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Biopharmaceutical studies of naftidrofuryl in hydrocolloid matrix tablets

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Summary

Absorption studies have been performed in nine healthy volunteers. Plasma concentrations of naftidrofuryl have been compared following administration of a single dose in three modified release explorative hydrocolloid matrix tablets and in an aqueous solution. The solution and one matrix tablet contained 100 mg, whereas the other two matrix formulations contained 300 mg of the drug. The amount of hydrocolloids used in the matrix tablets was varied to produce different in vitro release rates. The relative extent of bioavailability from the 300 mg tablet with a rapid drug release in vitro was significantly reduced, while it was unchanged from tablets with a comparatively slower drug release. This suggests that the absorption process has a limited capacity, and that the drug release rate is not controlling the absorption at this dose level. In contrast, the in vivo release rate from the 100 mg tablet, estimated by means of numerical deconvolution, showed a close agreement with the in vitro data.

Introduction

Naftidrofuryl is reported to be effective in the treatment of senile dementia (Cox, 1975; Brodie, 1977; Cox and Shaw, 1981; Grossmann et al., 1990), and in the treatment of patients suffering from chronic arterial diseases (Trübestein et al., 1984) such as intermittent claudication (Waters et al., 1980; Adhoute et al., 1986). The substance is claimed to be vasoactive, and thereby to increase peripheral and cerebral blood flow (Fontaine et al., 1968, 1969). It acts at the tissue level, facilitating tissue oxidative metabolism by activation of succinic dehydrogenase (Meynaud et al., 1973).

In early investigations on senile dementia (Cox, 1975; Brodie, 1977; Cox and Shaw, 1981), a standard daily dose of 3×100 mg naftidrofuryl hydrogen oxalate was used, whereas in a recently published study (Grossmann et al., 1990) the patients were treated daily with 3×200 mg. In the treatment of peripheral arterial occlusive diseases, a daily dose of 3×200 mg naftidrofuryl hydrogen oxalate has been shown to be active and safe (Waters et al., 1980; Trübestein et al., 1984; Adhoute et al., 1986).

Extended release tablets containing 100 and 200 mg naftidrofuryl hydrogen oxalate are at pre-

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sent commercially available, e.g., in Germany. However, an extended release tablet containing 300 mg of the drug, making administration only twice daily possible, might be advantageous, as it increases the compliance.

The purpose of the present study was to investigate the bioavailability of exploratory hydrocolloid matrix tablets, containing 300 mg of the drug. Two tablet compositions with different in vitro release rates, due to various amounts of the hydrocolloids xanthan gum and guar gum in the matrix, were tested. An explorative matrix tablet and an oral solution, both containing 100 mg of the drug, were used as references, since no pharmacokinetic data are available after acute oral doses of 300 mg drug. The absorption of the readily soluble naftidrofuryl was expected to be dependent upon the in vivo release rate, and a search was conducted in order to discover whether any relationship between the in vitro and in vivo release of the drug existed.

Materials and Methods

Dosage forms

Naftidrofuryl hydrogen oxalate is freely water soluble, and its pK_a is 8.2 at 30°C (Martindale, 1989). Each 100 ml dose of the plain aqueous solution (1 mg ml^{-1}) of naftidrofuryl hydrogen oxalate, was individually dispensed in a sealed bottle. The compositions of the three different hydrogel matrix tablets are listed in Table 1. The types of tablet excipients used and their relative amounts were the same as those described in another paper (Waaler et al., 1992). The tablets were produced on a laboratory scale in an identical manner to that reported in the same study.

TABLE 1

Composition of naftidrofuryl hydrogen oxalate sustained release tablets

Component	Amount (mg)		
	A	B	C
Naftidrofuryl hydrogen oxalate	100.0	300.0	300.0
Xanthan gum	18.7	10.7	35.5
Guar gum	18.7	10.7	35.5
Lactose	12.7	131.0	81.2
Excipients ad	233.3	700.0	700.0

In vitro release rate

The release rate of naftidrofuryl was determined by means of the USP Apparatus II method (Sotax AT 6, Basel, Switzerland) with the paddle operating at rotation speeds of 50, 75 and 100 rpm. Nets of stainless steel, placed on the bottom of the beakers, kept the tablets from sticking to the walls. 900 ml (37.0 ± 0.2°C) of degassed phosphate buffer (pH 7.4, ionic strength 0.1) or degassed HCl (0.1 N, ionic strength 0.1) was used as dissolution medium. The concentration of released naftidrofuryl was recorded on line at 242 nm with a spectrophotometer (Beckman DU 50, Beckman Instruments, München, Germany), connected to a computer (SAM 68 K, KWS Computersysteme, Ettlingen, Germany), using the program Pho-meter (Waßmus, 1989).

Assay

The frozen plasma samples were allowed to thaw at room temperature. A specific volume ranging from 200 to 700 μl of the plasma was spiked with 100 μl internal standard (2 μg ml^{-1} verapamil hydrochloride). The quantification was performed by HPLC analysis after solid-phase extraction of the plasma samples (Waaler and Müller, 1992). Precision analysis indicated a relative standard deviation between 1.1 and 3% for the method at plasma concentrations ranging from 10 to 300 ng ml^{-1}. The limit of detection was calculated to be 0.6 ng ml^{-1}, having a relative standard deviation of about 15%.

Design of the in vivo study

The study was performed at the clinic Rechts der Isar in München, Germany, and was approved by the local ethics committee. Nine volunteers (age 20–30 years, weight 51–81 kg) participated. The subjects fasted overnight before being given a single oral dose of a formulation in a cross-over manner. The tablet formulations used were given with 150 ml tap-water and the oral solution with 50 ml water. There was a wash-out period of 1 week between each dosing. The sub-

jects continued fasting for another 1 h after administration, and then received a standardized breakfast. A warm meal (1200 kcal) was given another 4 h later. The intake of water or lemonade was allowed ad libitum up to a volume of 2.5 l, and smokers were allowed to a maximum of three cigarettes. Blood samples (5 ml) were drawn at 0, 0.5, 1, 2, 3, 4, 6, 8 and 24 h after each dosing, and collected in heparinized tubes. Plasma was separated by centrifugation and stored at −20°C until analysis.

Pharmacokinetics

The area under the plasma concentration vs time curve (AUC) was calculated according to the trapezoidal method in the time interval 0–8 h. The residual area was estimated using the elimination rate constant assessed from the terminal slope after administration of the solution, assuming constant clearance in the different treatment periods. The calculations were performed using an RS/1 procedure (BBN, Software Products Corp., Cambridge, MA, U.S.A.) in a Vax computer. Maximum concentration (C_{max}) and time for reaching this concentration (t_{max}) were measured directly without interpolation.

No period effect is assumed, and the 95% confidence interval of the extent of bioavailability was determined according to Eqn 1

$$\frac{\overline{AUC}_{solution} + \overline{AUC}_{tablet-solution} \pm t_{\alpha/2,n-1} s/\sqrt{n}}{\overline{AUC}_{solution}} \quad (1)$$

where s denotes the standard deviation assessed for the difference in individual response ($AUC_{tablet}/AUC_{solution} \cdot dose_{solution}/dose_{tablet}$) of the subjects, n is the number of subjects receiving the tablet formulation.

The mean of the differences between the treatments was determined on the basis of Eqn 2:

$$\overline{AUC}_{tablet\text{-}solution} = \frac{\sum_{i=1}^{n_i} (AUC_{tablet(i)} - AUC_{solution(i)})}{n} \quad (2)$$

and the mean AUC of the solution according to Eqn 3

$$\overline{AUC}_{solution} = \frac{\sum_{i=1}^{n_i} AUC_{solution(i)}}{n} \quad (3)$$

The individual in vivo release rate data after administration of the extended release tablets were generated by applying a programme for numerical deconvolution (Langenbucher, 1982) developed within RS/1. The plasma concentration vs time course following administration of the tablets was used as the response function ($R(t)$) of the system, whereas the concentration vs time course obtained after administration of the solution was defined as the weighting function ($W(t)$). A time module of 1 h was used with linear interpolation in all estimations, and the differences in the dose given were accounted for by assuming that the superposition principle was applicable. The input function ($I(t)$) calculated illustrates the in vivo release rate from the different tablet formulations.

Results

Nine subjects received the solution and at least one solid dosage form, which made it possible to explore the behaviour of each tablet formulation in separate comparisons. Four female volunteers completed the whole study. The mean plasma concentration vs time curves for each of the four preparations are depicted in Fig. 1. The individual and mean pharmacokinetic data derived are given in Tables 2 and 3, and the curves for the in vitro release rate of the three matrix tablets are given in Figs 2–4.

Solution vs tablet A, 100 mg

The absorption of naftidrofuryl was rapid, and a maximum plasma concentration of 340 $\mu g\ l^{-1}$ was reached within 30 min after administration of 100 mg in solution to nine volunteers. The matrix tablet, containing 16% hydrocolloids, resulted in a slight retardation of the absorption rate, $t_{max} = 1$

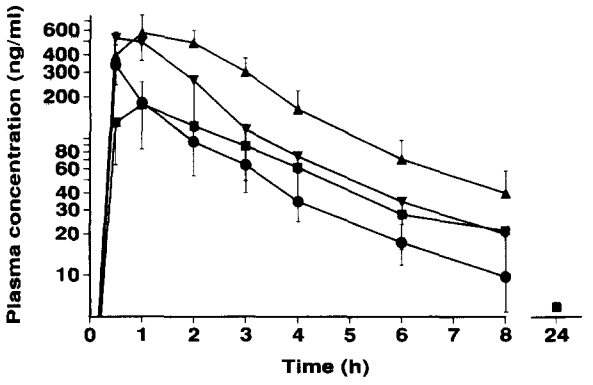

Fig. 1. Mean plasma concentration ± S.D. after p.o. administration of a single dose naftidrofuryl to healthy subjects. (●) Aqueous solution 100 mg ($n = 9$); (■) formulation A 100 mg ($n = 7$); (▼) formulation B 300 mg ($n = 8$); (▲) formulation C 300 mg ($n = 5$).

h, and a reduction of the peak concentration of about 40%, 210 $\mu g\ l^{-1}$. These tablets released at least 50 and 90% of the dose in vitro within 1 and 4 h, respectively. A comparison of the AUCs ($n = 7$) indicates a relative extent of bioavailability of 1.2 for the tablet.

The overall elimination rate of naftidrofuryl, estimated from the terminal slope of the plasma concentration vs time curve after administration of the solution, corresponded to a half-life of 1.6 h. In an earlier study, a half-life of 40 min, determined after injection of 50 mg was reported (Lartigue-Mattei et al., 1978).

Tablet A, 100 mg, vs tablet B, 300 mg

The matrix tablet B, containing 3% hydrocolloids, gave rise to a similar absorption rate ($t_{max} = 0.9$) to that of tablet A, which contained 16% hydrocolloids. After dose adjustment in the calculations, assuming dose linearity, the maximum average peak concentration was 80%, and the extent of bioavailability was 65% ($n = 6$) compared to tablet A. Tablet B showed about the same release profile in buffer, at 50 rpm, as tablet A, and at least 50 and 90% was released after 1 and 4 h. Drug release from tablet B was more dependent on both agitation and the dissolution liquid used, however, this does not explain the reduction in extent of bioavailability.

Tablet A, 100 mg, vs tablet C, 300 mg

The tablet showing the slowest rate of release in vitro (tablet C), containing 10% hydrocolloids, was compared to tablet A in five volunteers. No obvious differences were found in the pharmacokinetic parameters after administration of the two formulations. The average ratios of t_{max}, C_{max} and AUC between the tablets were 1, 1.1 and 1.2, respectively, after dose correction. The in vitro release rate from tablet C was significantly lower than from tablet A, irrespective of the conditions under which release rates were compared.

Tablet B vs tablet C, 300 mg

A comparison of the bioavailability of tablets B and C was explored only in four volunteers (Table 3). The values for t_{max} and C_{max} lie close to one another. However, the plasma concentration vs time curve obtained after administration of tablet C, suggests a 1.4-fold greater extent of bioavailability.

The in vitro differences of the two tablets are not reflected in the rates of absorption. By using 10% of the tablet weight as gelling agent (tablet C), it is possible to cause significant retardation of the dissolution rate in vitro, compared to when 3% hydrocolloid is used (tablet B) (Figs 3 and 4). Time periods of at least 2 and 5 h are required before 50 and 90% of the drug is released from tablet C compared to 1 and 4 h for tablet B, respectively. Additionally, the rate of release of drug from formulation C is independent of the dissolution medium and agitation intensities during the first hour. Subsequently, however, a dependence on the in vitro conditions becomes evident, albeit to a smaller extent in comparison with both tablet A and B.

In vitro vs in vivo release rate

The mean in vivo release rates estimated by deconvolution for the three tablets are included in Figs 2–4.

The release rate in vivo is close to that in vitro for formulation A at low agitation rates. The estimated in vivo release rate from tablet C is comparatively close to that in vitro during the initial 1 h from the beginning. During this time

TABLE 2

Pharmacokinetic data following oral administration of a single dose of naftidrofuryl hydrogen oxalate to healthy subjects

Subject	Sex	Weight (kg)	Formulation															
			Solution (100 mg)				Tablet A (100 mg)				Tablet B (300 mg)				Tablet C (300 mg)			
			C_{max} ($\mu g\,l^{-1}$)	t_{max} (h)	AUC ($\mu g\,h\,l^{-1}$)	k (h^{-1})	C_{max} ($\mu g\,l^{-1}$)	t_{max} (h)	AUC ($\mu g\,h\,l^{-1}$)	F [a]	C_{max} ($\mu g\,l^{-1}$)	t_{max} (h)	AUC ($\mu g\,h\,l^{-1}$)	F [a]	C_{max} ($\mu g\,l^{-1}$)	t_{max} (h)	AUC ($\mu g\,h\,l^{-1}$)	F [a]
1	F	51	417	0.5	582	0.46	257	1	767	1.32	484	1	1327	0.76	633	2	1824	1.04
2	F	55	291	0.5	396	0.30	220	2	708	1.79	524	0.5	942	0.79	488	1	1519	1.28
3	F	52	347	0.5	529	0.42	271	1	730	1.38	478	1	1182	0.74	706	1	2374	1.50
4	F	58	545	0.5	913	0.28	250	1	1012	1.11	756	1	2313	0.84	674	1	2384	0.87
5	M	75	252	0.5	564	0.39	206	1	573	1.02	– [b]	– [b]	– [b]	– [b]	726	1	1672	0.99
6	M	74	189	0.5	270	0.50	113	0.5	366	1.35	302	1	618	0.76	– [b]	– [b]	– [b]	– [b]
7	F	59	270	0.5	524	0.62	144	0.5	257	0.49	537	1	1260	0.80	– [b]	– [b]	– [b]	– [b]
8	F	56	206	0.5	396	0.58	– [b]	– [b]	– [b]	– [b]	505	1	974	0.82	– [b]	– [b]	– [b]	– [b]
9	M	81	525	0.5	835	0.42	– [b]	– [b]	– [b]	– [b]	1139	0.5	1549	0.62	– [b]	– [b]	– [b]	– [b]
Mean			338	0.5	557	0.44	209	1	630	1.21	590	0.9	1271	0.77	645	1.2	1955	1.14
S.D.			131	– [c]	206	0.11	60	– [c]	256	0.40	254	– [c]	507	0.07	95	– [c]	402	0.25

[a] Relative extent of bioavailability ($AUC_{tablet}/AUC_{solution} \cdot dose_{solution}/dose_{tablet}$).

[b] Dropouts.

[c] Not calculated.

TABLE 3

Mean pharmacokinetic data after cross-over administration to four female volunteers (subjects 1–4)

Formulation	C_{max} ($\mu g\,l^{-1}$)	t_{max} (h)	AUC ($\mu g\,h\,l^{-1}$)	F [a]
Solution	400	0.5	605	– [b]
Tablet A	250	1.25	804	1.3
Tablet B	561	0.9	1441	0.8
Tablet C	625	1.25	2025	1.1

[a] Relative extent of bioavailability ($AUC_{tablet}/AUC_{solution} \cdot dose_{solution}/dose_{tablet}$)
[b] Not calculated.

period, in vitro release is less dependent on agitation rate and dissolution liquid than later on. Additionally, a correlation exists for tablet B during the first hour, but only at low agitation intensities. After 1 h, no correlations exist between the calculated value of the in vivo rate and that in vitro from either of the two high dosage strength

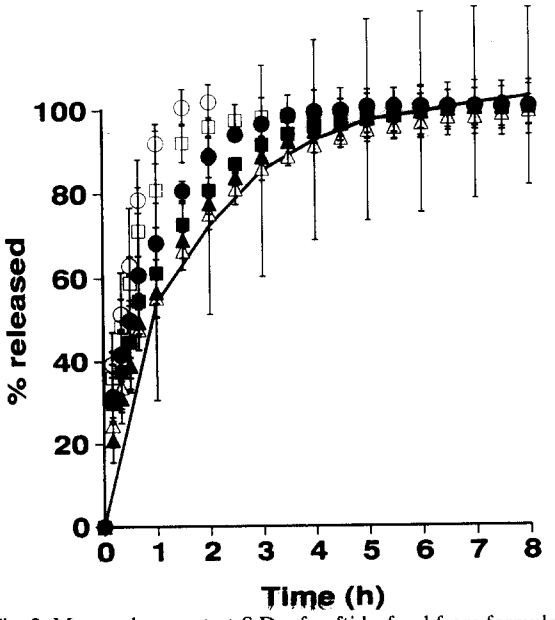

Fig. 2. Mean release rate ± S.D. of naftidrofuryl from formulation A. (△) In vitro, 50 rpm in phosphate buffer ($n = 6$); (□) in vitro, 75 rpm in phosphate buffer ($n = 6$); (○) in vitro, 100 rpm in phosphate buffer ($n = 6$); (▲) in vitro, 50 rpm in hydrochloric acid ($n = 6$); (■) in vitro, 75 rpm in hydrochloric acid ($n = 6$); (●) in vitro, 100 rpm in hydrochloric acid ($n = 6$); (———) in vivo by means of numerical deconvolution ($n = 7$).

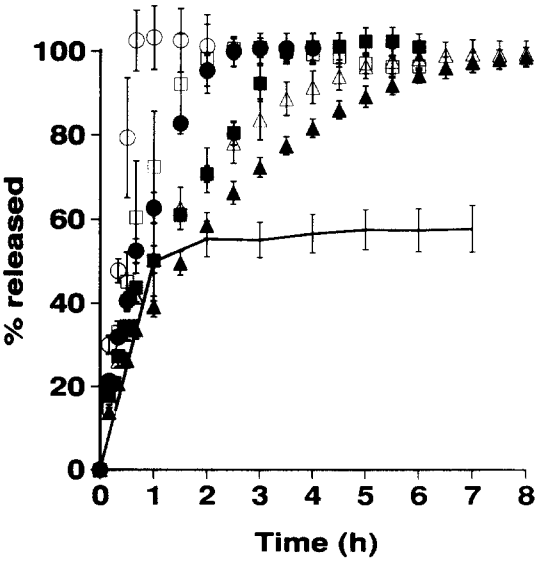

Fig. 3. Mean release rate ± S.D. of naftidrofuryl from formulation B. (△) In vitro, 50 rpm in phosphate buffer ($n = 6$); (□) in vitro, 75 rpm in phosphate buffer ($n = 6$); (○) in vitro, 100 rpm in phosphate buffer ($n = 6$); (▲) in vitro, 50 rpm in hydrochloric acid ($n = 6$); (■) in vitro, 75 rpm in hydrochloric acid ($n = 6$); (●) in vitro, 100 rpm in hydrochloric acid ($n = 6$); (———) in vivo by means of numerical deconvolution ($n = 8$)

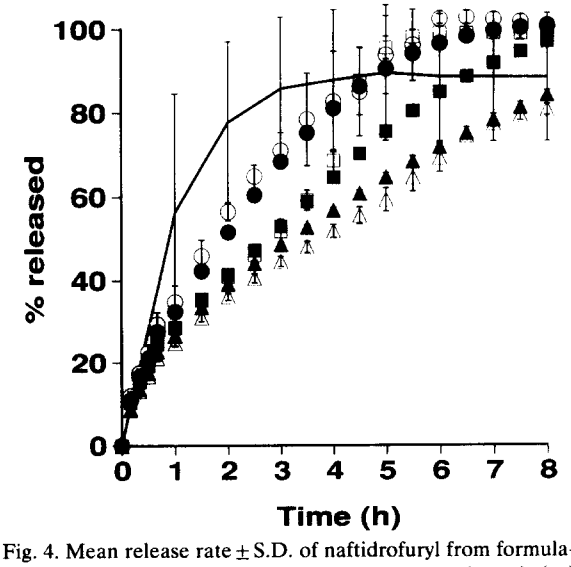

Fig. 4. Mean release rate ± S.D. of naftidrofuryl from formulation C. (△) In vitro, 50 rpm in phosphate buffer ($n = 6$); (□) in vitro, 75 rpm in phosphate buffer ($n = 6$); (○) in vitro, 100 rpm in phosphate buffer ($n = 6$); (▲) in vitro, 50 rpm in hydrochloric acid ($n = 6$); (■) in vitro, 75 rpm in hydrochloric acid ($n = 6$); (●) in vitro, 100 rpm in hydrochloric acid ($n = 6$); (———) in vivo by means of numerical deconvolution ($n = 5$)

formulations under any of the dissolution conditions used.

Discussion

Extent of bioavailability

Several authors (Westlake, 1972; Shirley, 1976; Metzler, 1989) have stressed the limited relevance of using ANOVA for testing the null hypothesis of no difference between drug treatments. The application of confidence intervals is proposed to be more useful. In this case, the application of ANOVA would be erroneous, as the observed variances of the treatments are inhomogeneous.

A 95% confidence interval for the relative extent of bioavailability (Table 4) indicates no difference after administration of 100 mg naftidrofuryl in aqueous solution compared to a hydrocolloid matrix tablet with a rapid release in vitro. A 3-fold increase in tablet dose results in changes that are impossible to explain as yet. When a 3-fold dose is given in a matrix tablet, having rapid release in vitro, a significant reduction in both the plasma peak concentration and the extent of bioavailability is observed. This suggests that the absorption capacity is limited. However, when the larger dose is given in a matrix tablet (C), with comparatively slower in vitro release, a similar plasma peak and extent of bioavailability are achieved. The results thus indicate that the bioavailability of naftidrofuryl is dose dependent. Other authors (Lartigue-Mattei et al., 1978) have determined a bioavailability of $F = 0.76$ for a p.o. capsule (50 mg) relative to i.v. injection (50 mg). However, it is not known whether the differences are due to first-pass metabolism, or to reduced absorption.

TABLE 4

95% confidence interval for the bioavailability ratio ($AUC_{tablet} / AUC_{solution} \cdot dose_{solution} / dose_{tablet}$)

Formulation	Confidence interval
Tablet A ($n = 7$)	1.17 ± 0.32
Tablet B ($n = 8$)	0.76 ± 0.12
Tablet C ($n = 5$)	1.09 ± 0.33

TABLE 5

Average fluctuations in plasma concentration calculated as mean of individual ratios from subjects 1–4 during 8 h and 12 h intervals

Formulation	$\frac{C_{max}}{C_{8\,h}}$	S.D. [b]	$\frac{C_{max}}{C_{12\,h}}$ [a]	S.D. [b]
Solution	50	20	230	160
Tablet A	10	3	50	30
Tablet B	25	10	110	50
Tablet C	15	4	70	30

[a] Estimated from the concentration measured 8 h after administration

[b] Standard deviation.

A 3-fold difference in the extent of bioavailability and peak concentrations was observed in the nine volunteers taking the aqueous solution. The reason for this might be explained by the interindividual variations in the pharmacokinetics of naftidrofuryl. It is also possible that the variations to some extent are due to interindividual differences in the dose ingested, since neither the amount remaining in the bottles was determined, nor was post-dose rinsing of the bottles performed. The interindividual variations after intake of tablet A are nevertheless at least as large, which appears to exclude this theory.

In vitro vs in vivo conditions

From the plasma curves obtained after a 100 mg tablet dose, it is apparent that the release and absorption of naftidrofuryl are rapid. The extended release effect of the matrix tablets is consistently small, as demonstrated by the average fluctuation in the plasma concentrations during the observed 8 h interval (Table 5). On consideration of a twice daily dosage regime, the estimated ratio, $C_{max}/C_{12\,h}$, reveals a reduction of the fluctuations within a dose interval of about a fifth. It is apparent that the 300 mg tablet B does not produce any extended release effect. The most promising results are provided by tablet C, which despite the 3-fold higher dose, is found to cause similar fluctuations to those of the low

dose tablet A. However, the amount of hydrocolloids in both tablets A and C still appears to be insufficient for achieving markedly extended release in vivo.

From the in vitro experiments, it is clear that the release rate is best controlled during the initial 1 h from the beginning. Thereafter, when the gel has formed, the environmental conditions exert an effect upon it. The same is expected to occur in the gastrointestinal tract. A similar xanthan gum based matrix tablet, with the characteristic of extended release controlled by a mixed erosion-diffusion process, has been studied by another research group (Wilson et al., 1989). By using gamma scintigraphy, the latter workers were able to identify a bimodal release pattern from the matrices in humans. The investigated matrix tablets contained more gelling agent than did our three formulations. It appeared from their study that once 50% of the matrix had eroded, the gel layer became more friable, and disintegration proceeded more rapidly. The in vivo release pattern was not evident from the in vitro tests employed.

When using a 100 mg dose, and thereby also a smaller tablet, it is possible to attain more uniform plasma levels, and a comparatively close association between the release rate in vivo and that in vitro. It is apparent that mild agitation (at 50 rpm) results in the nearest approach to simulating the in vivo conditions. At this rate of agitation, it appears to be unimportant whether the dissolution liquid in the in vitro test is a buffer or acid.

Conclusions

This study has shown that the rate of bioavailability of naftidrofuryl is dependent both on the dose and on the in vivo release rate of the drug. A close correlation between the rate of release in vitro and that estimated in vivo was obtained after administration of a 100 mg dose in hydrocolloid matrix tablets. However, no association was found when using tablets containing 300 mg of the drug. Matrix tablets of this strength and having a comparatively slow release in vitro showed bioavailability equal to that of the 100 mg tablet, and better than that of the faster releasing formulation. With the use of such tablets, it should be possible to bring about a significant reduction in the fluctuations in plasma concentrations during a dose interval of 12 h.

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