cases but one. In this subject, the tablet had reached the splanchnic flexure.

Tablet erosion could be approximated by two linear phases (Fig. 2). During the initial phase of faster erosion, the mean (SD) erosion rate was 9.4 (3.1) and 10.8 (4.3)%/hr during fasting and nonfasting conditions, respectively (Table II). The corresponding values for the second phase were 2.1 (1.5) and 1.7 (1.5)%/hr. The correlation coefficient (r) was ≥0.8 in 13 and 12 of the 16 linear regressions performed on individual data to determine the erosion rate during the first and second phases, respectively. The tablet erosion rate was not significantly affected by the concomitant administration of a light breakfast, as judged from the statistical analysis of the erosion rates. The shift from the initially faster erosion rate to the second slower phase occurred on average (SD) at 7.7 (2.8) and 5.4 (1.9) hr after dosing during nonfasting and fasting conditions, respectively. Tablet erosion could not be appropriately determined during the first hour after administration in the nonfasting experiment due to tablet movements.

No activity from ^{59}Fe was found in any subject about 1 week after the last study day. At most, 2.1% of the given ^{51}Cr dose was detected and this remaining activity was located in the GI tract.

Plasma Concentration Data

The mean (SD) pharmacokinetic variables are given in Table III and *in vivo* dissolution–time profiles, obtained by numerical deconvolution on mean data are shown in Fig. 3. Drug dissolution followed zero-order kinetics during the main part of the process in both study conditions. The dissolution rate decreased in both administrations after 5–6 hr. The asymptote of the profiles, indicating completed dissolution, was reached after 10–12 hr. The mean (SD) extent of bioavailability for the nonfasting experiment in relation to the administration without food was 89 (22)%, as determined from the individual AUC ratios.

DISCUSSION

The gastric emptying times of felodipine ER tablets observed in this study are comparable to data obtained for other tablet formulations (15). The delay of gastric emptying obtained in the nonfasting experiment also agrees with previously reported results for other formulations and is consistent with the physiological theories (16). The average residence time in the small intestine for felodipine ER tablets was slightly longer than the mean small intestinal transit of 3–4 hr often reported for single units in other studies (15). The transit time through the entire GI tract was more than 14 hr in all subjects. In previous studies of another type of extended-release formulation, i.e., nondisintegrating membrane-coated tablets, total transit times of less than 14 hr have occurred with an incidence of 5 in 44 subjects in one study and 2 in 8 in two other studies (17–19). The absence of such a rapid total transit in this study may be related to the subject selection or study conditions.

Continuous erosion of the hydrated outer layer has been shown *in vitro* for hydrophilic matrix formulations. For felodipine ER tablets, the significance of this parameter is clearly shown by the similarity of the *in vitro* rates of tablet erosion and felodipine dissolution, which were 9.0 and 8.3%/

Table I. GI Transit Times for Felodipine ER 10-mg Tablets After Administration Under Fasting (f) and Nonfasting (nf) Conditions[a]

	Gastric emptying (hr)		Small intestinal transit (hr)		Colon arrival (hr)	
	f	nf	f	nf	f	nf
Mean	0.6	3.2	4.7	5.1	5.3	8.3
Range	0.1–1.1	1.9–4.8	3.9–5.9	2.2–7.7	4.0–7.0	6.0–11.0
P value[a]	<0.001		>0.05		<0.01	

[a] Statistical significance for the difference between the fasting and the nonfasting administrations.

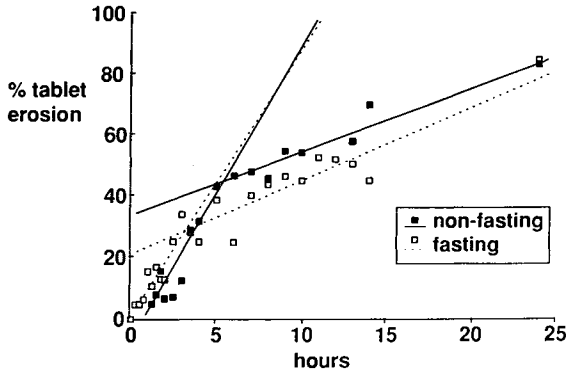

Fig. 2. Mean (n = 8) *in vivo* tablet erosion for felodipine ER tablets after administration during fasting and nonfasting conditions, also including linear regressions.

hr, respectively. Tablet erosion is thus the main determinant of drug release *in vitro*. Interestingly, the *in vivo* erosion of felodipine ER tablets followed a biphasic, linear profile, in contrast to the constant rate of erosion obtained *in vitro*. The mean erosion rate during the first phase, 9.4 and 10.8%/hr in the fasting and nonfasting experiment, respectively, closely corresponded to the *in vitro* erosion rate of 9.0%/hr. The tablet erosion rate also appeared to be unaffected by the presence of food in the stomach during this period. Thus, it should be possible to predict tablet erosion in the stomach and small intestine from simple *in vitro* experiments. The mean erosion rate for the second phase was about five times lower compared to the first period. The second phase of slower tablet erosion, which was not predicted from the *in vitro* experiment, might be related to the different environment in the distal parts of the GI tract. For example, the semisolid nature of the luminal contents and the more sluggish motor activity in the colon could potentially affect the erosion of a hydrophilic matrix. A further contributing explanation to the appearance of a second, slower phase could be that the erosion rate was somewhat underestimated. This could occur if material eroded from the tablet had not dispersed sufficiently to be discriminated from the region of interest defined as the tablet.

Table II. Mean Erosion Rate Constants Obtained by Linear Regression, the Time for the Shift Between the First and the Second Phase, and Statistical Test of Difference of Erosion Rates Between the Administrations Under Fasting (f) and Those Under Nonfasting (nf) Conditions

	Erosion rate (%/hr)				Time for shift (hr)[a]	
	Phase 1		Phase 2			
	f	nf	f	nf	f	nf
Mean	9.4	10.8	2.1	1.7	5.4	7.7
SD	3.1	4.3	1.5	1.5	1.9	2.8
P value[b]	>0.05		>0.05		>0.05	

[a] Time corresponding to midpoint between first data point in phase 2 and last data point in phase 1.

[b] Statistical significance of the difference between the fasting and the nonfasting administrations.

Table III. Mean (SD) Pharmacokinetic Variables After Administration of Felodipine ER Tablets 10 mg Under Fasting (f) and Nonfasting (nf) Conditions

	Fasting	Nonfasting
C_{max} (nmol/L)		
Mean	5.23	7.00
SD	1.56	1.90
t_{max} (hr)		
Mean	5.0	4.6
SD	2.0	0.5
AUC_{0-24} (nmol · hr/L)		
Mean	50.3	44.7
SD	12.6	11.0
F_{rel}(nf/f)		
Mean	—	0.89
SD	—	0.22

The pharmacokinetic data in this study agree with previous results on felodipine ER tablets taken with and without food (20). The mean *in vivo* dissolution–time profile is also very similar to corresponding data obtained after deconvolution of individual data in a previous *in vitro/in vivo* correlation study (4). The tablet remained in the stomach for about 3 hr when administered with food. During this period a substantial amount of drug was absorbed. However, after gastric emptying, the plasma concentrations increased more rapidly than during the first hours in several subjects, as exemplified by subject 3 (Fig. 4a). Although it could not be determined from the present data if absorption occurred in the stomach or if felodipine was emptied into the duodenum as a solution or suspension prior to absorption, the increase in the absorption rate after gastric emptying clearly indicated a low absorption capacity in the gastric region. The major part of the dose was absorbed in the small intestine, but a considerable amount of drug was also absorbed in the proximal parts of the colon. After administration under fasting condition, about 30% of the dose was absorbed in the colon and about 10% in the nonfasting experiment, according to the mean *in vivo* dissolution time profiles. The colon absorption was also reflected in the individual plasma concentration–time profiles by a continuing plateau level when the tablet had left the small intestine (Fig. 4b). This finding is in

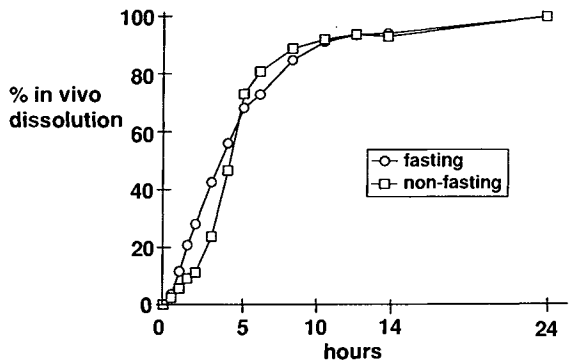

Fig. 3. *In vivo* dissolution, obtained by deconvolution of mean data, for felodipine ER tablets after administration during fasting and nonfasting conditions.

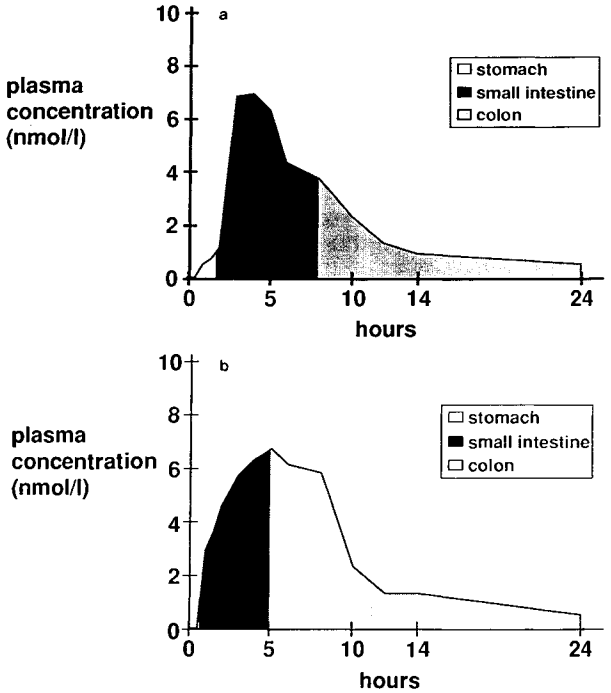

Fig. 4. Examples of individual felodipine plasma concentration profiles, also showing tablet localization. (a) Subject 3, nonfasting; (b) subject 3, fasting.

accordance with results from a previous study where a felodipine ER tablet of the same type as in this study, but with a slower release rate, showed continuous absorption over 24 hr (4). It should be noted, however, that the absorption of felodipine in the colon might be formulation dependent. The solubility enhancing properties provided by the tablet (21) are probably required to get this poorly water soluble drug (~0.5 mg/L) into solution and thereby available for absorption in the less water-containing contents of the colon.

The absorption of felodipine was related to tablet erosion. The shapes of the *in vivo* dissolution- and erosion-time profiles were similar, with an initial period of more rapid dissolution/erosion followed by a slower phase. The *in vivo* dissolution rate decreased at about the same time as when the *in vivo* erosion shifted to the slower phase. The decrease in the absorption rate, however, was not as pronounced as the corresponding retardation in the erosion process. This supports the hypothesis discussed above that the erosion rate during the latter part of the experiment was underestimated. Another explanation could be that diffusion of felodipine in the tablet matrix became a major determinant of drug absorption during the last hours of drug release.

In conclusion, felodipine can be absorbed in the colon, but for felodipine ER tablets the major part of the dose is absorbed while the tablet is in the upper part of the GI tract. Thus, GI transit is not a critical factor with respect to bioavailability and clinical effect for this formulation. This conclusion is supported by the fact that no tablet was expelled from the GI tract during the first 14 hr after intake. The drug absorption rate is related to the *in vivo* erosion of the hydrophilic matrix. The erosion rate seems to be unaffected by concomitant administration of the tablet together with food.

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