A Novel Drug Delivery Approach to Olanzapine Orally Dispersible Tablet (ODT) in the Phase of Schizophrenia and Its Pharmacokinetics

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ABSTRACT − The present work focuses on preparation of olanzapine, orally dispersing tablets by direct compression method. Effect of super disintegrant crospovidone, disintegration time, drug content on in vitro release has been studied. A factorial design was employed in formulating a prompt dispersible tablet. The selected independent variables crospovidone and fmelt showed significant effect on dependent variables i.e. disintegration time and percent drug dissolved. Disintegration time and percent drug dissolved decreased with increase in the level of crospovidone. The similarity factor f_2 was found to be 97.48 for the developed formulation indicating the release was similar to that of the marketed formulation. Pharmacokinetics of olanzapine after single-dose oral administration of orally disintegrating tablet in normal volunteers were evaluated and the results showed that PK parameters (Cmax, Tmax, AUC) of the designed ODT matrix were similar to those of commercial product, Zyprexa Zydis[®] as a reference.

Key words − Olanzapine, Schizophrenia, Crospovidon, Fmelt, Direct compression and orally dispersible tablet(ODT)

Second-generation antipsychotic agents are considered first-line treatments for schizophrenia and other manifestations of psychosis or agitation. Olanzapine was licensed in the USA by the Food and Drug Administration in 2003 for the prevention of relapse in patients with bipolar disorder when the acute manic episode had responded to treatment with olanzapine (Ciprani et al., 2009). However, olanzapine is commonly used in clinical practice for preventing relapse in patients with bipolar disorder even when acute response has not been demonstrated. Atypical antipsychotics are known to be associated with electroencephalogram abnormalities (Viana et al., 2009; Chang et al., 2009). Olanzapine can lower seizure threshold and induce epileptiform discharges (Behere et al., 2009). However in patients on olanzapine for the treatment of a primary psychiatric disorder, clinical seizure is a rare occurrence (Colin et al., 2009; Lui et al., 2009; Mendhekar et al., 2009). Treatment with olanzapine (atypical antipsychotic drug) is frequently associated with various metabolic anomalies, including obesity, dyslipidemia and diabetes mellitus. Recent data suggest that olanzapine orally disintegrating tablets (ODT), which dissolve instantaneously in the mouth, might cause less weight gain than olanzapine standard oral tablets (OST) (Vidarsdottir et al., 2009). Moreover, despite pharmacological difference, gut hormone concentrations are similar during treatment with olanzapine ODT and OST (Hoffmann et al., 2009). The clinical efficacy and tolerability of olanzapine orally disintegrating tablets (Zyprexa Zydis[®]) in ameliorating excitement symptoms in the acute phase of schizophrenia was performed whose results suggest that olanzapine orally disintegrating tablets are effective and well-tolerated for treatment excitement in the acute phase of schizophrenic patients (Hori et al., 2009). In addition, it is possible that adherence to medications is improved by using olanzapine orally disintegrating tablets. Patients with schizophrenia and bipolar disorder have frequently reported weight gain during olanzapine treatment. Previous studies have observed a decrease in weight gain, or weight loss, in patients switching from standard olanzapine tablets (SOT) to orally disintegrating olanzapine (ODO) tablets. In some study, patients treated with ODO experienced a similar mean change in Body Mass Index (BMI) and weight from baseline, to those patients treated with SOT(Karagianis et al., 2009; Suarez et al., 2009).

When orally dispersible tablet (ODT) is placed in the mouth, the dosage form disintegrates instantaneously or within a few minutes releasing the drug, which dissolves or disperses in the saliva. The saliva containing the medicament is then swallowed and the drug is absorbed in the normal way. Some fraction of the drug may be absorbed from pre-gastric sites such as the mouth, pharynx, and esophagus as the saliva passes down into the stomach. In these cases, the bioavailability of drugs from ODT may be greater compared to the standard oral dosage forms (Gohel et al., 2004; Costa and Lovo, 2001). Olan-

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zapine is a relatively new drug in the market and its therapeutic and secondary effects are not fully characterized. It has been found to be especially useful in treating refractory schizophrenic patients. Although, olanzapine has proved to be very efficient in treating schizophrenia, with no or minimal side effects, further research on olanzapine is needed for the long term effects of this drug and for the medical community to be more receptive to the newer treatment (Tatsuya et al., 1999). Therefore, in order to get better patient compliance in the treatment of psychosis, it is necessary to design a new drug delivery system of the drug olanzapine i.e. orally dispersible tablet. In our laboratory, we designed simple matrix system of ODT in comparison to commercial available product, Zyprexa Zydis® applied with Lyophilization high technology and two pair comparison was evaluated in terms of clinical trial. The focus of the present investigation is to minimize disintegration time and improved drug release with faster onset of action.

Materials and Methods

Materials

Olanzapine was obtained from Hetero Drug Limited, India and other materials such as fmelt, anhydrous citric acid, sodium lauryl sulfate (SLS), stearic acid, cross-povidon, sodium stearyl fumarate and sucralose were purchased from While Fine Chemicals, Korea. Reagents with HPLC analysis grade were obtained from Fisher Chemicals, USA.

Methods
Preparation of fast dissolving tablets of olanzapine
Optimization of crospovidon and fmelt

A factorial design was selected. The factors were evaluated each at 3 levels and experimental trials were performed for all 9 possible combinations as reflected from Table I. The amount

Table I. *Formulation Design of Orally Dispersible Tablets of Olanzapine*

Composition (mg)	Formulation Run								
	1	2	3	4	5	6	7	8	9
Olanzapine	10	10	10	10	10	10	10	10	10
Mannitol	95	95	95						
Erythritol				95	95	95			
Zyritol							95	95	95
MCC	30	30	30	30	30	30	30	30	30
Maltose	5	5	5	5	5	5	5	5	5
Lactose	100	100	100	100	100	100	100	100	100
Aspartam	6	6	6	6	6	6	6	6	6
Crosspovidon	45	40	35	45	40	35	45	40	35
Light anhydrous sillicate	4	4	4	4	4	4	4	4	4
Mg stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight	296.5	291.5	286.5	296.5	291.5	286.5	296.5	291.5	286.5
Tablet properties									
Hardness (kp)	5	4	3	5	4	3	5	4	3
Disintegration time (sec)	10	11	12	10	11	12	10	11	12

of superdisintegrant, crospovidone and the amount of fmelt were selected as independent variables. In vitro disintegration time and percent drug dissolved were selected as dependent variables. The actual improved solubility formulation design of orally dispersible tablets of olanzapine according to factorial design layout is shown in Table II. The data was interpreted and the resulting uniform blends of composition per tablet as mentioned in Table I and II were directly compressed using 10 mm, round convex faced tooling to make the tablets using sin-

Table II. *The Actual Improved Solubility Formulation Design of Orally Dispersible Tablets of Olanzapine*

Composition	1	2	3	4	5	6	7	8
Olanzapine	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Fmelt*	57 mg	57 mg	57 mg	57 mg	57 mg	57 mg	57 mg	57 mg
Anhydrous citric acid	3 mg	5 mg	8 mg	10 mg	10 mg			
SLS					3 mg	2 mg	5 mg	
Stearic acid								10 mg
Cross-povidon	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
Sodium stearyl fumarate	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg
Sucralose	0.5 mg	0.5 mg	0.5 mg	0.5 mg	0.5 mg	0.5 mg	0.5 mg	0.5 mg

*Fmelt compositions are microcrystalline cellulose(MCC) 18%, anhydrous dibasic calcium phosphate 4%, cross-povidon 8%, mannitol 65%, and zyritol 5%.

gle punch stations (Sejong compression machine, Korea). The tablet press setting was kept constant across all formulations.

Evaluation of orally dispersible tablets of olanzapine

The tablets were evaluated for appearance, weight variation, hardness, thickness, friability, disintegration time, drug content and content uniformity (Hitachi UV-Visible double beam spectrophotometer at 260 nm).

To effectively simulate the punishment that tablets may be subjected to during manufacturing, distribution and handling, samples should be tested in the Optimal Friability Tester. In addition to it, tablet hardness was checked ranging from 0.4 to 35 kiloponds (within ±1% full scale) and features jaws which automatically adjust to various tablet shapes and sizes up to 1.375 inches (34 mm) in diameter. Test results are reported via a large LED display which can be programmed for kiloponds or Strong-Cobb units. Data can be uploaded to a LIMS or other computer for centralized record keeping or integration into QC reports or spreadsheets via the RS232 port by using the Optimal Tablet Hardness Tester with small footprint (280×178 mm) fits easily onto even overcrowded bench tops. Both methodology was followed by EP and USP guideline.

In vitro dissolution study

Dissolution profiles of olanzapine ODT tablets were determined using the USP 24 Method II with paddle speed at 50 rpm. Dissolution study was performed in 900 mL water. Five milliliters of samples were withdrawn at specified time intervals. The volume of dissolution fluid was adjusted to 900 mL, by replacing each 5 mL aliquot withdrawn with 5 mL of dissolution medium, pre-warmed at 37±0.5°C. Samples withdrawn were filtered through Whatmann filter paper, suitably diluted with water, and analyzed at 260 nm, using UV-Visible double beam spectrophotometer.

Comparison with marketed product

The developed product was quantitatively evaluated and assessed for a tablet's properties and product quality was monitored for various specifications. Dissolution profiles of Zyprexa Zydis® tablets were determined using the USP 24 Method II with paddle speed at 50 rpm. Dissolution study was performed in 900 mL water, 0.1 N HCl (pH 1.2), pH 4.0 and pH 6.8 maintained at 37±0.5°C where, pH buffer medium was prepared according to USP method with different capacity of pH.

The following standards or quality control tests were carried out on marketed tablets for comparative evaluation of developed and marketed product and observations were represented.

Determination of similarity factor(FDA SUPAC Guideline)

The similarity factors are determined for comparison of dissolution profiles. The similarity factor (f_2) is a logarithmic transformation of the sum-squared error of differences between the test Tj and reference Rj products over all time points

$$f_2 = 50 \times \log\left[1 + (1/n)\sum_{j=1}^{n} W_j |R_j - T_j|^2 \right]^{-0.5} \times 100$$

Where, W_j is an optional weight factor. The similarity factor fits result between 0 and 100, It is 100 when the test and reference profiles are identical and tends to 0 as the dissimilarity increases. This method is more adequate to dissolution profile comparisons when more than three or four dissolution time points are available. In order to consider similar dissolution profiles, the f_1 values should be close to 0 and f_2 values should be close to 100. In general, f_1 values lower than 15 (0-15) and f_2 values higher than 50 (50-100) show the similarity of the dissolution profiles.

Chromatographic purity analysis by HPLC
Preparation of Standard solution

Weigh accurately about each 3.0 mg of olanzapine related compounds-A, B & C and 2.0 mg of olanzapine (Form-I) working standard into a 100 mL volumetric flask. Dissolve and dilute to the volume with diluent. Dilute 1 mL of the above prepared solution to 20 mL with diluent.

Preparation of test solution

Weigh accurately about 10 mg of test sample into a 10 mL volumetric flask. Dissolve and dilute to the volume with diluent.

Procedure

Inject 20 µL of diluent (Blank) into the system and record the chromatogram to a run time of 40 minutes. Programme the data processor to inhibit the integration of peaks due to blank. Inject 20 µL of Standard solution into the system and record the chromatogram to a runtime of 40 minutes to determine system suitability.

HPLC conditions

The separation was achieved at a temperature of 35°C on the column, YMC pack pro CIS 150×4.6 mm, 5 J. 1 m or equivalent using the mobile phase at a flow rate of 2.0 mL/min. The detector wavelength was set at 260 nm with a sensitivity of 0.2 a.u.f.s. Mobile phase was prepared with mixing 650 mL of

buffer, 200 mL of acetonitrile and 150 mL of methanol. After filtering and degassing the mixture, and it was applied.

Clinical study
Subjects and clinical protocol

Subjects : Twenty-four healthy male volunteers in the age range of 18-45 years and having Body Mass Index (BMI) in a range of 18 to 27 (both inclusive) kg/m² were allowed in the study, from volunteers group gave written informed consent to participate in this study approved by Green Cross Reference Lab. All were determined to be healthy by history, physical examination, and basic laboratory monitoring. All subjects were within 15% of ideal body weight and were non-smokers. Subjects were not taking prescription or over-the counter medications or supplements and were asked to abstain from caffeine-containing beverages.

Study medications

All study medications were provided directly by the manufacturer, The provided olanzapine ODT 10 mg formulation are approved by the Korean Food and Drug Administration and presently in general clinical use. The ODT 10 mg formulation uses the Zydis 10 mg dosage formulation, a freeze-dried tablet that disintegrates instantaneously, releasing drug into saliva. This pharmaceutical technology is used for more than a dozen therapeutic agents besides olanzapine.

Sample preparation

A plasma sample (0.5 mL) was transferred to a 15 mL glass test tube, then 25 μL of IS working solution (500 ng/mL) and 50 μL of sodium hydroxide (0.1 N) were added. After vortex mixing for 10 sec 4 mL aliquot of extraction mixture, diethyl ether/dichloromethane (70/30, v/v), was added using assembly. The sample was vortex-mixed for 3 min using Vortex. The organic layer (3 mL) was transferred to a 5 mL glass tube and evaporated to dryness using Evaporator at 40°C under a stream of nitrogen. Then the dried extract was reconstituted in 250 μL of mobile phase and a 10 μL aliquot was injected into the chromatographic system.

Blood collection

Immediately prior to each of the olanzapine dosing schedules, a baseline (0 hour) sample was drawn. This was followed by sampling at 30, 45, 90, 120 min and 3, 4, 5, 6, 7, 8, 9, 12 hr after the dose. Zero- to 12- hr blood samples were obtained from each subject via heparin lock venous catheter. After centrifugation, each plasma sample was split into duplicate samples and placed in labeled plastic sample vials. All samples

were then stored at -70°C until analysis.

Olanzapine analytical method

All olanzapine blood concentration determinations were performed by a commercial laboratory using a liquid chromatography which is 1200 solvent delivery system (Agilent, U.S.A) and equipped with column (Inertsil ODS 3 μm, 3.0×100 mm, GL Science, U.S.A) keeping at the temperature of 30°C. The Isocratic mobile phase composition was a mixture of 10 mM ammonium acetate/acetonitrile (10/90, v/v), which was pumped at a flow rate of 0.2 mL/min with a split ratio of 20:80. HPLC analysis condition was 10 μL in injection volume and loratadine was used as an internal standard. Plasma 500 μL was pretreated as the same method of calibration with LC-MS/MS.

Selected ion monitoring was used and the ions (m/z) were analyzed for olanzapine: 409.

Data and statistical analysis
Pharmacokinetic analysis

Non-compartmental, nonlinear, least square regression analysis of all plasma concentrations was performed using the pharmacokinetic software program KB star. The equation of best fit was determined by the Akakie information criterion and visual examination of residual errors. All area under the time versus concentration curve (AUC) were observed data and were calculated by the trapezoidal rule to the last measured time point. For each variable a *p* value of 0.05 was used as the minimal level of significance. A plasma concentration - time profile was generated for each subject. The mean pharmacokinetic parameters including C_{max}, T_{max} and AUC were analyzed for statistically significant differences between the two olanzapine administrations.

Statistical analysis

Two pair wise comparisons were made with the respective pharmacokinetics data. Assuming the standard deviation of the primary pharmacokinetic parameters of interest (C_{max}, T_{max}) is approximately 25% of the value of the parameter mean value of different treatments using a *p* value of α=0.05.

Results and Discussion

Evaluation of prepared tablets of olanzapine

The prepared tablets olanzapine were evaluated for appearance, weight variation (± %), hardness (kg/cm²), thickness (mm), friability (%), drug content (%), water absorption ratio, content uniformity (%), wetting time (sec), bitter mouth
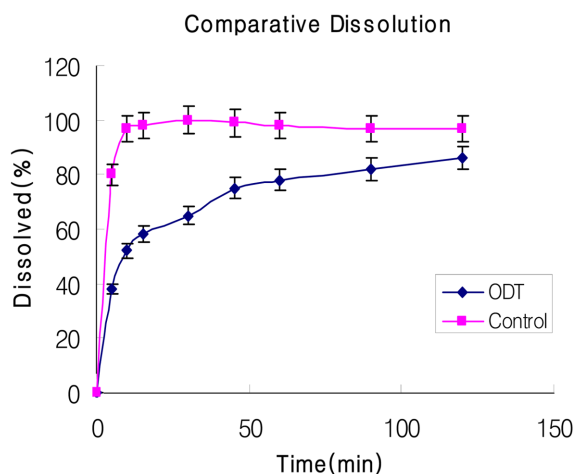
Figure 1. Comparative dissolution profiles from orally dispersible tablets of olanzapine and marketed product in water.
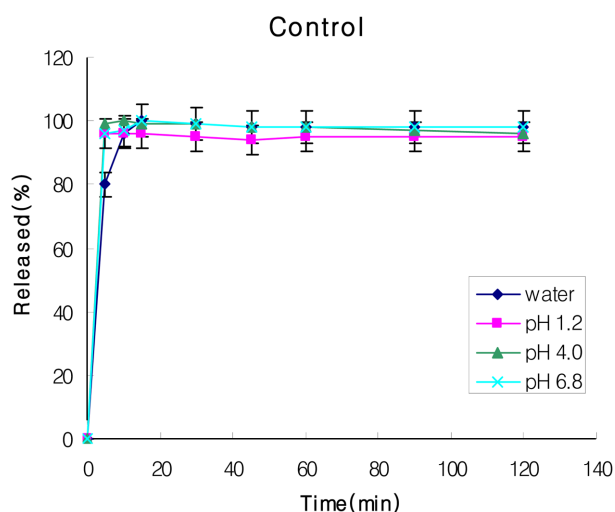

Figure 2. Dissolution profiles from marketed product of olanzapine in water, 0.1N HCl (pH 1.2), pH 4.0 buffer soln and pH 6.8 phosphate buffer soln maintained at 37±0.5ºC.

feel. The results were acceptable within limits and shown in Figure 1.

In preliminary study, our designed formulation showed that almost 60% drug was released within 15 min thus it should be taken into account for further enhancement in terms of drug solubility although the pharmaceutical compositions were validated. The designed orally dispersible tablet of olanzapine based on factorial design formulations showed poor dissolution profile in comparison to marketed product with the difference of more or less 20% (Figure 1.) whereas marketed product has almost similar dissolution profiles regardless of different pH dissolution medium (Figure 2).

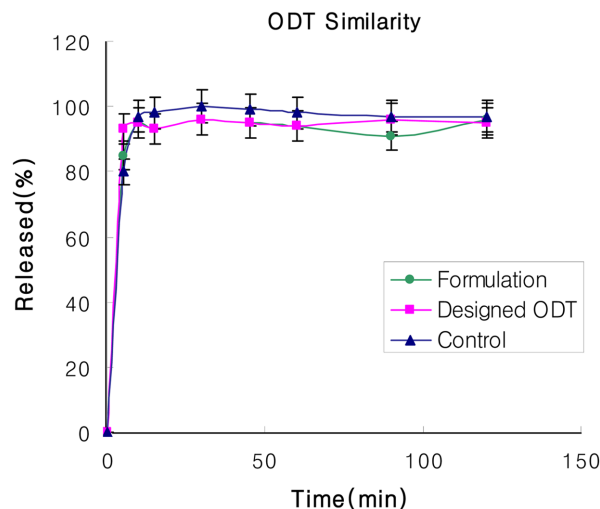Therefore, the optimized release profile which has 100% drug released within 15 min in control Zyprexa Zydis® was

Figure 3. Comparative dissolution profile from orally dispersible tablets of olanzapine with improved solubility (N=2 and N=4) and marketed product in water.

targeted and various formulation runs were manipulated. Furthermore, our laboratory improved the solubility of olanzapine manipulating pH environment around the microstructure of ODT with adjuvant excipients as described in Table II whose results are investigated in terms of the optimized formulation. The optimized formulation was selected in the process of 8 runs performances (Table II) as the solubility of olanzapine was seemed to be improved under more acidic environment, thus different amount of weak acids was regulated and the final optimized release profile (run no 4) was chosen due to stabilized microenvironment which gives the most similar release pattern to control.

Determination of similarity factor

Figure 3 showed that the comparative dissolution profiles from marked product and improved solubility formulations (N=2 and N=4) has similar pattern. Moreover, the prominence was placed on comparison of dissolution profile of developed (Test formulation) and marketed product (Reference formulation) by determination of similarity factor ($f2$). As FDA and EMEA suggest that two dissolution profiles are declared similar if $f2$ is between 50 and 100. The similarity factor ($f2$) for present work was found to be 97.48 exhibiting good similarity between marked and developed formulation.

Olanzapine chromatogram analysis
Calibration graph
Working standard solutions equivalent to 10 to 200 μg/mL olanzapine were prepared by appropriate dilution of stock standard solution (250 μg/mL) with the diluent solution. 10 μL ali-

quot of each solution was injected automatically on to the column in duplicate and the chromatograms were recorded. Calibration graph was prepared by plotting the mean peak area versus concentration of olanzapine. The concentration of the unknown was read from the calibration graph or computed from the regression equation derived using the mean peak area-concentration data. Using the regression analysis, the linear equation, $Y = 31.3774 + 21.0704\ X$, was obtained, where Y is the mean peak area and X concentration in μg/mL. The Linearity co-efficient of mean response of replicate determination plotted against respective concentration was found to be 0.99998. The percent y-intercept as obtained from the linearity data was less than 2%.

Detection and quantification limits

Limit of detection (LOD) and limit of quantification (LOQ) were calculated using signal-to-noise ratio method. LOD is taken as the concentration of analyte where signalto-noise ratio was 3, and it was found to be 0.1 ng/mL.

Precision

The precision of the method was evaluated in terms of inter-mediate precision (intra-day and inter-day). Three different concentrations of olanzapine were analysed in seven replicates during the same day (intra-day precision) and five consecutive days(inter-day precision). Within each series, every solution was injected in triplicate. The RSD values of intra-day studies (<1%) showed that the precision of the method was satis-

factory. The results of this study are given in Table III. The inter-day precision was slightly poor with RSD values in the range 0.75-1.95%. Precision of the injection repeatability was examined by analyzing seven injections of solutions containing olanzapine at four concentrations are shown in Table III respectively. The relative standard deviations(RSD) were calculated from the peak areas and retention times and found to be less than 1% and 0.5%, respectively.

Accuracy

The accuracy of an analytical method expresses the closeness between the reference value and found value. Accuracy was evaluated as percentage relative error between the measured mean concentrations and taken concentrations.

The results obtained for four concentrations are shown in Table III from which it is clear that the accuracy is excellent (RE <1%).

Pharmacokinetics

Non-compartmental pharmacokinetic parameters (C_{max}, T_{max}, AUC_{0-12h}) of olanzapine from all 3 administrations are presented in Table IV. In addition, 0 to 12 hr AUCs from all treatment phases are presented in Figure 4. Two pair wise comparisons were made between ODT control Zyprexa Zydis® versus ODT designed matrix. No significantly differences were noted in the AUC_{0-12h} value according to preset study criteria AUC : 0.9558 ~ 1.0444, Test/Ref ratio 0.999; C_{max} : 0.9274 ~ 1.0379, Test/Ref ratio 0.981. On the other hand, cross clinical trial gave more or less similar values as following; AUC : 0.9558 ~ 1.0444, Test/Ref ratio 0.999 Cmax : 0.9274 ~ 1.0379, Test/Ref ratio 0.981. These values were accepted within log 0.8 ~ log 1.25 with 90% confidence level as described in KFDA BE test guideline and F-distribution is lower than upper 5%. In addition, the difference between log converted average values of ODT control and ODT designed matrix was included in log 0.9 ~ log 1.11. Thus, two pair comparison study was bioequivalent as shown in Figure 4.

All the primary pharmacokinetic parameters calculated for

Table III. *An Accuracy and Precision for Analyzing Olanzapine Concentration in Human Plasma*

Conc. (ng/mL)	Precision (% C.V)		Accuracy (%)	
	Intrarday	Interday	Intraday	Interday
0.1	7.84	13.89	104.6	108.0
0.2	4.19	4.38	104.2	102.6
2	3.92	6.40	105.3	93.8
50	2.01	4.45	93.5	90.4

Table IV. *Non-compartmental Pharmacokinetic Parameters of Olanzapine*

Strength	AUC (ng·h/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
ODT control	38.08 ± 9.76	6.27 ± 2.15	4.37 ± 1.57	33.545 ± 7.525
IR* 2.5 mg	117(147~211)	4.49(3.42~5.56)	6.0(4.0~8.0)	30.0(24.0~36.1)
5.0 mg	351(304~397)	8.03(7.46~8.59)	6.0(2.0~8.0)	29.1(25.3~32.9)
10 mg	712(608~816)	17.3(15.3~19.2)	4.0(2.0~12.0)	28.7(24.6~32.8)
ODT Designed matrix	40.98 ± 9.58	6.39 ± 2.37	3.58 ± 1.03	32.687±5.823

IR* stands for Immediate Release and their parameters are excepted from published data (Green Cross CRO for BE test).
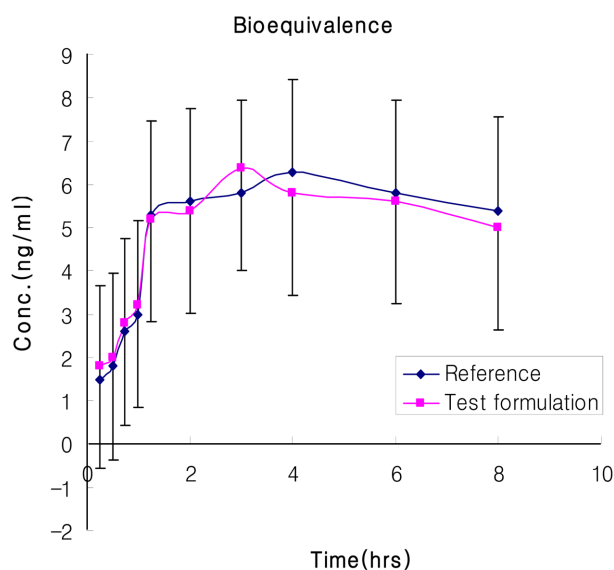
Figure 4. Two pair comparison study profile represented for bioequivalency from the designed orally dispersible tablet of olanzapine(test formulation) and marketed product(reference).

test formulations were close to those of the reference formulation and there were no statistically significant difference between the two formulations. Test and Reference formulations were bioequivalent with respect to the rate and extent of olanzapine absorption, which was expressed by similar values for C_{max}, $AUC_{0-\infty}$ and $t_{1/2}$. In conclusion, statistical comparison of C_{max}, AUC_{0-t} and AUC_{0-inf} clearly indicated that these values were within the acceptable bioequivalence limits of 80-125%. Thus, it can be assumed that the two formulations were therapeutically equivalent and interchangeable in clinical practice. In summary, these studies have demonstrated the bioequivalence of the olanzapine orodispersible 10 mg tablets (Test formulation) and Zyprexa® Zydis® (Reference formulation). The two formulations were rapidly and consistently absorbed and may be used interchangeably for the management of schizophrenia and bipolar disorder without any deleterious effects. Although these data were collected from healthy male volunteers, they may be relevant for the majority of the intended target population (i.e. elderly patients and other persons who have difficulty swallowing tablets).

Conclusions

A fast dissolving tablet of olanzapine of texture and sufficient structural integrity can be prepared by the cost effective direct compression technology. Of all the formulations studied, tablets containing 8% crospovidone resulted in improved disintegration time and drug release profile of olanzapine. In addition to it, bioavailability of the designed ODT matrix was equivalent to commercial available product, Zyprexa Zydis® in the market.

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