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BIOAVAILABILITY OF CEPHALEXINE DOSAGE FORMS

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ABSTRACT

The bioavailability of 3 brands of cephalexine (tablets, capsules and suspension) using a solution as a reference standard was evaluated in 8 healthy volunteers in a crossover design. Single oral doses of each product were administered at intervals of 1 week. Statistical analysis of the cumulative urinary amount of cephalexine excreted after 12 h, indicated no significant differences among them. Moment analysis was used to estimate the mean dissolution and mean absorption time, showing that dissolution is the rate limiting step in tablets and capsules.

INTRODUCTION

Cephalexine, a semisynthetic derivative of cephalosporine with a broad antibacterial spectrum against both gram positive and gram negative bacteria is advocated for the treatment of infections of the upper and lower respiratory tract genitourinary system, skin, soft tissue and bones and for certain other infections due to susceptible organisms. Blood concentrations of the drug after the usual therapeutic dose are high enough to be bactericidal against most susceptible organisms[1]. This drug is available for oral administration, in the mexican market there are 3 formulations available: tablets, capsules and suspension; therefore, this study was undertaken in order to determine the bioequivalence of the oral dosage forms and to determine if the absorption of this drug is dissolution rate limited.

MATERIALS AND METHODS

In vitro studies

Cephalexine content of the pharmaceutical dosage forms and the dissolution rates of tablets and capsules were determined using USP XXII method[2].

In vivo studies

All subjects received single doses of cephalexine in a different dosage forms:

a) Solution. A solution of 250 mg (as potency) of cephalexine in 150 mL of water was orally administered.

b) Suspension: 5 mL of a suspension containing 250 mg was administered with 150 mL of water.

c) Capsule: One 250 mg capsule was orally administered with 150 mL of water.

d) Tablet: One 500 mg tablet was orally administered with 150 mL of water.

Study was performed in 8 healthy male volunteers (age 23-28 years, weight 48-72 Kg, height 160-172 cm). Each subject gave written consent to participate in the study. Subjects did not take any other medications or alcohol for at least 2 weeks prior to and throughout the entire study. Study was carried out according a latin square design. Every subject fasted overnight prior to the experiment and food was withheld for 4 h after dosing. To ensure adequate hydration, each subject drank 200 mL of water 2 h prior drug administration.

Subsequentely 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 supper 4 h after lunch. This procedure was repeated at weekly intervals until all dosage units were administered.

Blank urine samples were obtained from each volunteers 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 - 2.5. 2.5 - 3.0, 3.0 - 3.5, 3.5 - 4.0, 4.0 - 6.0, 6.0 - 8.0, 8.0 - 10.0, and 10.0 - 12.0 horas. An alliquot of each sample was frozen and protected from light until the day of analysis.

Analysis of urine samples

A spectrofluorometric analytical procedure[3] was used to assay cephalexine in urine: One mL of urine sample was adjusted to pH 12 with the aid of a sodium hydrogen phosphate- sodium hydroxide buffer solution. After heating the sample at 100°C for 1 h, 1 mL of 2 N hydrocloric acid was added. The fluorophore was extracted into 7 mL of acetone-chloroform (2:3 v/v) by shaking for 5 min followed by centrifugation at 2000 rpm for 5 min. The organic layer was separated and the fluorophore re-extracted into 5 mL of borate buffer (pH 9.5) by shaking for 5 min followed by centrifugation at 2000 rpm. Fluorescence emission of the aqueous phase was measured in a spectrofluorometer Foci-Farrand model 2 using excitation and emission wavelength of 355 and 435 nm, respectively. The average relative standard deviation was 2.78% over the concentration range of 2.5 to 20 mcg/mL (R=0.998). The assay sensitivity was 0.5 mcg/mL. Samples were stable at least for 4 weeks at -4°C.

Statistical analysis

The urinary recovery and the mean residence time were evaluated by means of the linear trapezoidal integration and extrapolation. The statistical evaluation of the differences in MRT and urinary recoveries was achieved by means of the analysis of variance for complete crossover design. The 95 percent confidence limits of Westlake[4] were applied to the mean treatment differences for the amount of cephalexine excreted in 12 h. A paired T test was used to determine whether there were any significant differences in man absorption times.

RESULTS AND DISCUSSION

The results showed that the three pharmaceutical dosage meet the USP XXII requirements. Capsules and tablets also meet dissolution specifications (not less than 75% of the labeled amount dissolved at 45 min) water, 37°C and 100 rpm). At this time, percent dissolved for capsules was 100 % and for tablets 80% (figure 1).

The mean cumulative percent of cephalexine excreted up to 12 h after the intake of different formulations is shown in figure 2. Significant differences in percent excreted among products were observed at 0.5 and 1.0 h ($p < 0.05$), but at 4 h the percentages were similar for all formulations.

Table I shows the individual urinary excretion values for the different pharmaceutical preparations. It can be seen that the solution and suspension present the same time to attain the maximum excretion rate: 0.75 h, the capsule 1.25 h and tablet 1.75 h which indicate that absorption of tablet is slower. These values agree with dissolution profile which is showing that the capsule dissolves more rapidly than tablet. Relative bioavailability using solution as control was 97.1 % for suspension, 98 % for tablet and 98 % for capsules. Analysis of variance showed that there were differences among products. The statistical analysis with 95 % confidence limits: solution-capsule 94.35-105.67, solution-tablet 91.46-102.78, solution-suspension 92.96-104.3, show the biological equivalence of the treatments.

The oral and intramuscular absorption of cephalexine in normal human subjects has been

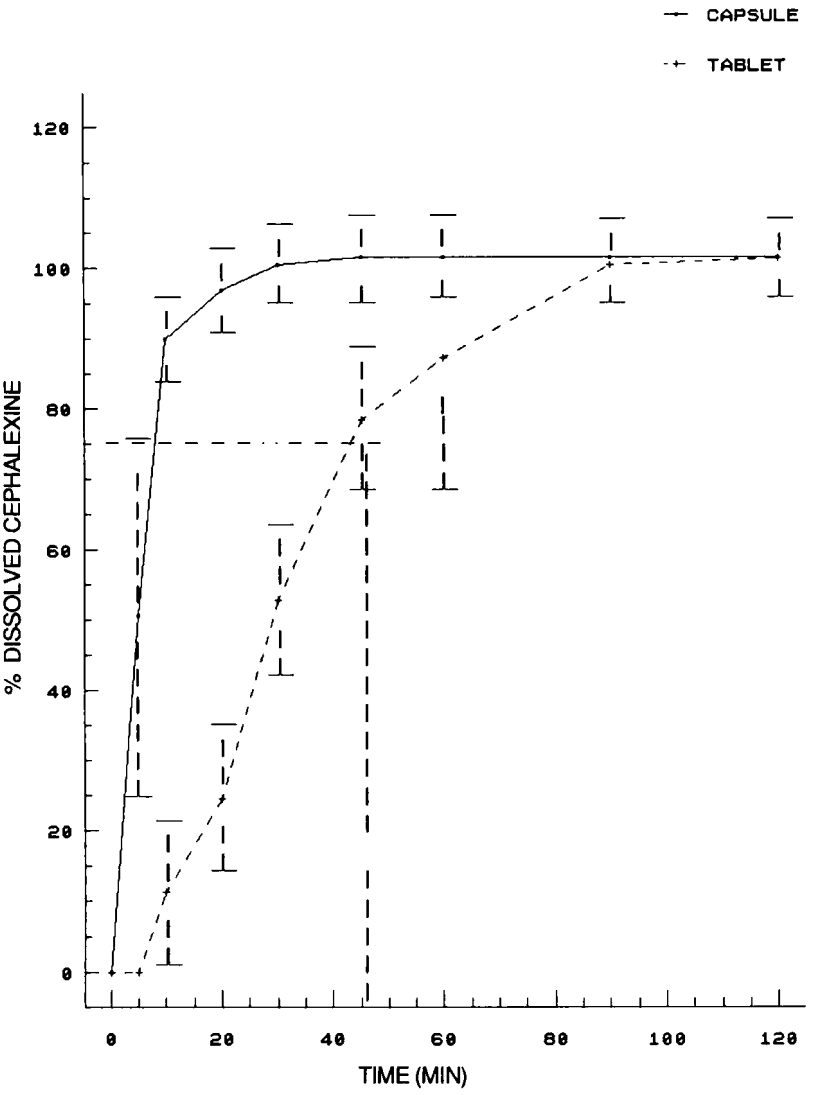

FIGURE 1

Dissolution Profile of Cephalexine Monohydrate Products Using USP XXII Method. (Mean ± SD).

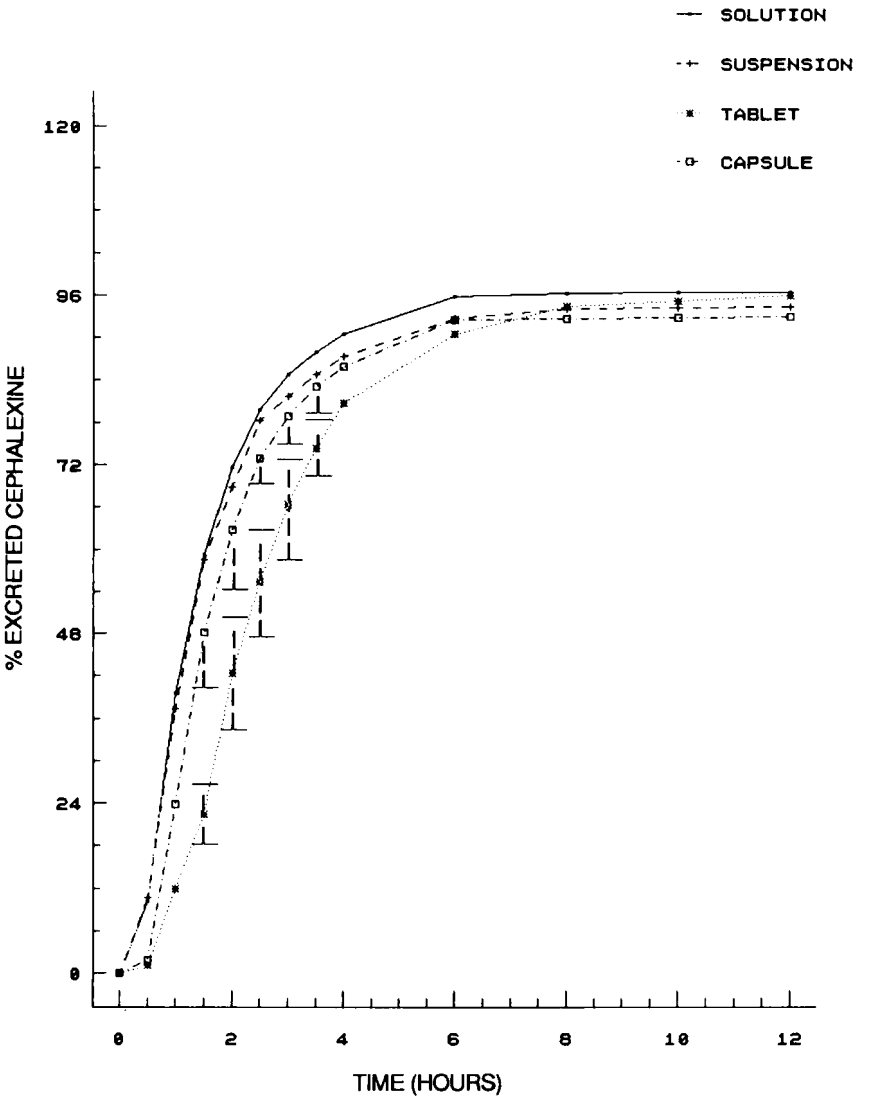

FIGURE 2

Mean Cumulative Percent of Cephalexine Excreted in Urine after Oral Administration in 8 Subjects. (Mean ± SD).

TABLE 1

Maximum Individual Excretion Rates After the Oral Administration of the Four Different Formulations

Volunteer	Solution		Suspension		Tablet		Capsule	
	$\frac{\Delta A_{ex}}{\Delta t}$	t_{max}	$\frac{\Delta A_{ex}}{\Delta t}$	t_{max}	$\frac{\Delta A_{ex}}{\Delta t}$	t_{max}	$\frac{\Delta A_{ex}}{\Delta t}$	t_{max}
1	47.29	1.25	43.81	1.25	46.46	1.75	64.54	1.25
2	49	0.75	77.17	0.75	74.04	2.25	63.90	1.25
3	48.52	1.25	54.48	1.25	40.77	1.75	63.44	1.25
4	83.47	0.75	43.59	0.75	48.65	1.75	58.71	1.75
5	70.07	0.75	51.13	0.75	50.61	1.75	67.26	0.75
6	69.79	0.75	64.74	0.75	54.30	1.25	64.29	0.75
7	61.62	0.75	60.25	0.75	43.28	1.75	50.69	0.75
8	60.91	0.75	70.88	0.75	50.05	1.75	58.28	0.75
$\bar{X}$	61.39	0.88	58.25	0.88	47.02	1.75	61.38	1.06
SD	12.85	0.21	11.46	0.21	4.27	0.25	4.93	0.35

TABLE 2

Moment Analysis of Orally Administered Cephalexine Products

	SOLUTION	SUSPENSION	TABLET	CAPSULE
MRT	1.89	1.90	2.98	2.22
MAT	0.51	0.5866	1.59	0.89
MDT	--	0.227	1.07	0.5158
F_{rel}		0.97	0.98	0.98

MRT = Mean Residence time
MAT = Mean Absorption time
MDT = Mean Dissolution time
F_{rel} = Relative bioavailability

studied[5-12]. Perkin et al, found that the drug is rapidly absorbed from gastrointestinal tract with peak levels being reached within 1 h. The time to reach peak levels may vary between individuals which can be attributed to a lag time in the absorption process due to dosage form effects[13]. Sulliman and Sayed[14] studied the bioequivalence of 6 brands of cephalexine tablets and capsules. They found that the products were bioequivalent. Results obtained in this work are in agreement with other investigators.

Statistical moment analysis which is model independent has been suggested to examine if dissolution is the rate limiting step[16]. Table II shows the individual values of mean residence time, mean dissolution and mean absorption time. Our results of

MRT of capsules agree with Cadorniga and col[15] results. Using a paired T test to determine whether there were significant differences between product MAT average and solution MAT average or not, we have found differences between capsule and solution and tablet and solution indicating that solid dosage forms of cephalexine are dissolution rate limited.

In vivo mean dissolution time values obtained agree with in vitro results being MDT from capsule lower than MDT from tablet.

The results of this study showed that cephalexine was absorbed faster from the suspension than the capsule or tablet under fasting conditions; however, the extent of absorption as refected by the cumulative amount excreted at 12 h was similar for all formulations. The drug is well absorbed as absorption is dissolution rate limited based on reported data.

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