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In vitro Dissolution and *in vivo* Bioequivalence Study of Controlled Release Carbamazepine Formulation (Epileptol CR® *vs* Tegretol CR®) in Healthy Male Korean Volunteers

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ABSTRACT – The bioequivalence of two carbamazepine preparations was conducted. The *in vivo* bioequivalence study in 20 healthy male Korean volunteers was designed by using a single dose, randomized, 2-period crossover with a 3-weeks washout period between the doses. Prior to the *in vivo* study, an in vitro comparative dissolution test was performed by the paddle and basket method as described in the bioequivalence guidance of the Korea Food and Drug Administration (KFDA). Based on the similar dissolution pattern between two preparations in the dissolution test, the two formulations are demonstrated to be pharmaceutically equivalent. In addition, *in vivo* bioequivalence test was used to reconfirm the *in vitro* dissolution results. In the *in vivo* bioequivalence study, the plasma concentrations of carbamazepine up to 144 h after the administration were determined using a validated HPLC method with UV detection and the bioequivalence between the two drug products was assessed by statistical analysis of the log transformed mean ratios of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. The mean maximum concentration (C_{max}) of the test and reference were found to be 1467.0±335.8 ng/mL and 1465.9±310.3 ng/mL, respectively. The 90% confidence intervals (C.I.) of C_{max} were in the range from 0.95 to 1.05. As for the AUC_{0-t} and $AUC_{0-\infty}$, test values were 110027.1±27786.4 ng/mL·h, 128807.0±34563.2 ng/mL·h and 105473.6±26496.2 ng/mL·h, 125448.5±35975.5 ng/mL·h, respectively. The 90% C.I. of AUC_{0-t} were 0.97 to 1.10 and of $AUC_{0-\infty}$, 0.99 to 1.09 and thus were within the log 0.8-log 1.25 interval proposed by the KFDA. A two-way ANOVA showed no significant difference between the two formulations. Based on these statistical analysis, it was concluded that the test formulation is bioequivalent to the reference.

Key words – Carbamazepine, Bioequivalence, Pharmacokinetics, Dissolution, Controlled release

Carbamazepine (CBZ), 5*H*-dibenz[*b*,*f*]azepine-5-carbozamide, is a widely used anticonvulsant drug as mono-therapy and as co-medication in the first-line treatment for partial and generalized tonic-clonic seizures. In addition, it is also used in bipolar depression.[1)]

CBZ is usually administered by oral administration at the dose ranging from 10 to 20 mg/kg per day for adults and has narrow therapeutic index, 4~12 μg/ml.[2)] In addition, it is not unpredictable to calculate proportionate relationship between oral dose and plasma concentration.[3)] This is because the plasma concentration can be affected by the patient's physiological state such sex, age and metabolic state caused by other drugs used for co-therapy.[4)] Thus, monitoring of plasma concentration of CBZ recommended for both high quality of treatment and prevention of side effects such as aplastic anaemia or agranulocytosis. However, drug monitoring of an outpatient who takes CBZ is not practically available. In this case, the patient compliance is an important factor to maintain constant therapeutic plasma concentration.[5)]

It has been suggested that there was an inverse relation between dosage frequency and patients' compliance. In other words, patient has a tendency to keep the regimen better as the number of daily doses is lower. In the treatment of epilepsy, the patient compliance for the medication is an important factor.[5,6)] For these reasons, controlled release (CR) dosage form of CBZ is advantageous. CR formulation makes it possible to manage with twice-daily dosage, which could improve patient compliance and convenience and also lead to lower incidence of adverse effects by remaining largely stable throughout the day.[7-9)]

There are some controversial reports regarding the therapeutic- and bio- equivalence between brand and generic CBZ. In some literatures, a loss of effectiveness in controlling of seizure and development of toxic side effects were reported when three patients switched from the brand product to a bioequivalent generic CBZ. On the other hand, other authors were very favourable with the generic products of antiepileptic drugs.[10)] Thus, it is important to demonstrate the bioequivalence of

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generic to original products prior to therapeutic substitution and switch-ability among the products having same strength of ingredient.

In this study, the bioequivalence of two kinds of controlled release CBZ products, Epileptol CR tablet® 200 mg as a test and Tegretol CR tablet® 200 mg as a reference, was studied in twenty healthy volunteers according the Korean Guidelines for Bioequivalence Test (KGBT, Notification No. 2005-31, 2005) of Korea Food and Drug Administration (KFDA). Then, from the pharmacokinetic parameters of area under the curve (AUC) and maximum plasma concentration (C_{max}), the bioequivalence of the two products was evaluated.

Materials and Methods

Materials

Standard CBZ was gift from Whanin Pharm Co. Ltd. (Seoul, Republic of Korea). N-desmethylclozapine as an internal standard (I.S.) was purchased from Sigma Chemical Co. (St. Louis, MO. USA). Acetonitrile, methanol and methyl *tert*-butyl ether were HPLC grade purchased from J.T. Baker (Phillipsburg, NJ, USA). The water was prepared with double distillation by a Milli-Q system (Millipore Corp., Bedford, MA, USA). All other chemicals were analytical grade and used without further purification.

In vitro comparative dissolution test

Prior to bioequivalence study of Epileptol CR tablet® 200 mg as a test and Tegretol CR tablet® 200 mg as a reference, the comparative dissolution test was carried out to assume the equivalence of the two products *in vitro*. It was performed according to the guidelines of KFDA for comparative dissolution test of controlled release tablets. The dissolution of tablets was studied with two methods. The first was the paddle method operated at 50 rpm in various pH conditions of dissolution media at 37 ± 0.5°C. The second was the basket method operated at 100 rpm in pH 6.8 of dissolution medium at identical temperature. Twelve tablets of each product were added to the medium for each dissolution profile. Samples of the medium were collected at 0.25, 0.5, 1, 1.5, 2, 3, 5, 6, 8, 10, 12 and 24 hr excluding the case at pH 1.2, in which the samples were drawn at 0.25, 0.5, 1, 1.5 and 2 hr. UV absorbance of the samples was measured at 239 nm.

In every condition, if the difference of average dissolution ratio is set in the range of ± 10% at the time, at which the average dissolution ratio reaches 30, 50 and 80%, the two products were considered equivalent. However, when the average dissolution ratio of the reference was under 80% during the test time, the difference was compared at the end time.

Standard solutions and sample preparation

Stock solutions of CBZ (50 μg/ml) and N-desmethylclozapine (50 μg/mL) as an internal standard (I.S.) were prepared by dissolving CBZ and N-desmethylclozapine in methanol. The stock solutions were prepared in bulk and then stored frozen. Standard solutions of CBZ in human plasma for the calibration curve were prepared by spiking the appropriate volume of various diluted stock solutions giving trial concentration of 0, 20, 50, 100, 200, 1000 and 2000 ng/mL.

The I.S. was added to each 0.5 mL of plasma standard or sample. 4 mL of methyl *tert*-butyl ether was added to each mixture for extraction and vortexed for 30 sec, and centrifuged at 3000 rpm for 10 min and the supernatant was transferred into another tube. Then, the tubes were put under N_2 gas at 60°C to remove organic solvents. Finally, the residue was reconstituted in 100 μL of mobile phase and 20 μL of aliquot was injected onto the HPLC.[11,12]

Chromatographic conditions

All experiments were performed using an HPLC system consisting of a model LC-10AS solvent delivery pump, a variable-wavelength UV detector from Shimadzu (Model SPD-10A, Japan) and a 717 plus autosampler (Waters, Milford, MA, USA) and column temperature controller. The signals were processed by dsChromN (Donam, Seoul, Korea).

The column inlet filter (3 mm × 0.5 μm, Shiseido, Tokyo, Japan) removed protein from plasma. The mobile phase consisted of acetonitrile, methanol and 15 mM phosphate buffer (18 : 19 : 63, v/v/v) and adjusted to pH 2.49. The plasma sample was separated on the Hypersil Gold column (150 mm × 3 mm i.d., 5 μm, Thermo) at a flow rate of 0.5 mL/min at 40°C of column temperature. The eluates were monitored with an UV detector at 237 nm.

Validation and calibration

The assay method for this study needs to be qualified prior to *in vivo* bioequivalence study. The suitability could be acquired by confirming the linearity, precision, accuracy and sensitivity. Linearity was checked by a six-point calibration test with standard solutions prepared as described above. And linearity was assessed by the least square linear regression method. Sensitivity was determined as the lower limit of quantification (LLOQ) in calibration curve and the lowest concentration of drug with precision less than 20% and accuracy between 80~120%.

Precision and accuracy were evaluated by inter- and intra-

day assays. Inter-day validation was performed on five consecutive days with four different concentrations (20, 50, 200 and 2000 ng/mL). For intra-day validation, the assay was done with five sets of the same four calibration standard solutions (20, 50, 200 and 2000 ng/mL) within a day. Precision was evaluated by the coefficient of variation (C.V.) and the criterion for precision was that the C.V. % should be set within the range of ± 15%, except for LLOQ (± 20%). Accuracy was determined by comparing the differences between the real concentrations and the calculated concentrations from the calibration curve. For the method to have acceptable accuracy, the deviation of the two concentrations should be within ± 15%, and the LLOQ 20%.

Bioequivalence study

Test and reference medications – The test medication, Epileptol CR® (200 mg of carbamazepine, lot No. 38012, Whanin Pharm Co. Ltd.) and the reference medication, Tegretol CR® (200 mg of carbamazepine, lot No. T5144, Novartis Korea Ltd.) were supplied as tablets.

Subjects – This study was performed on twenty healthy male volunteers in accordance with a Latin-square design. This study was performed according to the revised Declaration of Helsinki for biomedical research involving human subjects and the rules of Good Clinical Practices. The overall protocol of this study was approved by the Ethical Committee of Research Institute of Pharmaceutical Sciences, Seoul National University (Seoul, Korea). All participants signed a written informed consent after they had been informed of the purpose, protocol and risks of the study in accordance with Korean Guidance for Bioequivalence Test.[15] The subjects participated in this study had an age of 22.7 ± 2.4 year (19~28 years), body weight of 68.0 ± 9.8 kg (54~90 kg) and height of 174.8 ± 5.8 cm (165~185 cm). Every subject took physical examination to check that they are free from significant cardiac, hepatic, or renal systems diseases and they were proved to have normal clinical chemistry laboratory values. They also were forbidden to take alcoholic beverages, xanthine-containing foods and beverages 48 hr prior to each dosing and until the collection of the last blood sample. Subjects who administered any kind of medication within 2 weeks before the beginning or during the entire study were also excluded.

Drug administration and blood sample collection – This study was designed based on single-dose, randomized, two-treatment and two-period crossover period. Subjects were requested to fast for at least 12 hr overnight the day before each administration of drugs. Subjects were randomly divided into two groups and received a single dose (200 mg) of CBZ as both reference and test during the first period. They administered one tablet with 240 mL of water and fasting continued for further 4 hr. Subjects were provided a standard meal at 4 hr (lunch) and 8 hr (supper) after drug administration in each treatment. The washout period between the two treatment periods was 3 weeks, which is 10 times longer than the elimination half-life of this drug.

Heparinized blood samples (6 mL) were withdrawn from the forearm vein according to the time schedule, which included a blank before drug administration and then at 2, 4, 6, 8, 10, 12, 14, 24, 30, 36, 48, 72, 120 and 144 hr after dosing. Blood samples were transferred to Vacutainer® tube (BD., NJ., USA) and immediately separated by centrifugation at 3000 rpm for 10 min. Following centrifugation, plasma samples were separated and stored at −70°C prior to analysis.

Pharmacokinetic and statistical analysis – The following bioavailability parameters were assessed by BA Calc 2002, a program for calculation of bioavailability. The area under the plasma concentration-time curves was calculated from the time zero to the last sampling time ($AUC_{0\text{-}144h}$); maximum plasma concentration (C_{max}); time to reach the C_{max} (T_{max}) were obtained directly from the concentration-time profiles for CBZ. The area under the plasma concentration-time curves from time zero to the infinite time ($AUC_{0\text{-}\infty}$) was calculated by using log-linear trapezoidal formula for up to the last measured time in plasma and extrapolation to the infinity. The elimination rate constant (K_e) was obtained as the slope of the linear regression of the log-transformed concentration-time curve data in thermal phase. The half-life ($T_{1/2}$) was calculated from ln 2 divided by K_e.

According to the KGBT (Notification No. 2005-31, 2005), the criteria for the comparison of bioequivalence of reference and test drugs included $AUC_{0\text{-}t}$ and C_{max}. For the purpose of bioequivalence analysis a two-way analysis of variance (ANOVA) performed with the K-BE Test 2002 program at a

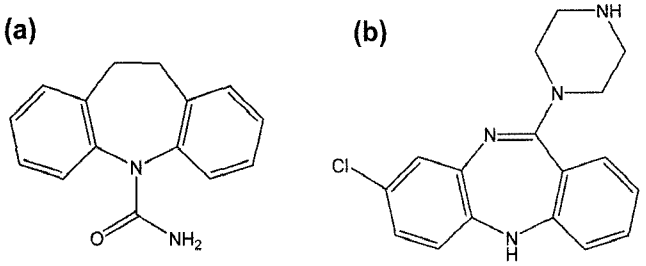

Figure 1—Chemical structures of carbamazepine (a) and N-desmethylclozapine (b).

significant level of 0.05. The test and reference treatments of each study were compared with respect to relevant pharmacokinetic variables using an analysis of variance with subject, treatment and period effects with the raw data. Bioequivalence of the test to the reference treatment was assessed on basis of the C.I. for the test/reference mean ratios of these raw variables

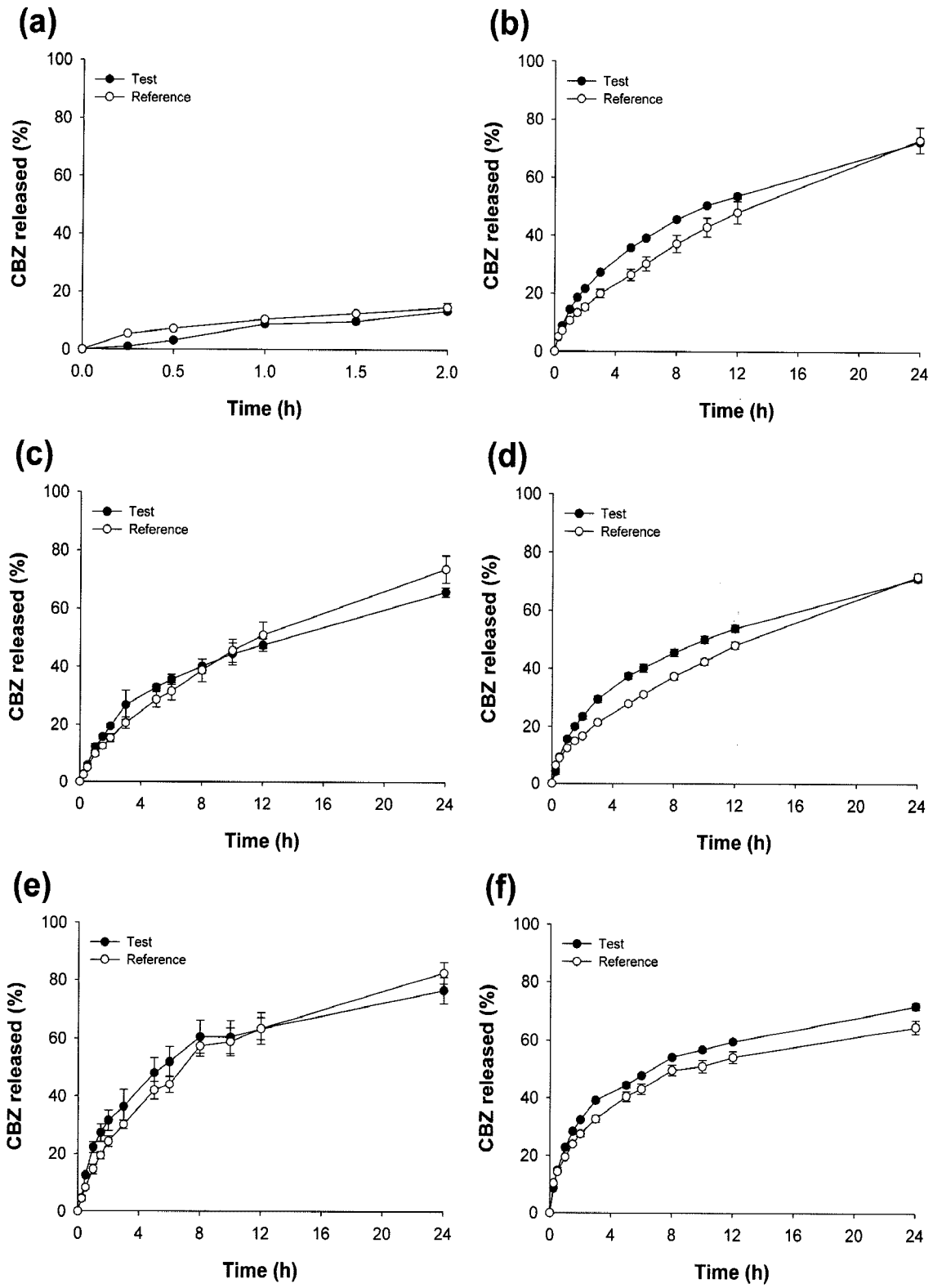

Figure 2–In vitro dissolution profiles of carbamazepine from the reference (Tegretol®) and test (Epileptol®) tablets. Dissolution tests were performed using the paddle method at 50 rpm with different dissolution media of pH 1.2 (a), pH 4.0 (b), pH 6.8 (c), water (d), pH 6.8 with 1.0 w/v % polysorbate 80 as solubilizer (e) and using the basket method at 100 rpm with dissolution medium of pH 6.8 (f) (n=12).

in relation to the bioequivalence range of log 0.8~log 1.25 for the raw data.[13-15]

Results

In vitro comparative dissolution test

According to the guidelines of KFDA for comparative dissolution test of controlled release tablets, the dissolution tests of the two CBZ tablets were conducted under six different conditions. Data shown in Figure 2 represents the mean of 12 tablets. When paddle method was used, the dissolution profiles of CBZ show the similarity between the reference and test irrespective of dissolution conditions such as pH and solubilizer (Figure 2a-2e). Two CBZ formulations showed the same profiles when the basket method was used at pH 6.8 (Figure 2f). Two products showed very similar dissolution profiles at the every time points set in the range of ±10% under every dissolution condition, indicating that the dissolutions of the reference and test had no significant difference between two tablets in terms of comparative dissolution patterns *in vitro*.

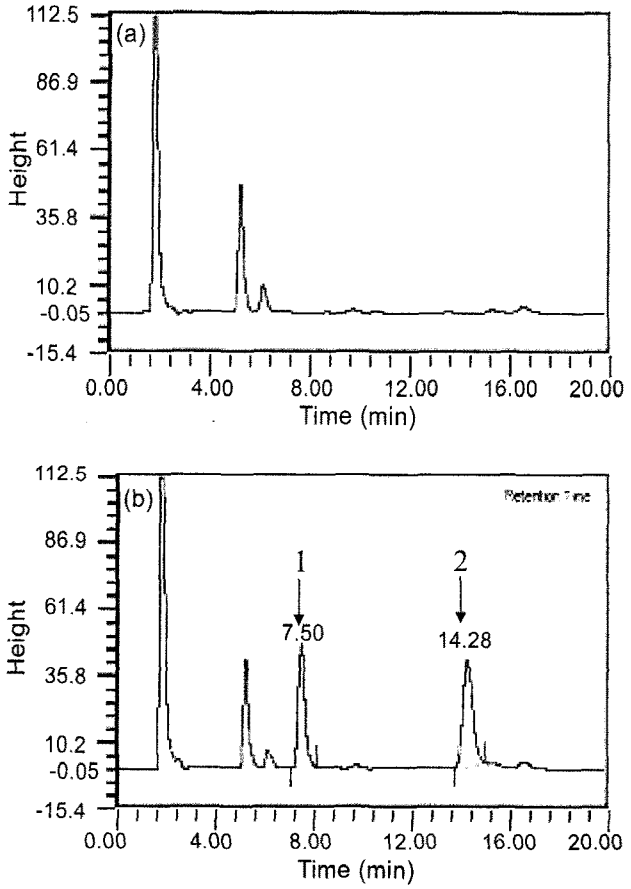

Figure 3–Chromatograms of (a) human blank plasma and (a) human plasma added with carbamazepine (1000 ng/mL) and I.S.(500 ng/mL) [1: N-Desmethylclozapine(I.S.), 2: carbamazepine].

Table I–*Precision and Accuracy of the Proposed HPLC Method*

Concentration (ng/mL)	Precision (CV %)		Accuracy (%) (n=5)
	Intra-day (n=5)	Inter-day (n=5)	
20	19.08	16.19	107.97
50	2.74	13.40	104.78
200	0.3	6.63	97.83
2000	0.62	7.93	100.02

Validation of the assay

The peaks of CBZ and I.S. on chromatogram were clearly separated and there was no interference from plasma endogenous components (Figure 3). Linearity was ascertained over a range of 20~2000 ng/mL. By applying the least square linear regression to the data, the equation for the calibration curve was $y=0.0013x-0.0141$ with a correlation coefficient of 0.9995. In the equation, x equals the concentration of CBZ and y is the ratio of peak area of CBZ to that of internal standard. From the standard calibration curve, the lower limit of quantification (LLOQ) was estimated to be 20 ng/mL. It reveals that this method has enough sensitivity for the analysis of CBZ in plasma samples after administration of 200 mg CBZ tablets.

Precision and accuracy were determined by inter- and intra-day assays. As presented in Table I, the accuracy values were distributed between 97.8~108.0%, which satisfied the acceptable range of ±15% (20% for LLOQ). For the precision, the intra-day C.V. (coefficient variance) values were within 19.1% and inter-day values were less than 16.2%. All of the C.V. values were less than 15% (20% for LLOQ), indicating that this analytical method exhibited sufficient precision.

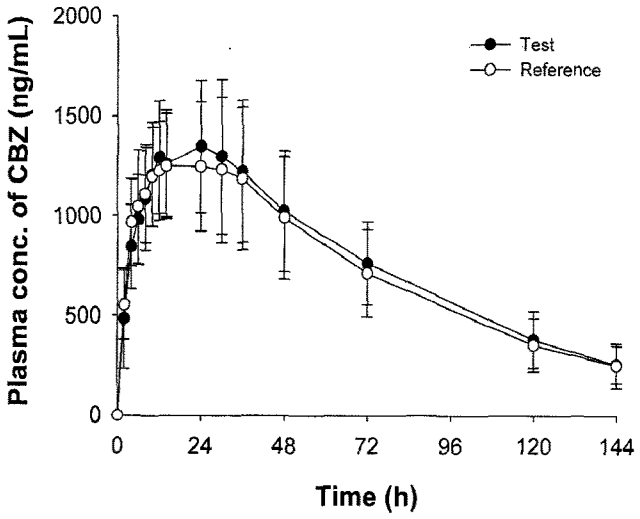

Figure 4–Plasma concentration-time profiles of carbamazepine following oral administration of the reference (Tegretol®) and test (Epileptol®) products (n=20).

Table II–*Raw Data after Single Oral Administration of Carbamazepine 200 mg for Reference and Test Products (n = 20)*

	$AUC_{0\text{-}144h}$ (ng/mL·hr)				C_{max} (ng/mL)				T_{max} (h)	
	Reference		Test		Reference		Test		Reference	Test
	Value	Log	Value	Log	Value	Log	Value	Log	Value	Value
A1	97832.31	4.99	94717.18	4.98	1163.042	3.07	1207.36	3.08	14	10
A2	104505.83	5.02	95408.54	4.98	1435.284	3.16	1393.344	3.14	14	14
A3	90904.09	4.96	81004.29	4.91	1307.466	3.12	1256.918	3.10	12	12
A4	110432.32	5.04	113047.03	5.05	1384.927	3.14	1276.278	3.11	36	24
A5	140963.08	5.15	146852.66	5.17	1453.819	3.16	1784.486	3.25	48	36
A6	72759.19	4.86	64390.24	4.81	1053.435	3.02	864.4955	2.94	14	12
A7	133928.65	5.13	136754.46	5.14	2007.426	3.30	1764.618	3.25	30	30
A8	131365.49	5.12	142714.96	5.15	1807.666	3.26	2017.797	3.30	12	30
A9	48794.56	4.69	61714.90	4.79	820.3391	2.91	940.0307	2.97	10	12
A10	75425.52	4.88	67416.04	4.83	1074.613	3.03	933.5798	2.97	10	12
B1	70870.68	4.85	87018.68	4.94	1390.566	3.14	1224.125	3.09	24	14
B2	106359.39	5.03	144207.21	5.16	1497.298	3.18	1549.783	3.19	24	14
B3	152477.37	5.18	139298.37	5.14	1697.997	3.23	1628.048	3.21	30	24
B4	129306.45	5.11	138793.39	5.14	1818.928	3.26	2026.282	3.31	24	30
B5	99158.44	5.00	111817.50	5.05	1400.678	3.15	1506.922	3.18	10	24
B6	119032.31	5.08	113077.45	5.05	1263.607	3.10	1798.081	3.25	30	36
B7	131104.75	5.12	123959.03	5.09	1938.64	3.29	1670.603	3.22	36	30
B8	102659.37	5.01	128836.53	5.11	1443.121	3.16	1445.976	3.16	8	36
B9	90044.95	4.95	104207.44	5.02	1614.022	3.21	1530.276	3.18	24	12
B10	101548.13	5.01	105305.53	5.02	1745.885	3.24	1560.718	3.19	30	10
Mean	105473.64	5.01	110027.07	5.03	1465.94	3.16	1468.99	3.16	22.00	21.10
SD	26496.23	0.12	27786.35	0.12	310.28	0.10	335.74	0.11	11.14	9.79

Bioequivalence test

Plasma concentration – Based on the validation result, our assay method was applied to bioequivalence study of two controlled release 200 mg CBZ tablets. Figure 4 shows the mean (± S.D.) plasma concentration of test and reference drugs-time curves of CBZ after single oral drug administration. The figure presents that there were no significant pharmacokinetic difference between two products *in vivo*. Plasma concentrations of both test and reference formulations increased until 22.1 hr and 22.0 hr after dosing, respectively, at which they reached their highest concentrations, and then decreased in detection until 144 hr.

Table III–*Pharmacokinetic Parameters after Single Oral Administration of Controlled Release Carbamazepine 200 mg for Reference and Test Products (n = 20)*

Pharmacokinetic parameters	Reference	Test
$AUC_{0\text{-}t}$ (ng/mL·h)	105473.64 ± 26496.23	110027.07 ± 27786.35
$AUC_{0\text{-}\infty}$ (ng/mL·h)	125448.45 ± 35975.53	128806.99 ± 34563.15
C_{max} (ng/mL)	1465.94 ± 310.28	1468.99 ± 335.74
T_{max} (h)	22.00 ± 11.14	21.10 ± 9.79
$T_{1/2}$ (h)	49.92 ± 17.76	48.38 ± 10.52
K_e (h)	4.70 ± 1.56	5.00 ± 1.49

Pharmacokinetic parameters – Table II and III show the raw data and mean values of pharmacokinetic parameters after single oral administration of reference and test products to 20 healthy volunteers. Comparing the parameters of test with those of reference, it is shown that the mean values of both formulations are almost identical.

Statistical analysis – From the *F* test values of ANOVA for AUC and C_{max} after log-transformation, no significant sequence, formulation and period effect were found for all of the bioavailability parameters. This results indicate that the

Table IV. Geometric Means and 90 % Confidence Intervals (C.I.) for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of Carbamazepine

Pharmacokinetic parameters	Geometric means			90% C.I.
	Reference (R)	Test (T)	T/R	
AUC_{0-t}	101950.08	106334.90	1.04	0.97-1.10
$AUC_{0-\infty}$	120065.80	123965.33	1.03	0.99-1.09
C_{max}	1432.76	1429.67	1.00	0.95-1.05

cross-over design was properly performed (Table IV).

All the results of 90% C.I. for the ratio of AUC and C_{max} values were set in the range of log 0.8~log 1.25, which is in content with the criterions of KGBT (Notification No. 2005-31, 2005).

Discussion

In this study, the bioequivalence of two controlled release 200 mg CBZ tablets were evaluated by *in vitro* and *in vivo* assays according to the KGBT (Notification No. 2005-31, 2005) of KFDA. In the *in vitro* comparative dissolution test, the two drug products showed similar dissolving patterns, which endorsed the pharmaceutical equivalence of them. In other words, it was observed that the two CBZ tablets were pharmaceutically equivalent and were manufactured under a good quality control, demonstrating a very similar dissolution profile. There has been increased confidence and success in using in vitro dissolution to evaluate and predict in vivo performance of modified release drug product[16] and some regulatory agencies accept the use of in vitro dissolution studies as the basis of a bioequivalence assessment without the need for human bioequivalence studies.[17] In our study, the correlation between in vitro and in vivo studies for bioequivalence of two CBZ tablets observed and showed to be possible confirmation of bioequivalence by in vitro dissolution test. However, the availability can be different by the absorption site and controlling of drug release from formulation controlled or not after dosing formulations. Therefore, in vivo bioequivalence study conducted to reconfirm result of in vitro dissolution although in vitro dissolution test showed bioequivalence of two CBZ tablets.

On the basis of validated assay method, single dose, randomized, double blind *in vivo* bioequivalence study was performed with plasma samples taken from twenty healthy volunteers. The analysis of plasma samples was carried out by HPLC and the evaluation of bioequivalence between the two drug products was accomplished by statistical analysis of the log transformed mean ratios of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ obtained from the analysis of the plasma samples. Considering that bioequivalence means similar bioavailability of two pharmaceutical drug products in terms of the absorption rate (C_{max} and T_{max}) and the extent of absorption (AUC) after administration of a molar dose, the assessment focused on comparing these pharmacokinetic parameters of the two drugs.

Test and reference exhibited overlapping or almost overlapping plasma concentration-time profiles and pharmacokinetic parameters of CBZ. The statistical comparison of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ clearly indicated no significant difference in the two brands of CBZ tablets. 90% confidence intervals for the mean ratio of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were 0.95~1.105, 0.97~1.10 and 0.99~1.09, respectively. And these values were within the acceptable limits of log 0.80~log 1.25. Based on the 90% C.I. of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ calculated in this study, the two CBZ products were evaluated to display no significant statistical difference and were concluded to be bioequivalent. Consequently, from all of these results, it was concluded that the test drug Epileptol CR® tablet was bioequivalent to the reference drug Tegretol CR® tablet both *in vitro* and *in vivo* and that the two products can be considered interchangeable in medical practice.

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References

1) E. Spina, Carbamazepine: chemistry, biotransformation, and pharmacokinetics. In: Antiepileptic Drugs. 5th ed. R.H. Levy, R.J. Mattson, B.S. Meldrum and E. Perucca, eds. Baltimore, U.S.A, pp. 236-46 (2002).

2) A. Verrotti, C. Salladini, G. Di Marco, F. Pisciella and F. Chiarelli, Extended-release formulations in epilepsy, *J. Child. Neurol.*, **22**, 419-26 (2007).

3) R. Mandrioli, F. Albani, G. Casamenti, C. Sabbioni and M.A. Raggi, Simultaneous high-performance liquid chromatography determination of carbamazepine and five of its metabolites in plasma of epileptic patients, *J. Chromatogr. B*, **762**, 109-16

(2001).
4) J. Moreno, A. Belmont, O. Jaimes, J.A. Santos, G. López and M.G. Campos, Pharmacokinetics study of carbamazepine and its carbamazepine 10,11-epoxide metabolite in a group of female epileptic patients under chronic treatment, *Arch. Med. Res.*, **35**, 168-71 (2004).
5) J.A. Cramer, R.H. Mattson, M.L. Prevey and R.D. Scheyer, Ouellette, V.L. How often is medication taken as prescribed? A novel assessment technique, *JAMA*, **261**, 3273-7 (1989).
6) KW. Sommerville. Bioequivalence in development of antiepileptic drugs, *Epilepsy Res.*, **68**, 82-4 (2006).
7) M. Bialer, Extended-release formulations for the treatment of epilepsy CNS, *Drugs*, **21**, 765-74 (2007).
8) J.K. Pandit, S. Singh and M.S. Muthu, Controlled release formulations in neurology practice, *Ann. Indian Acad. Neurol.*, **9**, 207-16 (2006).
9) Prescribing information [Pr]Tegretol. Novartis Pharmaceuticals Canada Inc., (2006).
10) M. Bialer, L. Arcavi, S. Sussan, A. Volosov, A. Yacobi and D. Moros, Existing and new criteria for bioequivalence evaluation of new controlled release (CR) products of carbamazepine, *Epilepsy Res.*, **32**, 371-8 (1998).
11) P. Pienimäki, S. Fuchs, J. Isojärvi and K. Vähäkangas, Improved detection and determination of carbamazepine and oxcarbazepine and their metabolites by high-performance liquid chromatography, *J. Chromatogr. B*, **673**, 97-105 (1995).
12) F. Bugamelli, C. Sabbioni, R. Mandrioli, E. Kenndler, F. Albani and M.A. Raggi, Simultaneous analysis of six antiepileptic drugs and two selected metabolites in human plasma by liquid chromatography after solid-phase extraction, *Anal. Chim. Acta.*, **472**, 1-10 (2002).
13) A. Marzo, L. Dal Bo, A. Rusca and P. Zini, Bioequivalence of ticlopidine hydrochloride administered in single dose to healthy volunteers, *Pharmacol. Res.*, **46**, 401-7 (2002).
14) J.J.I. Tamimi, I.I Salem, S.M. Alam, Q. Zaman and R. Dham, Bioequivalence evaluation of two brands of lisinopril tablets (Lisotec and Zestril) in healthy human volunteers, *Biopharm. Drug Dispos.*, **26**, 335-9 (2005).
15) Korean Guideline for Bioequivalence Test. Korea Food and Drug Administration, (2005).
16) S. Dutta, Y. Qiu, E. Samara, G. Cao and G.R. Granneman, Once-a day extended-release dosage form of diavalproex sodium III: Devalopment and validation of a level a *in vitro-in vivo* correlation (IVIVC), *J. Pharm. Sci.*, **94**, 1949-56 (2005).
17) S. Hayes, A.Dunne, T. Smart and J. Davis, Interpretation and optimization of the dissolution specifications for a modified release product with an *in vitro-in vivo* correlation (IVIVC), *J. Pharm. Sci.*, **93**, 571-81 (2004).