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J. Clin. Pharmacol. 2001; 41; 783

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Pharmacokinetics of Buspirone Extended-Release Tablets: A Single-Dose Study

Adel Sakr, PhD, and Mahalaxmi Andheria, PhD

The objective of this study is to evaluate the absorption of buspirone and its biotransformation to 1-(2-pyrimidinyl) piperazine (1-PP) from two different extended-release (ER) formulations of buspirone HCl tablets (12-hour and 24-hour in vitro release) and from a commercially available immediate-release (IR) tablet. A single dose of the 30 mg ER tablets was compared with two doses of the 15 mg IR tablet administered 12 hours apart. Eighteen healthy male subjects participated in this randomized, open-label, three-treatment crossover study. Blood samples were obtained at 22 time points from predose (0 hour) until 36 hours postdose, and plasma concentration of buspirone and 1-PP was determined by LC/tandem mass spectrometry method. The pharmacokinetic

parameters AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , t_{max} , K_e , and $t_{1/2}$ were calculated and statistically analyzed. The results indicated extended release of buspirone from the two test products in vivo with a 70% to 90% greater bioavailability in comparison with the IR formulation. The bioavailability of 1-PP from ER formulations appears to be equal to that from the IR formulation. Both buspirone ER tablets successfully delivered bioavailable buspirone with a reduction in peak drug and metabolite plasma levels, prolonged buspirone plasma concentrations, and decreased ratio of 1-PP to buspirone concentration with less intersubject variation when evaluated as a single-dose study in healthy human subjects.

Journal of Clinical Pharmacology, 2001;41:783-789
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Buspirone hydrochloride, an azaspirodecenedione,^{1,2} is a pharmaceutically active compound found to be effective for the treatment of anxiety disorders and depression.

Buspirone was first synthesized in the early 1970s³ and has been extensively studied for its pharmacodynamics and pharmacokinetics since then. It has become one of the most widely prescribed anxiolytic drugs, due to its proven safety and efficacy, with less sedation and potential for physical dependence as shown by the benzodiazepines.⁴

When administered orally, the drug is rapidly and completely absorbed and undergoes extensive first-pass metabolism, having a mean bioavailability in humans of approximately 4%.^{5,6} Studies have demonstrated high interindividual variations in buspirone absorption, with differences in C_{max} up to 10-fold.⁷ Its major metabolite,^{8,9} 1-(2-pyrimidinyl) piperazine (1-PP), is pharmacologically active with about 20% to 25% of the

anxiolytic potency of buspirone. But it also has been shown that 1-PP antagonizes the anxiolytic and/or antidepressant action of buspirone and is associated with the occurrence of undesired or adverse events.

The biological half-life in humans is very short and variable, ranging between 2 and 11 hours.¹⁰ The average daily dose prescribed for adults is 30 mg buspirone HCl, administered as 10 mg tid or 15 mg bid.^{11,12} This frequent daily dosing regimen has a negative effect on patient compliance, especially due to its indication in psychiatric treatment.

The high first-pass metabolism leading to a low buspirone bioavailability and a high plasma concentration of 1-PP, associated with its slower elimination, results in a low buspirone/1-PP ratio in humans. This, along with the observed high intersubject variability,¹³ causes undesired or adverse events in the beginning of treatment and requires individual dose titration.

To improve patient compliance and the pharmacokinetic performance, two oral extended-release (ER) once-a-day formulations of buspirone HCl were developed. These two 30 mg ER tablets with different in vitro dissolution profiles (12-hour and 24-hour release) were evaluated in a single-dose kinetic study for the absorption of buspirone HCl and its biotransformation to 1-PP

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in comparison with two doses of 15 mg immediate-release (IR) tablets administered 12 hours apart.

MATERIALS AND METHODS

In Vitro Dissolution Studies

Two tablet formulations were designed and developed to release the drug over an extended period of time of 12 hours and 24 hours, respectively. Drug release profiles were studied by paddle method (Apparatus 2, USP 24, VanKel VK 7000 Dissolution tester with automatic sampling). The dissolution medium was 1000 mL of pH 6.8 buffer solution, containing 750 mL 0.1 N HCl plus 250 mL of 0.20 M tribasic sodium phosphate (USP 24, delayed-release, enteric-coated article). Samples were automatically assayed using spectrophotometer (Beckman UV/Vis Spectrophotometer, Model DU 640, Beckman Instruments, Inc.). The effect of scoring design on weight, content uniformity, and dissolution of the ER matrix tablet halves was also studied in detail.¹⁴

In Vivo Absorption and Biotransformation Studies

A single-dose pharmacokinetics study was performed at PharmaKinetics Laboratories, Inc. (Baltimore, MD). Study protocol 11448 was approved by the National Institutional Review Board of PharmaKinetics prior to the beginning of the study.

Products Studied

The following products were studied:

- 30 mg buspirone ER formulation, 12-hour release in vitro (American Pharmaceutical International, Inc.);
- 30 mg buspirone ER formulation, 24-hour release in vitro (American Pharmaceutical International, Inc.);
- 15 mg buspirone IR formulation (BuSpar[®], Bristol-Myers Squibb).

Study Design

Eighteen healthy male subjects were enrolled in an open-label, three-treatment, three-period, parallel crossover study with a 1-week washout between the three periods of the study. On two occasions, a single dose of a 30 mg ER buspirone HCl tablet was administered (at 0 hours), and on the third occasion, two doses (at 0 and 12 hours) of a 15 mg IR buspirone HCl tablet were administered. The order of treatment administra-

tion was randomized in three sequences (ABC, BCA, CAB) in blocks of three.

Subjects

Written informed consent was obtained from each subject prior to entry into the study. Sixteen subjects completed the study. The mean age was 43.1 years (range: 20-59), and the mean body weight was 163.2 lb (range: 136.0-218.0). Five subjects had a smoking status of 6 to 30 cigarettes per day. The subjects were approved by the investigating physicians based on their medical history, physical examinations (height, weight, vital signs, blood pressure, and pulse rate), and diagnostic laboratory results (fasting blood chemistry, hematology, urine analysis, HIV antibody, alcohol and drug abuse). The subjects were housed in a dormitory at the clinical facility from at least 12 hours prior to drug administration until 36 hours after the initial drug administration of each period. They were instructed to refrain from prescription drugs, over-the-counter (OTC) medicines, and alcohol throughout the study.

Subject 12 was withdrawn prior to period III because of persistent difficulties to obtain blood samples. Subject 14 was withdrawn prior to period II due to blood pressure that exceeded the limit specified in the study protocol. Subject 12 was dosed only with test product B (30 mg ER formulation, 24-hour release in vitro) and the reference product (15 mg IR formulation, BuSpar[®]); subject 14 was dosed only with test product B (30 mg ER formulation, 24-hour release in vitro).

Drug Administration

Drug administration occurred after a fasting period of at least 12 hours, beginning at 8 a.m. The drug products were administered with 240 mL of water according to the randomization schedule at 2-minute intervals. Subjects were not allowed to smoke 1 hour prior and 4 hours after drug administration and were not permitted to be supine for 4 hours postdose. A standard meal (xanthine-free, caffeine-free food and beverages) was given at 4 hours and 7.5 hours after the first dose in each period.

Blood Sample Collection and Processing

Ten mL of venous blood samples were obtained at 22 time points from predose (0 hours) until 36 hours postdose (at 0, 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 12.33, 12.67, 13, 13.5, 14, 16, 20, 24, 30, and 36 hours)

by direct venipuncture in a heparinized Vacutainer and were analyzed for buspirone and 1-PP. The samples were centrifuged at 10°C and 2500 rpm for approximately 20 minutes. The plasma was separated and stored frozen at -20°C to await analysis.

Chemical Analysis

The plasma samples were analyzed by an in-house developed and validated liquid chromatography/tandem mass spectrometry (LC/MS/MS)¹⁵ method on a C-18 column using a solvent system containing methanol and ammonium formate buffer at a flow rate of 0.25 mL per minute. BMY7378 dihydrochloride and 1-phenylpiperazine hydrochloride were used as internal standards for buspirone and 1-PP, respectively. The validated concentration ranges were 0.0500 ng/mL to 10.00 ng/mL for buspirone and 0.250 ng/mL to 50.0 ng/mL for 1-PP. The samples obtained for all three periods from a single subject, a set of eight calibration standards, and a set of six quality control samples were analyzed as a single run.

Pharmacokinetic Analysis

The pharmacokinetic parameters for buspirone and 1-PP were calculated from the plasma concentration-time profiles.¹⁶ The areas under the concentration-time curves (AUC) were calculated by linear interpolation between consecutive blood drug levels. AUC_{0-t} was calculated from zero time to the last measurable concentration C_T , and $AUC_{0-\infty}$ was calculated by extrapolation of AUC_{0-t} to time infinity by adding C_T/K_e to AUC_{0-t} . The elimination rate constant K_e was estimated by fitting the logarithm of the concentration versus time to a straight line over the observed exponential decline. C_T is the estimated concentration at the time of the last measurable concentration. Half-life ($t_{1/2}$), the maximum drug concentration (C_{max}), time to maximum drug concentration (t_{max}), and $C_{max}/AUC_{0-\infty}$ (C_{RAT}) were reported. For the immediate-release treatment, C_{max} and t_{max} were also reported for each dosing interval (0-12 hours and 12-24 hours). For each treatment, the cumulative areas under the concentration-time curve were computed to each sampling time after dosing.

Statistical Analysis

The arithmetic mean and standard deviation were calculated for each pharmacokinetic metric and for the buspirone and 1-PP concentration at each time point. All pharmacokinetic metrics were analyzed by analy-

sis of variance using SAS® (version 6.12), GLM procedure, and an *F*-test to determine statistically significant differences ($\alpha = 0.05$). Pairwise comparisons of the drug treatments were reported with the ANOVA.¹⁷ To obtain a Bonferroni multiple-comparison *t*-test, the attained probability was compared with the test probability, $\alpha = 0.05/3 = 0.0167$, for the set of three possible drug treatment comparisons. The analysis of variance included sequence, subject nested within sequence, period, and drug treatment in the statistical model. The power of the study to detect a 20% difference in parameter means as statistically significant at the 5% level of the *t*-distribution (two-tailed)¹⁸ was calculated for each pharmacokinetic metric. Bioequivalence was determined using the two one-tailed tests procedure, and the products were considered bioequivalent if the confidence interval was contained within the limits, 0.80 to 1.25.

RESULTS

In Vitro Drug Release Profiles

The drug release profiles from the two ER products are shown in Figure 1. The tablets showed an ER profile over a period of 12 hours and 24 hours, respectively, as desired for the study.¹⁴

In Vivo Single-Dose Study Results

Drug Safety Evaluation

The subjects were monitored for adverse signs and symptoms. Seven subjects reported a total of 13 adverse events during the study, but none of the events recorded were unexpected. All events were mild in severity and were resolved by the conclusion of the study without medical intervention. Three of the 13 events

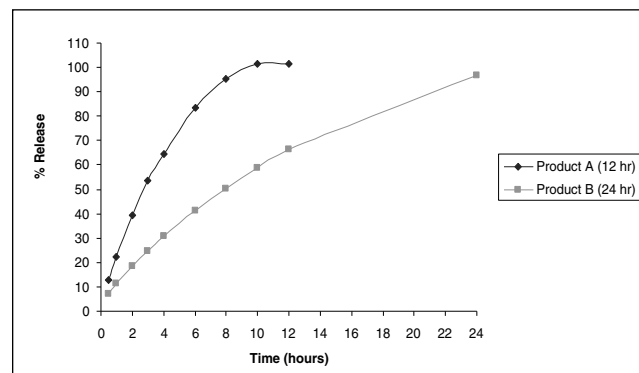


Figure 1. Dissolution profiles of the two test products.

Table I Pharmacokinetic Parameters for Plasma Buspirone: Arithmetic Means \pm Standard Deviation

Parameter	Number	Product A: Mean \pm SD	Number	Product B: Mean \pm SD	Number	Reference: Mean \pm SD
AUC _{0-t} (ng•h/mL)	16	20.00 \pm 22.58	18	19.14 \pm 21.28	17	11.97 \pm 14.64
AUC _{0-∞} (ng•h/mL)	16	20.96 \pm 22.85	15 ^a	22.24 \pm 23.61	16 ^b	12.90 \pm 15.05
C _{max} (ng/mL)	16	2.353 \pm 2.465	18	1.560 \pm 1.691	17	1.920 \pm 2.110 ^c
t _{max} (h)	16	5.438 \pm 1.711	18	7.741 \pm 4.077	17	0.85 \pm 0.39 ^c
C _{max} /AUC _{0-∞} (1/h)	16	0.1188 \pm 0.0613	15 ^a	0.0894 \pm 0.0411	16 ^b	0.1869 \pm 0.0393
t _{1/2} (h)	16	6.352 \pm 3.164	15 ^a	6.491 \pm 3.148	16 ^b	2.958 \pm 1.179

Product A = 30 mg buspirone extended-release (ER) formulation, 12-hour release in vitro. Product B = 30 mg buspirone ER formulation, 24-hour release in vitro. Reference = 15 mg buspirone immediate release (IR) (BuSpar®), administered at 0 and 12 hours.

a. From 3 subjects, insufficient values from terminal decay phase were obtained.

b. From 1 subject, insufficient values from terminal decay phase were obtained.

c. C_{max} and t_{max} were obtained from the first 12-hour dose of the IR reference product.

d. C_{max} and t_{max} were obtained from the second 12-hour dose of the IR reference product.

Table II Pharmacokinetic Parameters for Plasma 1-PP: Arithmetic Means \pm Standard Deviation

Parameter	Number	Product A: Mean \pm SD	Number	Product B: Mean \pm SD	Number	Reference: Mean \pm SD
AUC _{0-t} (ng•h/mL)	16	89.83 \pm 50.44	18	79.25 \pm 40.18	17	98.92 \pm 58.80
AUC _{0-∞} (ng•h/mL)	16	97.32 \pm 57.20	18	89.65 \pm 50.95	17	107.50 \pm 67.97
C _{max} (ng/mL)	16	6.256 \pm 2.396	18	4.953 \pm 2.154	17	6.223 \pm 1.886 ^a
t _{max} (h)	16	5.346 \pm 2.597	18	5.185 \pm 2.675	17	1.67 \pm 0.69 ^a
C _{max} /AUC _{0-∞} (1/h)	16	0.0741 \pm 0.0199	18	0.0594 \pm 0.0157	17	0.0736 \pm 0.0214
t _{1/2} (h)	16	7.373 \pm 1.712	18	9.665 \pm 5.487	17	5.729 \pm 2.235

Product A = 30 mg buspirone extended-release (ER) formulation, 12-hour release in vitro. Product B = 30 mg buspirone ER formulation, 24-hour release in vitro. Reference = 15 mg buspirone immediate release (IR) (BuSpar®), administered at 0 and 12 hours.

a. C_{max} and t_{max} were obtained from the first 12-hour dose of the IR reference product.

b. C_{max} and t_{max} were obtained from the second 12-hour dose of the IR reference product.

that were assessed as unrelated to the study drug included rhinitis, headache, and lightheadedness. The remaining 10 events were assessed as having a possible relationship to the drug, and these included drowsiness, dizziness, depression, tinnitus, and increased blood pressure.

Pharmacokinetic Evaluation

The plasma buspirone and 1-PP pharmacokinetic parameters with arithmetic mean and standard deviation are summarized in Tables I and II.

Immediate-release reference product. Given the large amount of variability in buspirone and 1-PP pharmacokinetics, the results observed for buspirone

and 1-PP after the IR buspirone HCl tablets are consistent with the results reported in the literature. For buspirone, the AUC of 12.90 \pm 15.05 (mean \pm SD) ng•mL⁻¹h for the total 30 mg dose; the t_{max} and C_{max} after the first 15 mg dose, observed at 0.85 \pm 0.39 hours with 1.92 \pm 2.11 ng/mL; and the average half-life of the immediate-release formulation of 2.958 \pm 1.179 hours were comparable to that reported.¹⁹ For 1-PP, the AUC of 107.5 \pm 67.97 ng•mL⁻¹h for the total 30 mg dose and the t_{max} and C_{max} after the first 15 mg dose, observed at 1.67 \pm 0.69 hours with 6.223 \pm 1.886 ng/mL, were also comparable to that reported.^{20,21}

Extended-release test products. Both ER products (12-hour and 24-hour release in vitro) showed evidence of ER in vivo and were absorbed throughout the

Table III Buspirone Bioavailability and 1-PP AUC_{0-∞} Ratio for Extended-Release (ER) Test Formulations Compared with the Immediate-Release (IR) Reference Product

Value	Buspirone AUC _{0-∞} : Product A/IR	Buspirone AUC _{0-∞} : Product B/IR	1-PP AUC _{0-∞} : Product A/IR	1-PP AUC _{0-∞} : Product B/IR
Maximum	4.42	3.22	1.26	1.22
Minimum	0.59	0.84	0.52	0.40
Mean	1.98	1.87	0.89	0.81
Intersubject variation (maximum/minimum)	7.49	3.83	2.42	3.05

Product A = 30 mg buspirone ER formulation, 12-hour release in vitro. Product B = 30 mg buspirone ER formulation, 24-hour release in vitro. Reference = 15 mg buspirone IR (BuSpar®), administered at 0 and 12 hours.

gastrointestinal tract, which is evident from the statistically significantly later observed t_{max} from the test products (5.438 ± 1.711 hours and 7.741 ± 4.077 hours) compared with that of the first 15 mg IR tablet (0.85 ± 0.39 hours). In addition, the apparent half-life from both ER products was found to be longer (6.352 ± 3.164 and 6.491 ± 3.148) than the half-life measured after the IR reference tablet (2.958 ± 1.179). Similar observations were obtained from the 1-PP metabolite data. The 1-PP t_{max} of the test products was significantly later (5.346 ± 2.597 and 5.185 ± 2.675) than that of the IR tablet (1.67 ± 0.69 hours), and the apparent half-life was found to be longer (7.373 ± 1.712 and 9.665 ± 5.487) in comparison to that measured after the IR tablet (5.729 ± 2.235). The difference in metabolite levels and half-life indicates that there may be a change in clearance between the ER formulations and the IR tablets.

The mean plasma concentration-time profiles for buspirone and 1-PP are illustrated in Figures 2 and 3, respectively. According to literature reports, mean peak plasma concentration of buspirone on oral administration ranges from 1 to 6 ng/mL, exhibiting therapeutic efficacy.^{5,6} The drug level obtained from the 12-hour ER formulation of 2.353 ± 2.465 ng/mL is higher, and that obtained from the 24-hour ER formulation of 1.560 ± 1.691 ng/mL is lower than that obtained from the reference IR product, which is 1.920 ± 2.110 ng/mL. This correlates to the in vitro release of the drug from the two test products that were designed to release the same amount of drug continuously over a period of 12 hours in product A and over a period of 24 hours in product B. The buspirone bioavailability from the extended-release formulations is indicated in Table III, and the AUC ratios for 1-PP and buspirone are listed in Table IV. A possible explanation for the unexpectedly higher bioavailability values for buspirone HCl obtained from the extended-release products has been discussed further.

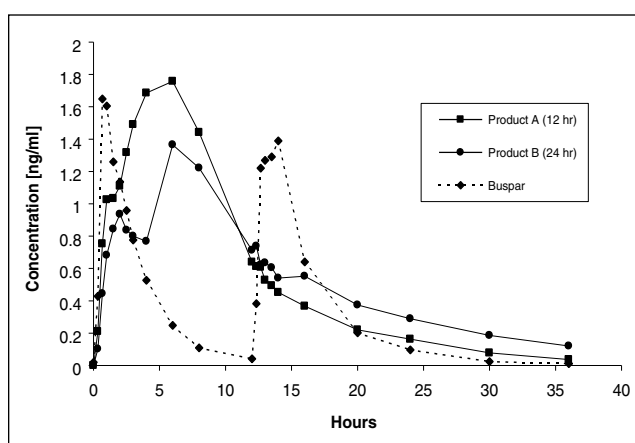


Figure 2. Mean buspirone plasma-level profiles for test and reference products.

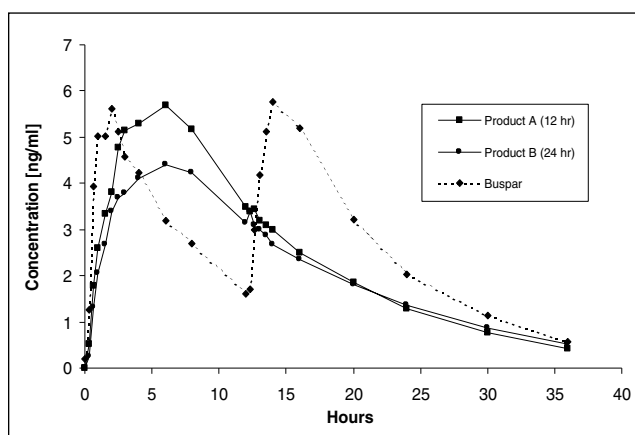


Figure 3. Mean 1-PP plasma-level profiles for test and reference products.

DISCUSSION

The measured concentration of buspirone and 1-PP at each time point after each product indicates a statistically significant difference at most of the 36-hour sampling periods among the three drug treatments. Based on pairwise comparisons, most of the significant difference resulted from differences between the ER formulations compared with the IR formulations.

Evidence of In Vivo Extended Release

The extended release of buspirone HCl from the 12-hour and 24-hour formulations is most evident from the cumulative AUC versus time data. It is also evident from the time of the observed maximum concentrations, which are statistically significantly later for the two ER products compared with that of the IR tablet. The actual values for the products are mentioned in the Results section and in Tables I and II.

The extent of absorption of buspirone from the ER formulations is not less than from the IR formulation, indicated by the mean C_{max} values, and this similarity of C_{max} is an evidence of ER in vivo for the two test products. A fourth observation that provides evidence of extended release is the statistically significant longer "apparent" half-life observed after the test formulations in comparison with the IR tablets. This indicates that buspirone was still being absorbed even as the concentrations were decreasing at the end of the sampling period.

Similar observations were also possible from the metabolite data, as indicated by the values listed in the Results section and Tables I and II.

The use of ER dosage forms in drug therapy has been increasing in recent years with a concomitant tendency toward once-a-day dosing formulation. This evidence of in vivo ER of drug from the two products being tested would allow at least a twofold reduction in dosage frequency as compared with the IR dosage form, thus improving patient compliance, especially due to its indication in psychiatric treatment.

Absorption of Buspirone

The ratio of buspirone $AUC_{0-\infty}$ after the 12-hour ER formulation to buspirone $AUC_{0-\infty}$ after the IR formulation ranged from 0.59 to 4.42, and that after the 24-hour ER formulation ranged from 0.84 to 3.22, as shown in Table III. The ratio of 1-PP $AUC_{0-\infty}$ after the 12-hour ER formulation to 1-PP $AUC_{0-\infty}$ after the IR formulation ranged from 0.52 to 1.26, and that after the 24-hour ER

formulation ranged from 0.40 to 1.22, as also shown in Table III. Based on the least squares means of the logarithmically transformed parameters, the AUC_{0-t} and $AUC_{0-\infty}$ for the 12-hour ER formulation for buspirone were 74% and 77% higher than the respective estimates for the IR formulation and were 91% and 72% higher for the 24-hour ER formulation. These differences were statistically significant ($\alpha = 0.05$). Based on the same, the AUC_{0-t} and $AUC_{0-\infty}$ for the 12-hour ER formulation for 1-PP were both 11% lower than the respective estimates for the IR formulation and were 15% and 11% lower for the 24-hour ER formulation. These differences were also statistically significant ($\alpha = 0.05$). The bioavailability of ER formulations thus unexpectedly exceeded that of the IR formulation. For most drugs, as usually observed, ER formulations have lesser bioavailability than the IR formulations. Buspirone is reported to be rapidly absorbed and extensively metabolized on oral administration, and thus it was expected that the bioavailability of the two ER formulations tested would be lower than that of the IR product. One possible reason for this could be that by delaying the release of drug from the dosage form, the first-pass enzymes for buspirone, which may be located at the proximal small intestine, are avoided. Thus, metabolism is reduced, and more unchanged drug is available for absorption.

Biotransformation to 1-(2-pyrimidinyl)piperazine

That increased bioavailability of buspirone from the ER formulations may be due to inhibition of its clearance is also evident from the ratio of 1-PP to buspirone AUC values obtained. The average ratios of $AUC_{0-\infty}$ of 1-PP to buspirone were 9.8061 ± 10.95 and 8.6319 ± 9.13 after the 12-hour and 24-hour ER formulations, respectively, and 19.1621 ± 20.15 for the IR formulation, as shown in Table IV.

Comparison of the Two ER Formulations

The $AUC_{0-\infty}$ values for both formulations are shown in Tables I and II, and no significant difference in the $AUC_{0-\infty}$ values indicates that buspirone and 1-PP are equally available from the two ER formulations. Thus, both ER formulations successfully delivered bioavailable buspirone. Based on the mean C_{max} values, it can be said that the concentrations were more consistent over a longer interval after administration of the 24-hour formulation.

Table IV AUC_{0-∞} (1-PP)/AUC_{0-∞} (buspirone) Ratio for Extended-Release (ER) Test Formulations and Immediate-Release (IR) Reference Product

Value	Product A (n = 16)	Product B (n = 15)	Reference (n = 16)
Maximum	40.0213	29.6913	70.1808
Minimum	0.5072	0.5358	1.0163
Mean	9.8061	8.6319	19.1621
Intersubject variation (maximum/minimum)	78.9	55.4	69.1

Product A = 30 mg buspirone ER formulation, 12-hour release in vitro. Product B = 30 mg buspirone ER formulation, 24-hour release in vitro. Reference = 15 mg buspirone IR (BuSpar®), administered at 0 and 12 hours.

CONCLUSION

The results of this study indicate that the two test products exhibited ER in vivo, with buspirone being well absorbed from the 12-hour and 24-hour ER formulations as compared with the IR formulations. A slower in vivo absorption of buspirone over an extended period of time—and hence lower plasma peak values—would reduce the occurrence of undesired side effects, avoid underdosing between dosage intervals, and lead to the possibility of once-daily dosing. The unexpected result obtained was that the bioavailability of buspirone (with low intersubject variation) from ER formulations was 70% to 90% greater than that from the IR formulation. Thus, the initial objectives for these buspirone ER formulations to have an improved pharmacokinetic profile for buspirone blood levels and reduction of 1-PP peak blood levels were achieved.

The study thus provides an improved method for administration of the useful drug buspirone. The dosing interval is lengthened, drug tolerability is improved, and these effects promote patient compliance.

The authors appreciate the financial support of American Pharmaceutical International, Inc. (Cincinnati, OH) and the University of Cincinnati Medical Center (Cincinnati, OH).

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