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Bioavailability from felodipine extended-release tablets with different dissolution properties

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Summary

The objective of the present study was to investigate the relationship between in vitro dissolution and absorption of felodipine, a calcium antagonist of the dihydropyridine type, from three types of extended-release (ER) tablet. Felodipine was released in vitro over 6, 12 and 20 h, respectively. The tablets were studied in vivo after a single oral dose in a cross-over study in 16 healthy and informed volunteers. A completely absorbed oral solution served as reference. Statistical moment and deconvolution analyses were performed. The slower the drug release, the lower was the peak plasma level and the longer the time to peak. Only the slowest releasing tablet had a reduced extent of bioavailability. There was a good correlation between tablet dissolution in vitro and in vivo. The results indicate that the absorption of felodipine from the gastrointestinal tract can continue for up to 20 h after administration.

Introduction

Felodipine is a vasodilating calcium antagonist of the dihydropyridine type developed for the treatment of hypertension. Felodipine effectively reduces blood pressure in hypertensive patients as monotherapy and in combination with other substances (Satiel et al., 1988). The solid dosage form initially developed for this poorly water soluble drug (0.5 mg l^{-1}) was a rapidly absorbed plain tablet clinically effective in a twice daily dosage (Satiel et al., 1988). The reduction of blood pressure is closely related to the concentration of felodipine in plasma (Edgar and Elmfelt, 1987).

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Absorption of dissolved felodipine from the gastrointestinal tract is rapid and complete (Edgar et al., 1987). Due to extensive first-pass metabolism the systemic availability is 15% (Edgar et al., 1987). An extended-release (ER) tablet was specifically developed for felodipine in order to achieve more sustained plasma levels and thereby minimize peak concentration dependent side-effects and to extend the duration of the antihypertensive effect. The felodipine ER tablet given once daily is equally effective when it comes to lowering blood pressure as the plain tablet given twice daily and is well tolerated (Hart and Westberg, 1990).

The purpose of the present study was to determine the bioavailability of felodipine ER tablets with different release rates of drug. The relationship between the in vitro and in vivo characteristics of the ER tablets was also studied.

Materials and Methods

Study drugs

Three different felodipine 10 mg ER hydrophilic matrix tablets (A–C) were used (Table 1). In contact with the gastrointestinal fluids, a hydrated, viscous gel layer is formed around the tablet. The drug is released by slow erosion of the gel layer. The tablets were made by conventional granulation followed by tablet compression on circular, 11-mm punches. A 10 ml volume of an oral, hydroalcoholic solution (1 mg ml^{-1}) of felodipine was used as reference.

In vitro dissolution rate

The rate of felodipine release from ER tablets was determined using a USP dissolution apparatus no. 2 (paddle), operating at a rotation speed of 50 rpm. To maintain 'sink' conditions, 1% of sodium dodecyl sulphate specially pure (BDH, England) was added to the dissolution medium, 500 ml of phosphate buffer. Six individual tablets were tested. Each was put into a stationary basket above the paddle during the experiment to achieve reproducible hydrodynamic conditions (Fig. 1). The amount of drug dissolved was determined spectrophotometrically at 362 nm.

The three ER tablets, A–C, released felodipine in vitro at clearly different rates (Table 2). Felodipine was released and dissolved at a virtually constant rate over 6, 12 and 20 h, respectively, and the variability between tablets was low.

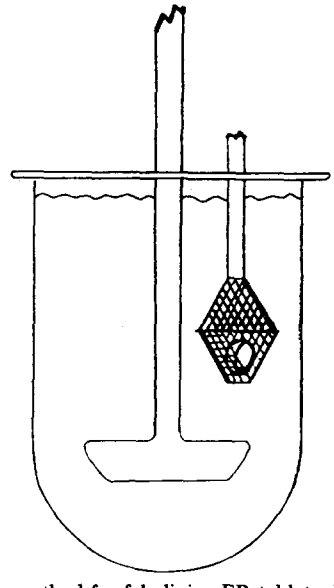

Fig. 1. In vitro method for felodipine ER tablets; USP dissolution apparatus no. 2 with a stationary basket.

In vivo study

This was an open, four-way randomized crossover study in 16 healthy and informed male subjects. The study was performed in accordance with the Declaration of Helsinki and approved by the local ethics committee. All subjects gave written consent to participate. The subjects had a mean age of 24 (20–35) years and weighed 64–81 kg with a mean of 72 kg.

Each subject participated in four experimental days at weekly intervals. On each of the four study days, felodipine 10 mg (solution or ER tablet) was

TABLE 1

Composition of felodipine extended-release tablets

	Tablet component (mg)		
	A	B	C
Felodipine	10	10	10
Gel-forming excipients			
hydroxypropyl methylcellulose (6 mPa s)	230		
hydroxypropyl methylcellulose (50 mPa s)		230	261
ethylcellulose			20
carboxypolymethylene			2
Tablet excipients	qs ad 460	470	460

TABLE 2

Per cent felodipine dissolved in vitro (mean ± S.D. for six tablets) and the corresponding mean dissolution time (in h) in vitro (MDT_{vitro})

Time (h)	Tablet		
	A	B	C
2	36±2	16±1	8±1
4	74±4	–	–
6	98±3	54±3	28±1
10	–	85±3	48±2
24	–	–	99±2
MDT_{vitro}	2.7	5.8	10.5

administered orally in the morning with 200 ml of water, following an overnight fast. Standardized lunch, snacks and dinner were served 4, 6 and 10 h after drug administration. Blood samples (5 ml) were collected at frequent intervals up to 14 h after dose. In addition 24 and 24.5 h samples were collected.

Analysis of drug in plasma

The concentration of felodipine in plasma was determined by gas-chromatography with electron capture detection (Ahnoff, 1984; Ahnoff et al., 1987). Precision was typically 2–8% (coefficient of variation) at both 1.0 and 2.0 nmol l^{-1}. The lowest determinable concentration was 0.5 nmol l^{-1} with a coefficient of variation of $< 15\%$.

Bioavailability

The highest felodipine concentration, C_{max}, and the corresponding time, t_{max}, were identified for each subject and formulation. The area under the plasma drug concentration-time curve, AUC, was calculated by the trapezoidal rule. The residual area was estimated using the elimination half-life assessed from the terminal slope after administration of the solution.

The pharmacokinetic variables C_{max}, t_{max} and AUC were tested for differences by means of two-way analysis of variance (ANOVA). Each possible pair of formulations was assessed using Student's *t*-test. The standard error used in the *t*-tests was obtained from the residual error given in the ANOVA.

Analysis of statistical moments

The mean residence time, MRT, i.e. the time for in vivo dissolution, absorption, distribution and elimination for the average unchanged drug molecule, is defined as the ratio between the area under the first moment of the plasma drug concentration-time curve, AUMC, and the AUC (Yamaoka et al., 1978). The MRT was calculated for each subject and each of the four preparations. According to the additivity of mean times, the mean dissolution time in vivo, MDT_{vivo}, for the ER tablets was calculated as follows: $MDT_{vivo} = MRT_{ER} - MRT_{sol}$ (Riegelman and Collier, 1980).

The mean dissolution time in vitro, MDT_{vitro} was estimated from the time when 50% of drug had dissolved as the in vitro dissolution kinetics was of zero order (Riegelman and Collier, 1980).

Numerical deconvolution

The individual in vivo dissolution vs time curves after administration of the ER tablets were generated by numerical deconvolution (Langenbucher, 1982). The drug concentration-time curve for the solution was used as the weighting function and the felodipine concentration curve after an ER tablet was used as response function. Accordingly, the input function obtained by deconvolution illustrates the in vivo dissolution process from the ER tablet. The applied time module was 30 min in all estimations. Data points between the measured plasma concentrations were generated by linear interpolation.

Results

In vivo study

The mean concentrations in plasma following each of the four preparations are shown in Fig. 2. For the three ER tablets, the differences in the rate of felodipine release were reflected in the plasma profiles obtained; the slower the release, the lower the C_{max} and the longer the t_{max} (Table 3). The differences in C_{max} were significant in all

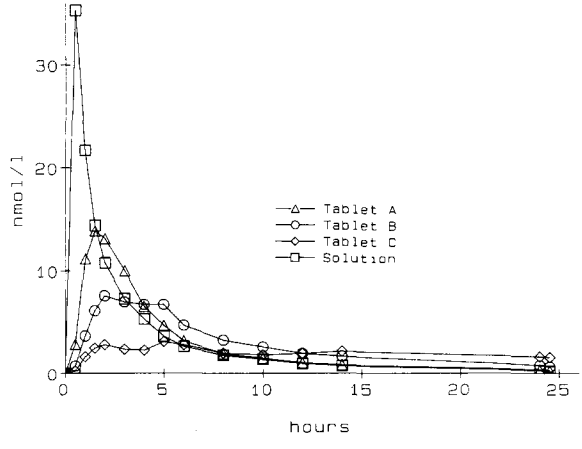

Fig. 2. Mean felodipine plasma concentrations after a single 10 mg dose to 16 healthy subjects.

TABLE 3

Pharmacokinetic variables (mean ± S.D.) after administration of a single dose of 10 mg felodipine to healthy subjects (n = 16)

	Solution	Tablet A	Tablet B	Tablet C
C_{max} (nmol l^{-1})	36.7 ± 13.6	15.0 ± 8.5	9.2 ± 4.7	4.0 ± 2.2
t_{max} (h)	0.6 ± 0.2	2.1 ± 1.2	2.8 ± 1.0	8.2 ± 6.2
$t_{1/2}$ (h)	8.5 ± 4.7	–	–	–
AUC (nmol h l^{-1})	87 ± 35	80 ± 44	78 ± 35	70 ± 39
F_{rel} (%)	–	92 ± 37	95 ± 29	81 ± 32

comparisons whereas tablet C was the only formulation with a mean t_{max} significantly different from that of the others.

Between the three ER tablets there was no statistically significant difference in the extent of absorption, measured as AUC. However, there was a tendency to a lower bioavailability for the slowest tablet, C, the only tablet with an AUC significantly lower than the solution.

Analysis of statistical moments

The mean residence time for felodipine, MRT, was clearly influenced by the properties of the formulation administered, i.e. the rate of drug dissolution, as shown in Table 4.

For each of the 16 subjects the derived individual MDT_{vivo} values were related to the corresponding MDT_{vitro} for the preparations and a mean of these individual regression lines calculated. This average linear relationship is shown in Fig. 3 together with the mean values for each preparation. There is a good correlation (mean $r = 0.76$) between the MDT_{vitro} and MDT_{vivo} values for the three tablets.

TABLE 4

Mean residence time (MRT) and mean in vivo dissolution time (MDT_{vivo}) after administration of a single 10 mg felodipine dose to healthy subjects (n = 16) (means ± S.D. are given)

	Solution	Tablet A	Tablet B	Tablet C
MRT (h)	6.6 ± 3.4	9.3 ± 6.9	11.8 ± 3.9	18.2 ± 6.1
MDT_{vivo} (h)	–	2.7 ± 5.2	5.2 ± 2.5	11.6 ± 4.5

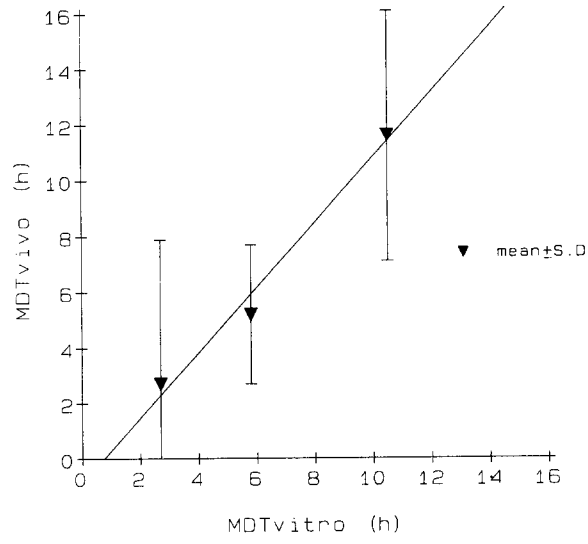

Fig. 3. Mean dissolution time in vivo (MDT_{vivo}) for felodipine ER tablets as a function of the mean dissolution time in vitro (MDT_{vitro}). The mean of the 16 individual regression lines was $Y = 1.17X - 0.86$ and the correlation coefficient was $r = 0.76 \pm 0.35$ (mean ± S.D.).

Numerical deconvolution

The mean of the individual in vivo dissolution curves for the three tablets obtained through deconvolution are given in Fig. 4a–c together with the corresponding in vitro data. The curves have a shape characteristic for each tablet and the rate of dissolution from the dosage form clearly governs the rate of absorption during the first hours after administration. From tablet B, most of the drug is absorbed within 6 h and the process then seems to continue at a lower rate. The absorption of the fastest dissolving tablet, A, is in most cases completed within 2–3 h whereas it will continue for 24 h when the slow tablet, C, is administered.

Discussion

A solution of felodipine is known to be rapidly and completely absorbed from the gastrointestinal tract (Edgar et al., 1987) and also in this study a high peak concentration is obtained within an hour after dosing. The present study shows that if only the rate of felodipine dissolution from an oral dosage form is extended, then the absorption

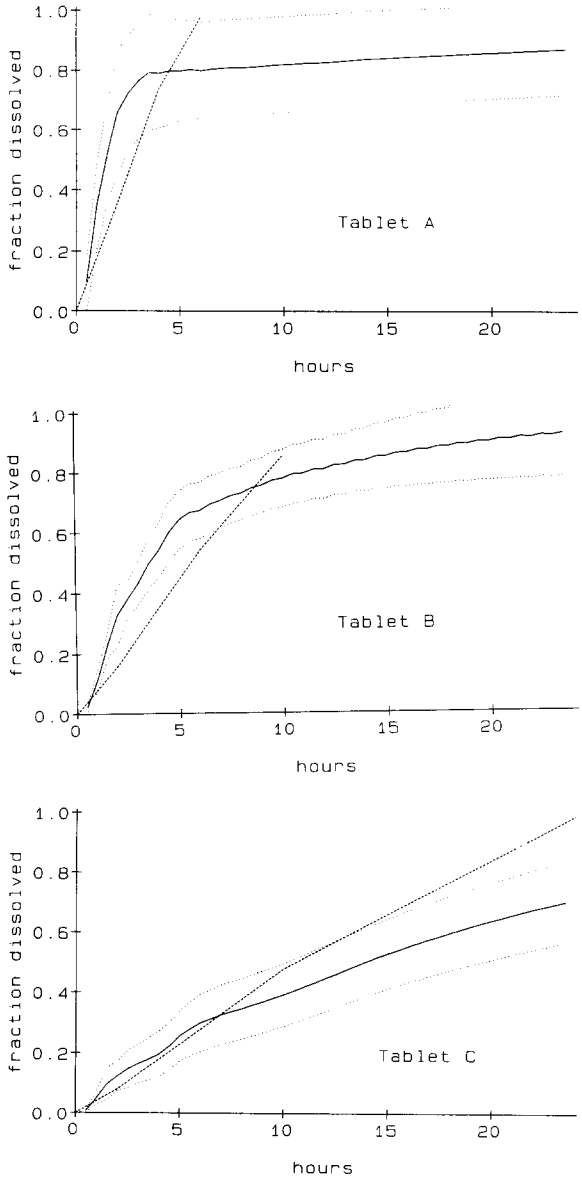

Fig. 4. (a–c). Cumulative in vitro dissolution (mean ------, $n = 6$) of felodipine ER tablets and the corresponding in vivo dissolution (mean ——— and 95% confidence limits ·····, $n = 16$) obtained through deconvolution.

phase will be prolonged and more sustained plasma levels are produced (Fig. 2).

It is generally considered a difficult task to develop well-functioning ER dosage forms for drugs which are poorly water-soluble and have a high first-pass metabolism (Bogentoft, 1982; Skelly, 1986). For felodipine the hydrophilic matrix ER tablet was specifically designed and patented (Falk et al., 1989). The felodipine ER tablets show behaviour characteristic of controlled and reproducible dissolution in vitro (Table 2). Furthermore, the variability (S.D.) in rate and extent of bioavailability, as judged from the pharmacokinetic variables (Table 3), is of the same magnitude for the ER tablets as for the solution. The increased intra- and inter-individual variability sometimes associated with poorly soluble drugs and extended-release dosage forms is thus not observed for the felodipine ER tablets.

The systemic availability of orally administered felodipine is approx. 15%. This first-pass elimination is attributed to metabolism in both the liver and the gut wall (Regårdh et al., 1989). Interestingly, no change in bioavailability of felodipine was observed for tablets A and B in spite of a lower rate of presentation and absorption which probably takes place partly at distal sites of the gastrointestinal tract. In a series of studies summarized by John et al. (1985), average total gastrointestinal transit time in 35 healthy subjects of a single dose unit was 27.4 h with a wide variation both within and between subjects (5.1–58.3 h). From tablet C felodipine is dissolved and absorbed in vivo over more than 24 h and the apparently lower bioavailability of this tablet could be attributed to the fecal excretion of the dosage form prior to complete release of drug. Moreover, the AUC for tablet C may be underestimated as the sampling of plasma ended after 24.5 h and the residual area was extrapolated assuming elimination only.

The correlation between the in vitro and in vivo dissolution times was good (Fig. 3) and the in vitro method is evidently capable of discriminating between ER tablets of different in vivo performance. Although the actual rates of dissolution in vitro and in vivo are not identical, they are clearly of a similar magnitude (Fig. 4).

From Fig. 4a–c it seems that during the initial hours after administration dissolution is somewhat faster in vivo than in vitro. After about 5–6 h, there is a shift as the dissolution in vivo from both tablets B and C becomes slower and more similar in magnitude. The average transit time to colon is

about 5 h (Davis et al., 1984) and it may well be that the changes in motility, intestinal contents or availability of liquids alter the release rate from the tablet. The liquid flow rate into the duodenum is 6–10 l per day whereas it is 0.7–1.2 l per day by the end of the ileum and only 0.1 l per day at the distal part of the colon (Hirtz, 1985). In the deconvolution of data, absorption was assumed to be rapid over the entire gastrointestinal tract and an explanation for this shift in rate could further be that absorption from colon is slower and becomes rate-limiting. In a study of another dihydropyridine, nitrendipine, administered orally with an osmotic pumping device, (Osmet®) a decrease in absorption rate was similarly observed in the lower part of the gastrointestinal tract, i.e. 6 h post-administration (Soons, 1989).

Conclusion

Similarly to an oral solution, felodipine ER tablets are characterized by a high extent of absorption. The rate of absorption is dependent on the dissolution of felodipine and the ER tablets produce sustained plasma levels. Felodipine seems to be absorbed in both the small and large intestine, possibly at different rates. A close correlation exists between in vitro and in vivo dissolution and the in vitro method used is thus well suited for routine quality control of felodipine ER tablets.

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