International Journal of Pharmaceutics, 28 (1986) 167–175
Elsevier

IJP 00949

Bioequivalence study of nitrofurantoin tablets: in vitro–in vivo correlation

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(Received April 8th, 1985)
(Modified version received July 31st, 1985)
(Accepted September 20th, 1985)

Key words: nitrofurantoin – bioequivalence – urinary excretion – in vitro–in vivo correlation – USP dissolution test – bioavailability

Summary

The USP dissolution test was used to select products with a wide range of dissolution characteristics for in vivo examination. The bioequivalence of five (100 mg) chemically equivalent NTF products was evaluated in two crossover urinary excretion experiments. First, three products were compared with the innovator lot (Furadantin) in 12 subjects according to a 4×4 latin square design. In the second experiment, one product was compared to the same innovator lot in a 10 subject 2×2 latin square design. A significant rank order correlation was observed between the first-order dissolution rate constant and the calculated in vitro mean residence time ($r = 0.67$, $P < 0.05$). Significantly different, lower bioavailability was observed in three NTF products in relation to that of the innovator product. Linear in vitro–in vivo correlations were found between the ln of the amount dissolved in 1 h and the cumulative amount excreted in the urine up to 10 h ($r = 0.912$, $P = 0.03$), and between the mean dissolution time and the slow rate constant ($r = 0.90$, $P = 0.03$).

Introduction

Nitrofurantoin (NTF), a drug which has been widely used in treating urinary infections, is listed among those possessing potential bioavailability problems (Gardner, 1977). These characteristics have been reviewed (Cadwallader et al., 1975). Furthermore, bioinequivalency among NTF commercial products has been documented (McGilveray et al., 1971; Mattok et al., 1972; McGilveray et al., 1973; Meyer et al., 1974; DiSanto et al., 1976).

One objective of dissolution tests and in vitro–in vivo correlations is to identify poor bioavailable products from those considered therapeutically acceptable. In vitro–in vivo correlations between dissolution and bioavailability data for NTF products have been discussed in the literature. The dissolution test specifications of the United States

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Pharmacopeia XVIII, XIX, XX and XX Suppl. 5 (United States Pharmacopoeia, 1970, 1975, 1980, 1984) for the NTF tablets have been changing but keeping the same procedure. Mattok et al. (1977) reviewed the in vitro–in vivo correlations for NTF and pointed out that physicochemical and physiological factors, which affect the bioavailability of NTF, make it difficult to achieve a satisfactory dissolution test for NTF. Recently, Bron et al. (1979) studied the bioavailability and dissolution characteristics of 3 NTF products using the USP XX disintegration apparatus with dissolution media of pH 7.2; their results indicate an in vitro–in vivo correlation with the disintegration apparatus, and no correlation when the USP XX dissolution test was used. On the other hand, the Sartorious apparatus was a better predictor of absorption than the USP XX method for 4 different tablets of NTF (Gladigau et al., 1978). Partially, this study addresses the question: is the USP dissolution test for NTF tablets achieving the proposed objetive?

Although 4 tablet dissolution tests are considered in the Mexican Pharmacopoeia, the NTF dissolution test has not yet been included (Mexican Pharmacopoeia, 1974). For practical purposes, manufacturers and government drug quality centers in Mexico adopt the USP dissolution tests since more information is available about them. The objectives of this study were to examine the bioequivalence of several NTF commercial products from Mexico and to determine if differences in dissolution rate, using the USP XX method, would correlate well with bioavailability parameters. Dissolution of NTF was determined in 21 commercial tablet preparations according to the USP XX procedure. The bioequivalence of five chemically equivalent products was evaluated in two urinary excretion studies, using latin square designs. The first study was conducted on 12 volunteers in order to determine the bioequivalence among four NTF products; in the second study, with 10 volunteers, the bioavailability of a Mexican product was compared to that of the reference material. In the two bioequivalence studies, Furadantin was included as the standard.

Materials and Methods

In vitro studies

Nitrofurantoin products. One to 6 lots of NTF products from 7 Mexican manufacturers and the innovator's product [Furadantin, lot 273705] from a US manufacturer, were examined. All Mexican dosage units were donated by the manufacturers. Table 1 summarizes the 21 commercial NTF tablets evaluated in vitro, 17 labeled with 100 mg and 4 with 50 mg. Each product was designated with a specific letter for identification, assigning letter A to the innovator product. Since the Mexican Pharmacopoeia does not specify product content assay and content uniformity for NTF tablets, these tests were conducted according to the British Pharmacopoeia procedure (British Pharmacopoeia, 1973), in view of its simplicity and equipment availability. The values presented are expressed in terms of the mean percentage and standard deviation of labeled content actually found by analysis. Since the limits in the B.P. are 90.0–100.0% of the labeled amount of NTF, all products met the specification. The content uniformity determinations of each of the 21 nitrofurantoin products are also summarized in Table 1. In all cases the average of the content uniformity was in agreement with the product composite assay.

Disintegration test. The disintegration test of each product was conducted according to the USP XX procedure.

Dissolution test. The release characteristics of the 21 NTF products were obtained using the USP XX Suppl. 5 procedure. Four ml samples were removed and filtered at 5, 10, 15, 30, 60, 90, 120, 130 and 150 min. The samples were assayed spectrophotometrically at 367 nm.

In vivo studies

Bioequivalence protocol. Two separate relative bioavailability studies were performed using the same innovator product as reference. These studies were carried out according to latin square designs. Every subject fasted overnight prior to the experiment and food was withheld for 4 h after dosing. Each subject ingested a single 100 mg oral dose of NTF product with 150 ml of water. To ensure adequate hydration, each subject drank 300 ml of

TABLE 1

PHYSICOCHEMICAL CHARACTERISTICS OF THE NITROFURANTOIN TABLETS TESTED

Product	Manufacturer	Product content assay (%) (n = 3)	Content uniformity (%)	Disintegration time (min) (n = 6)	MDT (min) (b)	(K_{dis} ($min^{-1} \times 10^{-3}$) (c)
A	Innovator	99.5(1.6)	100.4(1.6)	0.7 (0.1)	48.8	10.0
B(a)	1	102.0(2.3)	101.4(3.5)	1.6 (0.1)	15.6	68.5
C	1	99.3(3.0)	99.2(3.2)	3.4 (1.2)	35.1	117.0
D	2	96.6(1.4)	96.5(3.9)	0.4 (0.1)	30.5	227.0
E	2	99.0(1.6)	98.2(2.8)	2.2 (2.4)	31.6	31.3
F	3	90.3(2.7)	88.6(1.2)	85.8(23.5)	58.6	2.5
G	3	104.0(2.7)	97.8(5.5)	49.0(14.3)	68.9	1.8
H	3	101.0(3.8)	100.3(2.8)	3.5 (1.7)	46.0	0.3
I	3	96.0(1.1)	96.8(1.1)	20.7 (2.2)	60.8	1.7
J	3	101.0(1.7)	99.9(2.2)	46.9 (2.2)	79.3	0.6
K	3	92.5(3.8)	91.8(2.7)	8.8 (1.5)	57.8	1.0
L	4	100.0(2.7)	101.5(1.7)	23.1 (3.7)	50.4	7.0
M(a)	4	101.8(3.5)	101.6(1.6)	12.2 (1.6)	59.8	4.4
N	6	90.5(2.0)	91.8(1.3)	40.2 (4.9)	48.7	0.3
O	4	100.3(1.4)	101.3(1.4)	9.6 (3.0)	53.8	10.2
P	4	98.3(1.8)	97.5(2.7)	5.0 (2.6)	53.4	7.6
Q(a)	4	100.8(1.4)	102.2(4.5)	6.4 (0.4)	55.1	12.7
R	4	101.0(1.6)	100.3(2.3)	3.5 (1.7)	51.0	11.3
S	5	92.1(3.8)	92.0(6.2)	27.3(15.9)	61.5	7.0
T(a)	5	101.8(1.4)	102.8(1.9)	(d)	56.2	21.7
U	7	95.5(1.9)	94.5(5.5)	(d)	111.7	0.3

Results are expressed as the mean and (S.D.).

(a) 50 mg labeled product; (b) MDT, mean dissolution time determined from the percent labeled content (n = 6); (c) K_{dis}, first-order dissolution rate constant determined from the average of the percent labeled remaining to be dissolved vs time; (d) it was not determined.

water 2 h prior to drug administration. Subsequently, 150 ml of water were administered at 1, 2, 3 and 4 h after dosing. A standard lunch was ingested by all subjects 4 h after dosing, and a standard supper 4 h after lunch. This procedure was repeated at weekly intervals until all dosage units were administered.

Selection of the subjects. Twenty healthy male and two female volunteers participated in the studies after being informed of the purpose, protocol and risks of the study (age 20–30 years; weight 60–70 kg; height 160–170 cm). Each subject gave written consent to participate in the study. All subjects were in good health according to findings from physical examinations and hematological and urinary laboratory tests. Subjects did not take any other medication or alcohol for at least 7 days prior to and throughout the entire study.

Urinary excretion. Blank urine samples were obtained from each volunteer prior to dosing. Quantitative urine collections were obtained during each of the following time intervals: 0–0.5, 0.5–1.0, 1.0–1.5, 1.5–2.0, 2.0–3.0, 3.0–4.5, 4.5–6.0, 6.0–8.0, 8.0–10.0 and 10.0–12.0 h. Since no significant amount of NTF was excreted in urine from 10–12 h, the same sample urine collection intervals were used in the second study, up to 10.0 h. An aliquot of each sample was frozen and protected from light until the day of analysis.

Analysis of urine samples. A spectrophotometric analytical procedure (Conklin et al., 1965) was used to assay NTF in urine. One ml of urine was acidified with 1.0 ml of saturated solution of ammonium sulfate. Three ml of nitromethane were added, mixed and centrifuged. One ml of the nitromethane layer was combined with 0.5 ml of

0.04 M hyamine hydroxide (Sigma Chemicals, U.S.A.) in absolute methanol. The absorbance of this solution was determined at 400 nm in a Zeiss PM 2DL spectrophotometer. The concentration of NTF in urine was determined by means of a standard calibration curve. Blank urine samples, collected prior to drug administration, were also analyzed. Each sample's absorbance was corrected for the blank urine value.

Study I. The bioavailability of NTF tablets designated as treatments I, J and M were compared with treatment A, the recognized innovator product (Furadantin). This study involved 12 volunteers, 10 male and 2 female. Each subject ingested a single 100 mg dose of NTF.

Study II. The purpose of this study was to examine the relative bioavailability of 100 mg NTF tablets (Treatment L) with the reference product (Treatment A). This study included 10 healthy adult male volunteers in a 2×2 latin square crossover design.

Statistical analysis. The Cochran's test for homogeneity of variance was conducted on all in vivo and in vitro parameters. When significant nonadditivity of untransformed data was found, all the data of that parameter were subjected to a ln(x) transformation. The analysis of variance for complete crossover design was utilized to determine whether there were differences in bioavailability. Each cumulative amount of NTF excreted at each time, and the bioavailability parameters: time to reach the maximum rate of excretion; maximum rate of excretion achieved; time for NTF to appear in urine after administration, T_{lag}; mean residence time, MRT; slow and fast (from non-linear fitting) rate constants, K_2 and K_1, respectively, were statistically analyzed.

The fitting constants K_2 and K_1 for NTF were obtained according to a one compartment open model, using the following relationship:

$$X_t = 100\left[(1 - 1/K_2 - K_1)(K_2 e^{-K_1 t} - K_1 e^{-K_2 t})\right]$$

where X_t is the percent of drug excreted to time t. The percent amount remaining to be excreted was subjected to digital computer least square iterations using the NONLIN program (Metzler et al., 1976) to obtain the best estimates.

Results and Discussion

In vitro

Disintegration test. According to the USP XX the disintegration times of NTF tablets should be less than 30 min. As shown in Table 1, Products F, G, J and N failed this test; all 6 tablets from each product had disintegration times greater than 30 min. Four tablets from Product S had disintegration times greater than the limit, thus also failing the test.

Dissolution test. The USP XXI dissolution test requires 'not less than 25% of the labeled amount of NTF is dissolved in 60 min and not less than 85% of the labeled amount of NTF is dissolved in 120 min'. The percentage of NTF dissolved at different times for each of the 21 products is shown in Fig. 1. The percent dissolved in 60 min was less than 25% for Products I, F, J, L, M, N and U. In addition, only Products B, D and T dissolved more than 85% in 120 min. Moreover, the innovator's product lot did not meet the upper limit. Significant differences in dissolution between products were determined at 60 and 120 min; Table 2 presents the analysis of variance for the percentage of NTF dissolved at 60 min. Ranges of dissolution characteristics for the mean of the percentage dissolved at 60 min among the 21 NTF tablets were determined by the Fisher's least significant difference test (Table 2). Significant interlot variation of NTF dissolution from manufacturers 1–5 is observed, Tables 1 and 2. Interlot variations from the same manufacturer have been observed with the USP dissolution test (Mattok et al., 1972; Meyer et al., 1974). These observations support the idea of Mattok et al., 1972, of utilizing the USP dissolution test as a tool in controlling the variability of the manufacturing process, since it discriminates among different lots.

Statistical moment analysis, which is model independent, has been suggested to examine in vitro–in vivo correlations (Riegelman et al., 1980). Relationships between the mean in vitro dissolution times (in vitro MDT) and several dissolution models have been presented, i.e. the MDT is inversely related to the first-order dissolution rate constant (Tanagawara et al., 1982). The mean in vitro MDT of the 21 NTF products were calcu-

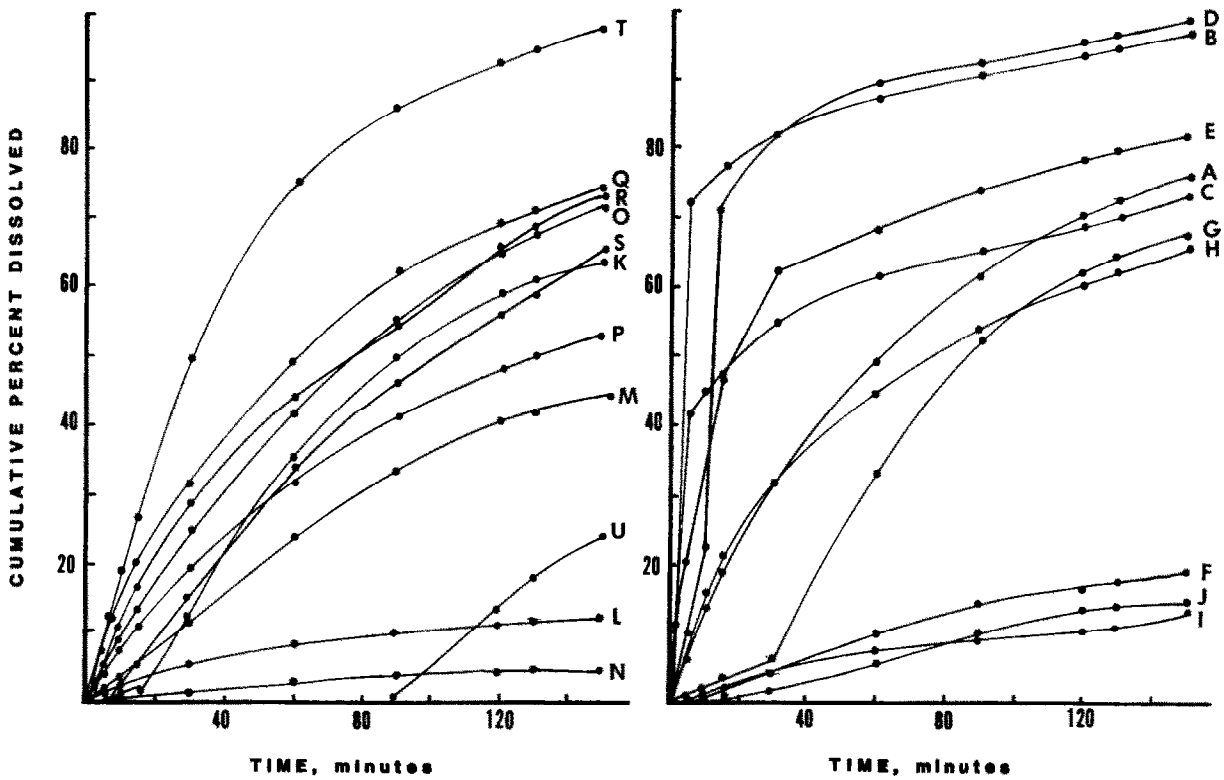

Fig. 1. Mean cumulative labeled percent of nitrofurantoin dissolved from 21 different products using the U.S.P. XX dissolution test. Each data point is the mean of 6 determinations. Product code letters (Table 1) appear beside the 150 min sample.

lated by the linear trapezoidal rule without extrapolation to infinite time (Yamaoka et al., 1978). Dissolution rate constants were calculated assuming first-order kinetics from the percent remaining to be dissolved of the content assayed; for most of the products this assumption seemed to be adequate since a significant inverse rank order correlation was determined between the first-order dis-

TABLE 2

ONE-WAY ANALYSIS OF VARIANCE OF PERCENT DISSOLVED OF LABELED NITROFURANTOIN AFTER 60 MIN [a]

Source of variation	Degrees of freedom	Sum of squares	Mean squares	F ratio	Significance level
Total	137	94980.5			
Between products	22	89636.5	4074.3	87.7	$P < 0.05$
Within products	115	5344.0	46.46		

[a] By use of Fisher's Least Significant Difference Test [b,c]: U N J I L F M P S G K O H R Q A C E T D B

[b] Products underlined by the same line are not significantly different ($P > 0.05$).

[c] See Table 1 for code letters.

solution rate constant and the in vitro MDT ($r = -0.67$, $P < 0.05$). Furthermore, as would be expected, for the five in vivo products studied (A, I, J, L and M) perfect rank order correlation was found between the dissolution rate constant and the in vitro MDT. This model independent parameter may describe the drug input of the NTF products according to the in vitro–in vivo correlations discussed in the following sections.

In vivo

In Study I, significant differences in NTF bioavailability parameters were found among products by means of analysis of variance. Table 3 presents the bioavailability parameters from products A, J, I, and M. Differences in amount excreted, K_2, K_1 and T_{lag} were significant between products ($P < 0.05$). Even though a flip flop model for NTF has been demonstrated in rabbits (Watari et al., 1983, 1984) and in a human (Garcia and Lopez, 1981), the fast and slow rate constants of NTF were statistically tested and significant differences were found between products ($P < 0.05$). Such differences can only be attributed to differences between the preparations studied. Fig. 2 shows the mean cumulative amount of NTF excreted in urine up to 10 h; significant differences in the cumulative amount excreted between products were observed after 1.0 h ($P < 0.05$). The

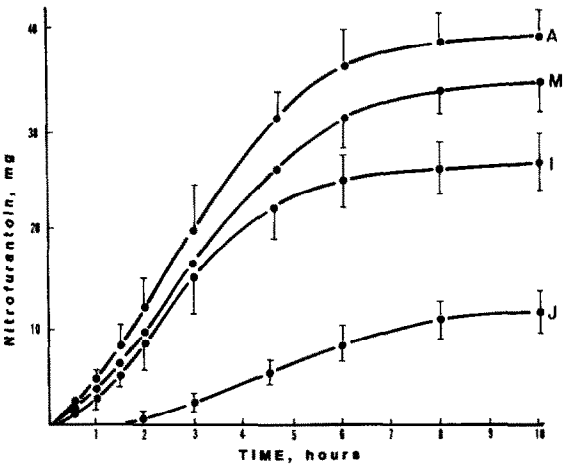

Fig. 2. Mean cumulative amount of nitrofurantoin excreted in urine after single oral administration of nitrofurantoin products. Each data point is the mean of 12 subjects; bars indicate 1 S.E. Product code letters (Table 1) appear beside the 10 h sample.

Fisher's least significant difference test was employed to rank the total amount (mg) of NTF excreted among the products, showing that preparations A and M were not significantly different:

A	M	I	J
38.1	34.4	26.4	11.0

TABLE 3

STUDY I: AVERAGE AND (S.D.) OF NITROFURANTOIN BIOAVAILABILITY PARAMETERS FROM TWELVE HEALTHY VOLUNTEERS FOLLOWING A SINGLE 100 mg ORAL DOSE

Bioavailability parameter	Product				Significance level of difference among treatments
	A	J	I	M	
Cumulative amount excreted up to 10 h (mg) [a]	38.1 (13.3)	11.0 (7.0)	26.4 (11.7)	34.4 (10.9)	$P = 0.001$
Fast rate constant (h^{-1}) [b]	0.90 (0.35)	0.57(0.18)	1.20 (1.08)	0.95 (0.54)	$P = 0.021$
Slow rate constant (h^{-1}) [b]	0.70 (0.24)	0.43(0.24)	0.70 (0.24)	0.61 (0.19)	$P = 0.006$
Lag time (h) [a]	0.38 (0.38)	2.21(0.96)	0.46 (0.45)	1.08 (1.12)	$P = 0.001$
Peak excretion rate (mg/h) [a]	13.2 (5.7)	4.2 (2.8)	13.8 (11.7)	13.1 (4.8)	NS
Peak excretion time (h) [a]	2.9 (1.64)	4.1 (1.27)	2.9 (1.18)	3.3 (1.72)	NS

[a] Experimental data.

[b] Obtained after fitting of the experimental data to a one-compartment open model (Metzler, 1969).

Significant differences were observed at the last three sampling times between products I and M, and no differences at all times among products A and M. Furthermore, after the ln(x) transformation, significant difference between products in peak rate of excretion was observed, ($P < 0.05$).

In Study II, significant difference in extent of bioavailability, as measured by total NTF excretion over 10 h, was observed with Product L, giving a ratio of 68% of A. In addition, significant differences in cumulative NTF excretion were detected for each collection period from 1.5 h. However, no differences were found in other bioavailability parameters, Table 4. The mean cumulative amount of NTF excreted in urine vs time is presented in Fig. 3.

No statistical differences were found, by means of a t-test ($P > 0.05$), between all Product A bioavailability parameters from Study I and those from Study II.

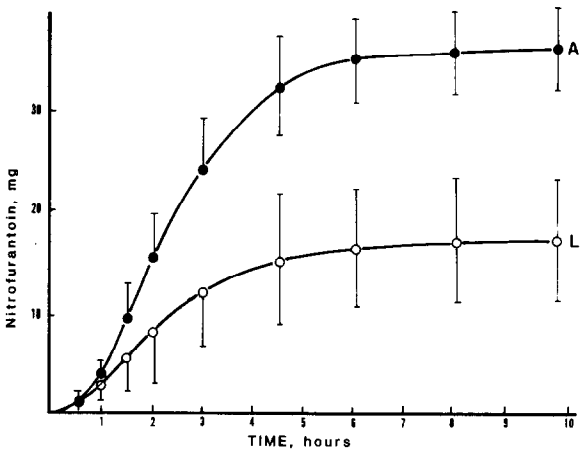

Fig. 3. Mean cumulative amount of nitrofurantoin excreted in urine after single oral administration of nitrofurantoin products. Each data point is the mean of ten subjects; bars indicate 1 S.E. Product code letters (Table 1) appear beside the 10 h sample.

In vitro–in vivo correlations

No significant in vitro–in vivo correlations could be determined by considering disintegration from the five NTF products (Studies I and II). However, the disintegration times were correlated with the bioavailability parameters of the 4 products of Study I. The in vitro disintegration time correlated significantly with the cumulative amount of NTF excreted at the first h ($r = 0.999$, $P < 0.05$) and with the cumulative amount of NTF excreted at 12 h ($r = 0.974$, $P < 0.05$). In contrast with these results, Mattok et al., (1972) reported two NTF products that failed the USP disintegration test but had bioavailabilities of 96 and 89%, while one product that passed the disintegration test had a lower relative bioavailability.

TABLE 4

STUDY II: AVERAGE AND (S.D.) OF NITROFURANTOIN BIOAVAILABILITY PARAMETERS FROM TEN NORMAL VOLUNTEERS FOLLOWING A SINGLE 100 mg ORAL DOSE

Bioavailability parameter	Product		Significance level of difference among treatments
	A	L	
Cumulative amount excreted up to 10 h (mg) [a]	36.2 (4.9)	17.1 (5.5)	$P = 0.01$
Fast rate constant (h^{-1}) [a]	1.00(0.34)	1.00(0.49)	NS
Slow rate constant (h^{-1}) [b]	0.72(0.20)	0.83(0.40)	NS
Lag time (h) [a]	0.25(0.20)	0.16(0.15)	NS
Peak excretion rate (mg/h) [a]	11.07(6.80)	6.57(3.22)	NS
Peak excretion time (h) [a]	2.63(0.53)	2.28(1.27)	NS

[a] Experimental data.

[b] Obtained after fitting of the experimental data to a one compartment open model (Metzler, 1969).

Mattok et al. (1977) suggested a comparison between the amount of NTF recovered in urine in 1 or 2 h after drug administration with the dissolution parameters. Mendes et al. (1978) using the USP dissolution test on 6 experimental formulations and a commercial innovator tablet product as a reference, found a significant linear correlation ($r = 0.80$, $P < 0.05$) between the percentage of NTF excreted in urine after 3 h versus the amount dissolved in 1 h. In agreement with their observations, in Study I, a significant correlation was found between the first-order dissolution rate constant and the amount of NTF excreted in 1 h after the administration of the four NTF products ($r = 0.970$, $P < 0.05$). Likewise, the in vitro MDT correlated with the cumulative amount excreted of NTF in 1 h ($r = 0.977$, $P < 0.05$).

In vitro–in vivo correlations were found when dissolution characteristics were considered. Fig. 4 presents a linear correlation between the ln of the amount dissolved at 60 min and the cumulative amount of NTF excreted in urine up to 10 h ($r = 0.912$, $P = 0.03$). Furthermore, the in vitro MDT was correlated with the slow rate constant ($r = 0.90$, $P = 0.03$) and also with T_{lag} ($r = 0.90$, $P = 0.03$). No significant in vitro–in vivo correlations were found when the amount dissolved at 120 min was considered.

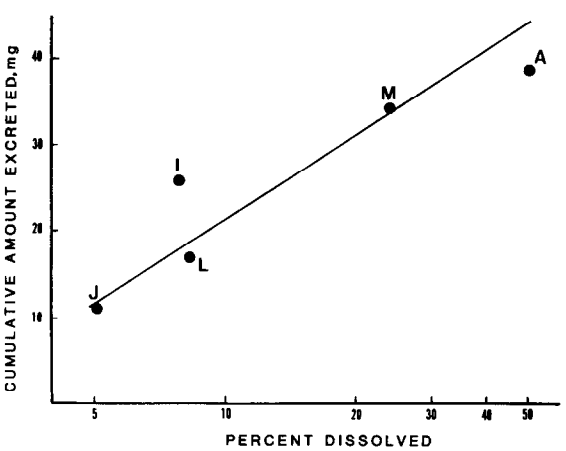

Fig. 4. Linear correlation between the ln of the amount dissolved at 60 min and the cumulative amount of NTF excreted in urine up to 10 h ($r = 0.91$, $P = 0.03$). The amount excreted for product A was considered from bioequivalence Study I. Product code letters are shown next to each observed data point (see Table 1).

As can be seen from Fig. 4, the in vitro–in vivo correlation presents a scatter, such that, its reliability could not be adequate for predictible purposes. The direct application of the USP dissolution standard at 60 min fails to discriminate bioequivalent from inequivalent products, since product M fails to meet the specifications although of acceptable bioavailability. Nonetheless, the studies do show that NTF tablet products which dissolve very slowly (less than 10% in 60 min) under USP conditions had poor bioavailability.

Conclusions

The bioinequivalence of three marketed NTF products has been shown. Differences in NTF release characteristics from products of the same manufacturer have been established. These results indicate the need to further evaluate the quality of NTF drug products in the Mexican market. An official requirement is needed to assure the bioequivalence of NTF products, or at least indicate products with poor bioavailability characteristics. Finally, the results of this study also point out the need to evaluate the bioequivalence of other drugs with poor absorption characteristics in countries like Mexico, where most of the pharmaceutical technology has been transferred.

Acknowledgements

We are especially grateful to M. Luisa Garcia P., Isaura Carrera and Rosa Lorenia M. for technical assistance in some analytical determinations, as well as to Mary E. de Lopez for the hematological and urinary laboratory tests. This study was supported by a grant from the American States Organization (OAS) under the name of 'Special Project No. 4: Biopharmaceutical Evaluations'.

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