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RESEARCH PAPER

Bioequivalence Study of Paracetamol Tablets: In Vitro–In Vivo Correlation

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ABSTRACT

The bioequivalence of three chemically equivalent paracetamol generic Mexican products (500 mg tablets) was evaluated in 12 healthy volunteers using the American innovator product (Tylenol, McNeil, Fort Washington, PA), as the reference. Single oral doses of each product were administered at 1-week intervals using a 4 × 4 Latin square design balanced for the first residual effect. The total amount of paracetamol excreted in urine in 24 hr was taken as a measure of bioavailability. In addition, moment analysis was used to estimate in vitro mean dissolution time (MDT) from dissolution profiles obtained following the USP 23 dissolution test specified for paracetamol tablets and to estimate in vivo mean residence time (MRT) from urinary excretion data. Significant differences in the dissolution performance and in the cumulative amount of paracetamol excreted in urine up to 24 hr were observed when the data were analyzed by analysis of variance (ANOVA) ($p < .05$*). Classical and Westlake 90% confidence limits, as well as the two-sided* t *test proposed by Schuirmann, and the Anderson-Hauck power analysis supported the final conclusion that only one of the three generic paracetamol products studied can be considered equivalent to the reference product Tylenol. A linear correlation between in vitro MDT and in vivo MRT was found.*

Key Words: *Bioavailability; Bioequivalence; Generic products; In vitro–in vivo correlation; Paracetamol.*

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INTRODUCTION

Paracetamol is a nonsteroidal analgesic and antipyretic drug widely used as a substitute for aspirin. It has also been included since 1991 among the 200 essential drugs recommended by the World Health Organization. The popularity of this drug has increased to the point that it is now available around the world from many sources in several dosage forms. The pharmacokinetics, metabolism, and bioavailability of this drug have been extensively studied (1–5); however, the bioequivalence of the marketed drug products is poorly described, and the information about in vitro–in vivo correlation is scarce and frequently controversial. Since 1971, several authors have documented inequivalence among some formulations of marketed generic drug products of paracetamol (6,7). Several formulation factors of the manufacturing process may modify the dissolution rate and the bioavailability of paracetamol from solid dosage forms (8–13). It has also been established that absorption of paracetamol from oral tablet preparations can be dissolution rate limited (8,14). Moreover, van Bommel et al. (15) demonstrated that two controlled-released formulations with different release profiles of paracetamol also showed different plasma concentration profiles. On the other hand, the USP dissolution test for paracetamol tablets has failed for some formulations that are bioequivalent, and some authors have proposed alternative dissolution methods (16).

Over 10 different pharmaceutical solid dosage forms in the Mexican market contain paracetamol alone. However, information about the bioequivalence for these generic drug products is not available. The in vitro dissolution characteristics for seven paracetamol tablet products from different manufacturers were presented in a previous paper (17). Three of these products were selected on the basis of differences found in their dissolution performance when compared to the innovator product (Tylenol, McNeil, Fort Washington, PA), and they were included in the present study. So, the objectives of this study were to investigate the bioequivalence of three commercial generic drug products from the Mexican market containing paracetamol and to examine if differences in the dissolution rate using the USP 23 method could correlate well with bioavailability parameters.

MATERIALS AND METHODS

Preparations

Three different products of 500 mg paracetamol tablets from Mexican manufacturers were studied: Tempra lot FDE16, Mead Johnson, Mexico; Tylenol 22273, Cilag Mexico; Febrim lot 2138, Rimsa Mexico; and Tylenol lot JBA145, McNeil, Fort Washington, PA, which was used as the reference product (innovator). Each product was randomly designated with a specific letter for identification: C, D, E, and I (innovator).

In Vitro Studies

Weight variation, content, and content uniformity assays were conducted on 20 tablets of each brand according to the USP 23 procedure for paracetamol tablets (18).

The release characteristics of the paracetamol Mexican products and the innovator product (500 mg tablets) were determined using the USP 23 procedure on 12 tablets of each lot (18).

From the filtered samples, 5 ml were removed at 1, 3, 5, 10, 15, 30, 45, 60, 90, and 120 min. Samples were diluted with the dissolution medium (phosphate buffer at pH 5.8) and were assayed spectrophotometrically at 242 nm by a previously validated method (17). The amount of paracetamol dissolved at each time was calculated in comparison with a calibration curve that was prepared the same day of the study.

In Vivo Studies

Protocol

The in vivo studies were performed on 12 healthy volunteers, 6 men and 6 women (aged 21–26 years, weight 48–72 kg, height 160–172 cm). All volunteers were in good physical health according to findings from physical examinations and hematological and urinary laboratory tests.

Each subject was informed about the purpose, protocol, and risk of the study and gave written consent to participate. Subjects did not take any other medications or alcohol for at least 2 weeks prior to and throughout the entire study. Each subject was assigned randomly and administered each of the four products according to a complete crossover Latin square design (4×4) with balance for first residual effect.

Each subject fasted overnight prior to the experiment, and food was withheld for 4 hr after dosing. The tablets were swallowed with 150 ml of water. In addition, each subject drank 300 ml of water 2 hr prior to drug administration and 150 ml of water at 1, 2, 3, and 4 hr after dosing to ensure adequate hydration. A standard lunch was given to all subjects 4 hr after dosing, and a standard supper was given 4 hr after lunch. This procedure was repeated at weekly intervals until all products were administered.

A washout period of 1 week was included between the administration of each product.

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, 3.0–4.0, 4.0–6.0, 6.0–8.0, 8.0–10.0, 10.0–12.0, and 12.0–24.0 hours after dosing. The total volume of urine voided over each time interval was measured, and aliquots of each sample were frozen in labeled containers until the day of analysis.

Analytical Procedure

Paracetamol in urine samples was determined by a colorimetric method previously developed and validated in our laboratory. This method is linear from 0.1 to 0.5 mg of paracetamol per milliliter of urine ($r^2 = 0.998$, $n = 10$), with a mean variation coefficient of 1.7%. Paracetamol is stable in urine samples at least for 4 weeks at −20°C (19).

Statistical Analysis

The accumulative amount of total paracetamol excreted in 24 hr Xu_{24hr}, the peak urinary excretion rate V_{max}, the time to reach the peak urinary excretion rate t_{max}, the mean residence time (MRT), and the pharmacokinetic constants k_2 and k_1 (obtained by adjusting data to a one-compartment model from urinary excretion data) were statistically analyzed. Analysis of variance (ANOVA) for complete crossover design (Latin square) was utilized to determine whether there were differences among products. Classical and Westlake 90% confidence intervals were estimated for Xu_{24hr}, t_{max}, and V_{max}, and two one-sided t tests (proposed by Schuirmann and Anderson-Hauck) were also performed to assess the final bioequivalence decision.

Confidence limits greater than 20% were considered statistically significant. The statistical analysis was performed using Biopack, version 2.0 (Scientific Consultants, Inc., Apex, NC).

RESULTS AND DISCUSSION

In Vitro Studies

All products met the pharmacopoeial specifications for weight variation, content assay, and content uniformity assay. Dissolution behaviors of the four brands studied are shown in Fig. 1. The results represent the mean of 12 units (mean ± SEM). All tablets met the USP 23 dissolution specifications (not less than 85% of the labeled amount of paracetamol dissolved in 30 minutes), although significant differences in dissolution rates along the entire profile were found ($p < .05$). Products C and E showed faster dissolution rates, especially during the first 30 min, compared to the innovator product. Significant differences were also found in the total amount of paracetamol dissolved at 120 min for product D compared with the rest of the products.

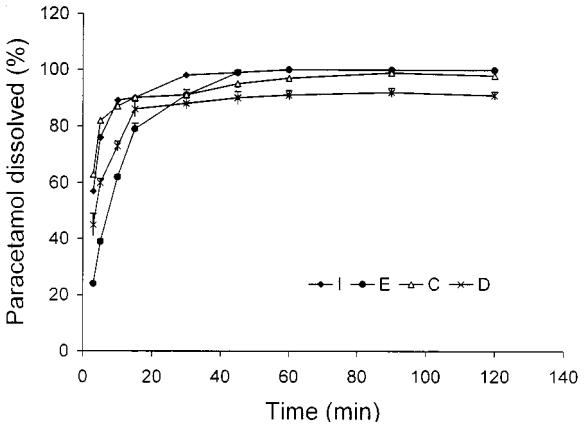

Figure 1. Dissolution profiles for generic (C, D, E) and innovator (I) paracetamol tablet products following USP 23 dissolution test specifications for paracetamol tablets. Data represent the mean of 12 tablets plus and minus the standard error.

Dissolution rate constants were calculated, assuming first-order kinetics for fast dissolution products, from the logarithm of plot of the remaining percentage to be dissolved versus time (20). Profiles obtained indicate that dissolution is associated with apparent first-order kinetics for fast dissolution products. These results confirm data obtained by Najib and Jalal (21), who observed first-order dissolution kinetics in the case of fast-release paracetamol tablets.

Dissolution t_{50} and t_{85} were also calculated. In this study, t_{50} agrees with experimental data obtained for all products. Statistically significant differences were found in t_{50} and t_{85} among the products studied in the present study ($p < .05$), so they cannot be considered equivalent in their in vitro release characteristics.

Statistical moment analysis, which is model independent, has been suggested as a better parameter to examine in vitro–in vivo correlation (22,23). The in vitro mean dissolution times (in vitro MDTs) for the products studied were calculated by linear trapezoidal rule without extrapolation to infinite time. The in vitro MDT has been

inversely related to the first-order dissolution constant. In this case, this assumption seemed to be adequate since a significant correlation was found between the first-order dissolution rate constant and the in vitro MDT ($r = .941$). Products C, D, and E showed statistically significant differences in their dissolution characteristics. In addition, differences were found in t_{50}, t_{85}, dissolution rate constant, and dissolution efficiency and especially in their in vitro MDT when they were compared to the innovator product by Dunnet's test.

In Vivo Study

The total amount of paracetamol excreted (free plus conjugated) in urine was taken as a measure of bioavailability. In many cases, the best way to estimate bioavailability is by analyzing drug blood levels, but although a plasma method for paracetamol and its metabolites exists, the use of a noninvasive method (urine method) might allow us to discriminate bioavailability characteristics of different paracetamol generic products in a rapid and easy way. So, this study might be considered as an alternative for ''screening'' bioequivalence properties of paracetamol commercial products existing in the Mexican market.

It has been well documented that urinary excretion rates of paracetamol are directly proportional to serum concentrations (7,24); therefore, urinary data were considered adequate to assess differences in the absorption of paracetamol from generic drug products. Mean cumulative percentages of paracetamol excreted up to 24 hr after the intake of the four preparations are shown in Fig. 2. Differences in the accumulative amount of paracetamol excreted can be observed among products, especially at initial times. Moment analysis was also used to estimate in vivo MRT from urinary excretion data. ANOVA for the Latin square statistical model design utilized demonstrated significant differences in the total amount of paracetamol excreted at 24 hr (Table 1).

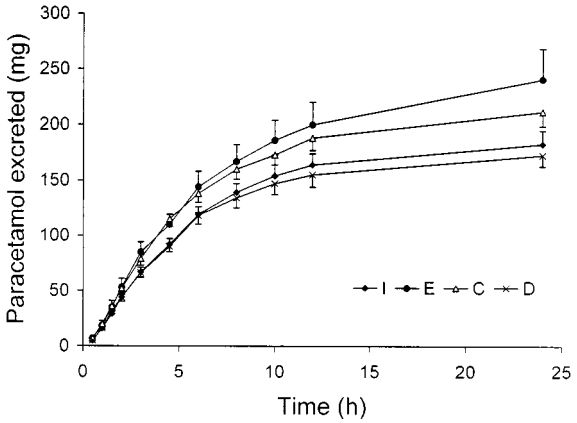

Figure 2. Mean cumulative amount of paracetamol excreted in urine after oral administration of paracetamol tablet products. Data represent the mean of 12 subjects plus or minus standard error.

Mattok et al. (24) compared efficiencies and rates of absorption of eight lots of tablets, one elixir, and an aqueous solution of paracetamol. No differences in rate of extent of availability were observed from either blood or urinary excretion data (both free and total levels). Vila-Jato et al. (25) studied the effect of the molecular weight

Table 1

Bioavailability Parameters Following Oral Administration of Paracetamol Commercial Tablets

Bioavailability Parameter	Product				
	C	D	E	I	*p*
Cumulative amount excreted at 24 hr	212.72 (13.6)	173.30 (10.1)	241.25 (28.3)	183.50 (12.1)	<.01
Peak excretion rate (mg.hr^{-1})	39.4 (2.0)	36.3 (5.2)	46.7 (6.0)	34.4 (3.2)	<.05
Peak excretion time (hr)	2.0 (0.3)	2.2 (0.1)	2.2 (0.2)	1.8 (0.1)	n.s.
Fast rate constant k_1 (hr^{-1})	1.59 (0.08)	1.67 (0.23)	1.50 (0.19)	1.50 (0.14)	n.s.
Slow rate constant k_2 (hr^{-1})	0.21 (0.01)	0.21 (0.03)	0.19 (0.02)	0.19 (0.01)	n.s.
In vitro mean dissolution time (min)	8.9 (0.11)	9.3 (0.17)	14.7 (0.14)	7.4 (0.09)	<.05
Mean residence time (hr)	7.2 (0.6)	6.9 (0.9)	8.4 (0.8)	7.1 (0.5)	<.05
Relative bioavailability (%) IC_{90}	115.9 (70.5–129.5)	94.4 (84.8–115.2)	131.4 (60.7–139.3)	100	<.01

Mean values from 12 subjects (SEM).
p = level of significance.

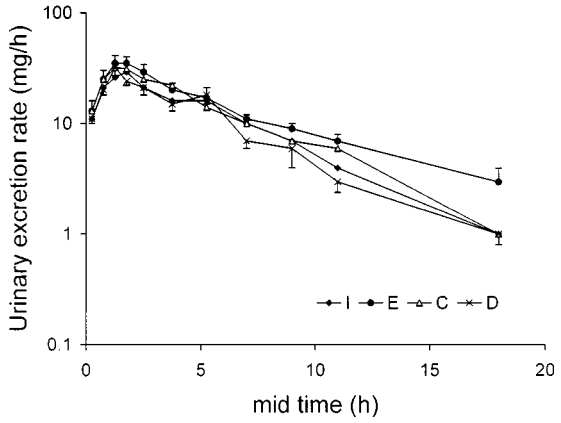

Figure 3. Mean urinary excretion rate for paracetamol commercial products and the reference product. Data represent the mean of 12 subjects plus or minus standard error.

of polyethylene glycol on the bioavailability of paracetamol–polyethylene glycol solid dispersions (25). They observed that the total amount of drug excreted was the only bioavailability parameter affected, and no significant differences were observed among the MRTs. These authors attributed their results to the wide intersubject variability observed in the kinetics of the orally administered drug. Similar variations have been found by other authors, with absorption constants ranging from 0.25 to 4.25 hr^{-1} and coefficients of variation up to almost 50% (6,26). On the contrary, Concheiro et al. (7) developed a relative bioavailability study of orally and rectally administered dosage forms using urinary excretion data of 15 subjects. In their study, the total amount excreted was similar for the three formulations, but showed significant differences between the MRTs of capsules and suppositories. In the present study, the coefficients of variation in the bioavailability parameters evaluated were similar to other studies previously reported in the literature and even much lower. In this case, the total amount of paracetamol excreted up to 24 hr was considered as the most reliable bioavailability parameter to reflect the extent of paracetamol absorption of the products studied.

Figure 3 shows the mean urinary excretion rates obtained from 12 subjects after the administration of the four preparations. Urinary excretion data were fitted to Eq. 1 using the nonlinear regression PCNONLIN program, version 4.0:

$$dXu/dt = \frac{kekaFXo}{ka - K}\,(e^{-Kt} - e^{-kat}) \qquad (1)$$

where dXu/dt is the urinary excretion rate, ke is the apparent first-order renal excretion rate constant, ka is the apparent first-order absorption rate constant, K is the apparent first-order elimination rate constant, F is the fraction of dose absorbed, and Xo is the dose administered.

The above equation represents a simple one-compartment model with first-order input. This model gave a good fit between the observed and predicted values indicated by correlation coefficient values greater than 0.96 and residual plots in which the standard residuals were evenly spread around the zero value. Some pharmacokinetic parameters calculated from these data are included in Table 1. Even so, as the present study is not a real pharmacokinetic study, we assumed the previous model, where $ka \gg K$ or $k_1 \gg k_2$, and considered that k_1 corresponds to the apparent rate constant for the first process (or fast rate constant or absorption rate), and $K = k_2$, the slow rate constant (or apparent elimination rate constant or terminal process rate constant). To support these assumptions, we compared the values obtained for k_2 (apparent elimination rate constant) with those previously reported by other authors in pharmacokinetic studies using blood samples after intravenous or oral administration. Average values obtained for the slowest rate constant ranged from 0.19 to 0.21 hr^{-1}. No significant differences were observed for the apparent terminal rate constants of paracetamol after the administration of the different products ($p > .05$). Values for paracetamol elimination half-life in the present study obtained from slow rate values agree with those previously reported in the literature (2,8,14,15). Other bioavailability parameters such as peak excretion rate V_{max} and time to reach peak excretion rate t_{max} are included in Table 1.

Bioequivalence Decision

The currently accepted criteria in the United States for bioequivalence for most dosage forms requires that the mean pharmacokinetic parameters of the test dosage form should be within 80% to 120% of the reference dosage form using the 90% confidence interval (27,28). In this case, the total amount of drug excreted in urine was taken as the more reliable measure of bioavailability. Relative bioavailability obtained by comparing Xu_{24hr} of the products tested in relation to the innovator product I (reference product) was greater, 131.4% for product E and 115.9% for product C; in addition, 90% confidence limits and Westlake's confidence interval (WCI 90%) were invariably greater than 20%. Further, both products were not found bioequivalent to the reference formulation by Schuirmann's two one-sided t test ($p > .05$) or the Anderson-Hauch test. These results justify the conclusion of the nonbioequivalence of these two products; however,

product D lies within the bioequivalence acceptable ranges.

It must be emphasized that, although significant differences were found between the dissolution behavior of product D and the innovator product I, this is not reflected in the in vivo performance (bioequivalent). On the other hand, products E and C, which also differ in their dissolution characteristics (especially in their MDTs), also differ in their in vivo performance. Therefore, it can be stated that, although dissolution profiles from generic products can be used as a tool to ensure the quality control of drug products, it does not always reflect the in vivo performance; therefore, bioequivalence studies must be conducted for generic paracetamol drug products to ensure their in vivo equivalence.

In Vitro–In Vivo Correlation

For immediate-release products, a single in vitro–in vivo correlation may be predictive of the in vivo performance of several formulations. For instance, in vitro MRT may be correlated with a single in vivo pharmacokinetic parameter such as AUC, C_{max}, Xu_t, and the like. Although the dissolution test was established in 1971 in USP 21, there are no studies for paracetamol tablets on the correlation of the in vivo bioavailability parameters and the official dissolution test. Mattok et al. (24) investigated the dissolution of different lots of paracetamol tablets by means of three simple dissolution procedures. None of the methods provided complete correlation with physiological availability of paracetamol when estimated from blood or urine profiles. On the other hand, Evora et al. (16) observed discrepancies between the in vitro results obtained following the pharmacopoeial dissolution test and the bioavailability shown with a tablet formulation. Sotiropoulus et al. (8) also suggested a comparison between the amount of paracetamol recovered in urine after drug administration and the dissolution parameters when using different dissolution conditions from those specified by the USP method. Recently, van Bommel et al. (15) confirmed a direct relation between the MRT and the in vitro MDT of two slow-release paracetamol formulations. In agreement with the observations of van Bommel et al., a significant correlation ($r = .9321$) was found in the present study between MRT and the in vitro MDT for the four products (Fig. 4). This kind of correlation has been considered as a level B correlation by official organisms (27,28).

Since neither intravenous data nor solution data for paracetamol formulations were gathered, an approach based on cumulative relative fraction absorbed (CRFA) was also utilized to achieve an in vitro–in vivo correlation. The CRFA in vivo was calculated from Eq. 2 and correlated to the cumulative fraction dissolved (CFD) in vitro in 2 hours (29).

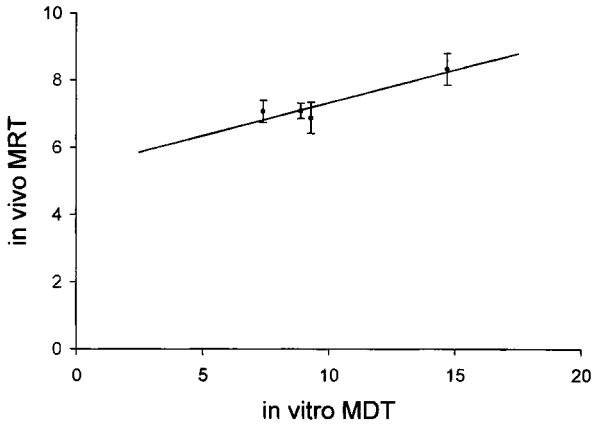

Figure 4. Correlation between mean dissolution time (MDT) (calculated from in vitro dissolution data) and mean residence time (MRT) (calculated from urinary excretion data. Data represent the mean of 12 determinations plus and minus the standard error.

$$\text{CRFA} = \frac{(dXu/dt)_T + K(Xu)_T}{K(Xu)_\infty} \quad (2)$$

where dXu/dt is the urinary excretion rate, $(Xu)_T$ is the cumulative urinary amount excreted in urine at time T, $(Xu)_\infty$ is the cumulative urinary amount excreted at infinite time, and K is the apparent first-order elimination rate constant.

Absorption profiles were constructed for the four products using the above equation and the same urinary excretion data. The fraction absorbed in vivo was then plotted against fraction dissolved in vitro to obtain in vitro–in vivo correlation. It was also observed that all products showed an adequate correlation between CFD in vitro and CRFA in vivo up to 2 hr: $r = .9963$ for product I, $r = .9905$ for product C, $r = .9321$ for product D, and $r = .9203$ for product E. However, it is important to emphasize that it might be necessary to demonstrate an in vitro–in vivo correlation from a greater number of paracetamol products studied as the number of products included in the present study was small.

Finally, Fig. 5 was constructed by plotting CFD versus CRFA up to 2 hr for the four products ($n = 20$). Although a statistically significant correlation was obtained in this case ($r = .55$, $p > .05$), it is obvious that a scatter exists, so it cannot be useful for prediction purposes. So, we

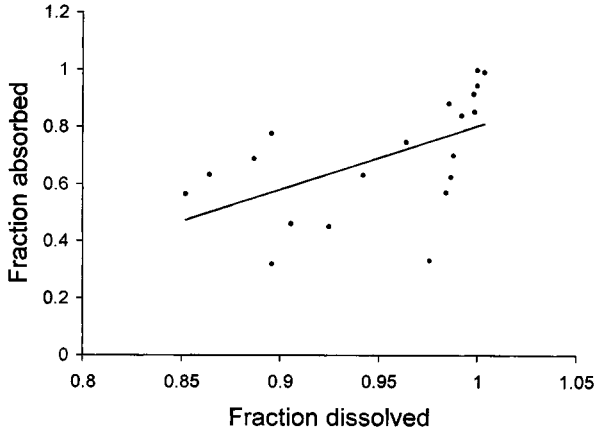

Figure 5. In vitro/in vivo correlation between the fraction dissolved (in vitro) and the cumulative fraction absorbed (in vivo) up to 2 hr for the four paracetamol products studied. Each point represents the mean of 12 determinations.

recommend conducting a bioequivalence study as the only accepted way to ensure the interchangeability of paracetamol generic drug products.

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