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DEVELOPMENT AND BIOEQUIVALENCE STUDY OF OLANZAPINE 10mg TABLETS

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ABSTRACT

Generic drugs are lower-cost versions of patent-expired original brand-name medications. According to guidelines of regulatory agencies of the Canada, US and European Union, a generic drug must be "identical, or bioequivalent to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use". Bioequivalence is decreed when the ratio of the generic to the reference compound for the area-under-the-curve and maximum plasma concentration (C_{max}) fall within a 0.80-1.25 range. The present study was to develop Olanzapine Tablets and compare pharmacokinetic profile of Zyprexa 10 mg film-coated tablets, Zyprexa Velotabs 10 mg orodispersible tablets and Olanzapine 10mg tablets. Multi media dissolution studies in 0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer were carried out for Reference (Zyprexa Velotab 10 mg and Zyprexa 10 mg) and test product (i.e. Olanzapine 10mg). A single centre, open-label, single-dose, randomised, 3-way crossover bioequivalence study, performed under fasting conditions. Based on the results obtained, it can be concluded that the test olanzapine (Treatment A) is bioequivalent to both references Zyprexa Velotab (Treatment B) and Zyprexa (Treatment C) following a 10 mg dose under fasting conditions. All formulations were well tolerated, with no major side effects and no relevant differences in safety profiles were observed between the preparations, particularly with respect to the number and pattern of adverse event.

INTRODUCTION: Generic drugs are lower-cost versions of patent-expired original brand-name medications. According to guidelines of the regulatory agencies of the Canada, US and European Union, a generic drug must be "*identical, or bioequivalent to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use*" [1,2,3]. Bioequivalence is decreed when the ratio of the generic to the reference compound for the area-under-the-curve and maximum plasma concentration (C_{max}) fall within a 0.80–1.25 range. A therapeutic equivalence of generic and brand name medication is, however, not required by regulatory agencies.

Two pharmacokinetic measures are used to determine bioequivalence: the area-under-the-curve (AUC) of the drug concentration-time curve and the maximum plasma concentration (C_{max}). Bioequivalence is decreed if the 90% confidence interval (CI) of the ratio of the generic to reference compound for the AUC and C_{max} falls within a 80-125% range.

Recent market studies indicate that more than half of the patient population prefers ODTs to other dosage forms and most consumers would ask their doctors for ODTs (70%), purchase ODTs (70%), or prefer ODTs to regular tablets or liquids (>80%) [4, 5].

Olanzapine, a thienobenzodiazepine derivative, is an atypical antipsychotic agent with broad efficacy, eliciting a response in both the positive and negative symptoms of schizophrenia and bipolar I disorder. Olanzapine is approved in the US and Europe for the oral treatment of schizophrenia and bipolar I disorder within the dose range of 5-20 mg/day [5-7].

The purpose of this investigation was to develop mouth dissolving tablets of Olanzapine using Crospovidone as disintegrant [8]. Mouth dissolving tablets of Olanzapine were prepared by dry mixing and direct compression. The present study was to develop Olanzapine Tablets and compare pharmacokinetic profile of Zyprexa 10 mg film-coated tablets, Zyprexa Velotabs 10 mg orodispersible tablets and Olanzapine 10mg tablets. The overall target was to produce a tablet bioequivalent to the reference medicinal product Zyprexa 10 mg film-coated tablets and Zyprexa Velotabs 10 mg orodispersible tablets.

MATERIAL AND METHODS: Mannitol, Microcrystalline cellulose, Aspartame, Crospovidone and Magnesium Stearate are found in the brand products so these excipients were presumed compatible with the drug substance [9]. This hypothesis tested in a set of compatibility screening studies. The proposed method of manufacture was dry mixing and direct compression [10-12]. During tablet compression the tablets are tested for appearance, weight, hardness, thickness, disintegration and friability. Blend assay and uniformity are part of the inprocess controls.

The scientific approach used begins with identification of the desired dosage form and performance attributes through the target product profile [13]. From this target product profile, an initial list of critical quality attributes was developed. A risk assessment was undertaken to identify the variables and unit operations which are most likely to impact the critical quality attributes [14].

TABLE 1: RISK ASSESSMENT TO IDENTIFY VARIABLES POTENTIALLY IMPACTING PRODUCT QUALITY

Drug Product- Critical Quality Attributes	Variables and Unit Operations			
	Formulation Composition	Dry Mixing	Lubrication	Compression
Appearance	Low	Low	High	High
Assay	Low	Low	Low	High
Impurities	High	Low	Low	Low
Content Uniformity	High	High	High	High
Dissolution	High	High	High	High

Solubility Studies and Selection of Dissolution medium: Solubility studies were done in 0.1 N HCl, pH 4.5 acetate buffer, pH 4.5 phosphate buffer, pH 6.8 phosphate buffer and water by dissolving the highest dose 20mg of Olanzapine in 250 ml of each of these media. Except water and 0.1N HCl, 20mg of Olanzapine was completely soluble in 250 ml of each of the chosen media.

Calculated dose solubility volume: 20.0 mg (highest strength)/ (0.03mg/ml)= 666.67ml > 250 ml. Therefore, Olanzapine Form I is considered as a low solubility molecule according to the Biopharmaceutics Classification System (BCS) [15].

Multimedia Dissolution Studies: Multi media dissolution studies in 0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer were carried out for Reference (Zyprexa Velotab 10 mg and Zyprexa 10 mg) and test product (i.e. Olanzapine 10 mg) as given in **figure 2, 3 and 4** [16-19].

Bioequivalence Study Design: A single centre, open-label, single-dose, randomised, 3-way crossover bioequivalence study, performed under fasting conditions [20].

The objective of this study was to compare the rate and extent of absorption of Olanzapine 10 mg tablets against Zyprexa 10 mg coated tablets (Eli Lilly, UK) and Zyprexa Velotab 10 mg orodispersible tablets (Eli Lilly, UK).

Subjects were confined to the clinical facility from at least 10 hours prior to drug administration, until after the 72-hour post-dose blood draw, in each period. The study was performed in accordance with the Declaration of Helsinki for biomedical research involving human subjects and the Guideline for Good Clinical Practice [21-25].

The Independent Ethics Committee reviewed the protocol, the informed consent form and other required documents for this study. No study specific procedure was carried out until written approval was obtained from the Independent Ethics Committee & DCGI. Study was conducted as per the IEC approved protocol and there were no amendments implemented during the conduct of the study. The protocol was first approved by the sponsor, Independent Ethics Committee and subsequently from the DGCI.

The Informed consent form was explained to all volunteers (in English, Marathi or Hindi as understood by the volunteer) through an oral presentation regarding the purpose, procedures to be carried out, investigational product, potential risks and rights of the volunteers. All the queries and doubts of the volunteers regarding any aspect of the study were clarified. They were made to understand and were asked to sign the pre approved consent form before check-in Period.

Blood samples were collected prior to the study drug administration and 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0, 120 and 168 hours postdose.

BE parameters: $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ (90% CI: 80-125%); C_{max} (90% CI: 75-133%).

Population Studied: Based on data from literature, the intra-subject coefficient of variation (CV) of olanzapine (by oral route) was expected to be approximately 8% and 15% for AUC and C_{max} respectively. Thus, assuming that the actual ratio of AUC and C_{max} is within 0.90 and 1.11, it was estimated that the minimum number of subjects to be included to meet the 80-125% confidence interval limits was about 26.

Therefore, it was planned to include 30 subjects in order to allow for drop-outs.

Determination of Plasma Olanzapine analysis: Analysis of olanzapine was performed using a validated high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). Sample preparation was performed by liquid liquid extraction technique. The loratadine (Internal Standard) solution (200 ng/mL) was added to plasma sample or olanzapine spiked plasma and mixed for 10 seconds. All samples were mixed with n-Hexane: Isoamyl alcohol, and centrifuged at 15,000 rpm for 10 min. Chromatographic separation was carried out on a HPLC-MS/MS with C18 column. An isocratic mobile phase of acetonitrile and 10 mM ammonium acetate (60:40, v/v) was delivered with a flow rate of 0.2 µL/min. Mass spectra were obtained using a mass spectrometer equipped with electrospray ionisation source. The mass spectrometer was operated in the multiple reaction monitoring mode. Electrospray ionization was in the positive ion mode. The method was validated for specificity/selectivity, linearity, precision, accuracy, recovery of extraction and stability.

Pharmacokinetics: Following pharmacokinetic parameters were determined: Cmax, $AUC_{(0–t)}$, $AUC_{(0–inf)}$, K*el*, t_{max}, t½. Statistical Analysis was performed using SAS software on the data obtained from subjects. The analysis included data from the subjects completing both periods of the study.

The log–transformed pharmacokinetic parameters C_{max}, $AUC_{(0–t)}$ and $AUC_{(0–inf)}$ were analyzed using ANOVA model with the main effects of sequence, subject nested within sequence, period and treatment. Each analysis of variance included calculation of least–square means, adjusted differences between treatment means and the standard error associated with these differences.

The residual variability for each of the pharmacokinetic parameters reflected the intra-subject variability after accounting for the difference between subjects, periods and treatments and were reported in terms of the overall coefficient of variation (% C.V.), from the ANOVA results using log-transformed data. Point estimates and 90% confidence intervals for the test/reference, mean ratios of the pharmacokinetic parameters C_{max}, $AUC_{(0–t)}$ and $AUC_{(0–inf)}$ were calculated using the ANOVA output from the analysis of the log-transformed data.

RESULT AND DISCUSSION: The Formulation development trial was undertaken to identify the variable and unit operations which were most likely to impact the critical quality attributes. The target product profile are presented in **figure 1.1, 1.2 & 1.3**.

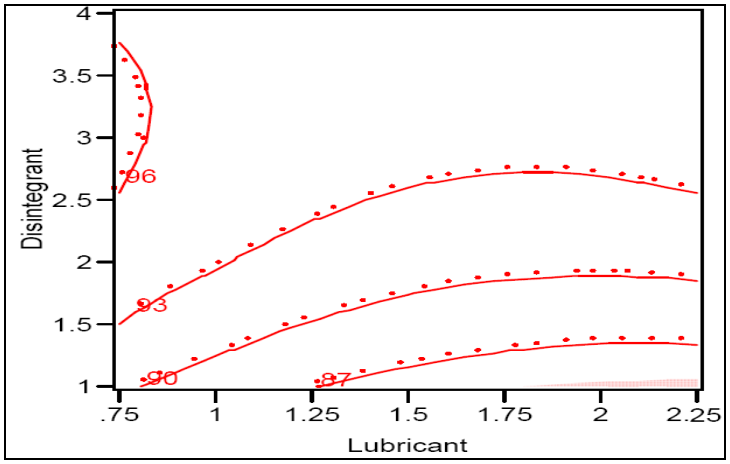

FIGURE 1.1: TARGET PRODUCT PROFILE- CONTOUR PLOT OF DISSOLUTION RESPONSE FOR 10% DRUG LOAD AT A SET TARGET TABLET HARDNESS

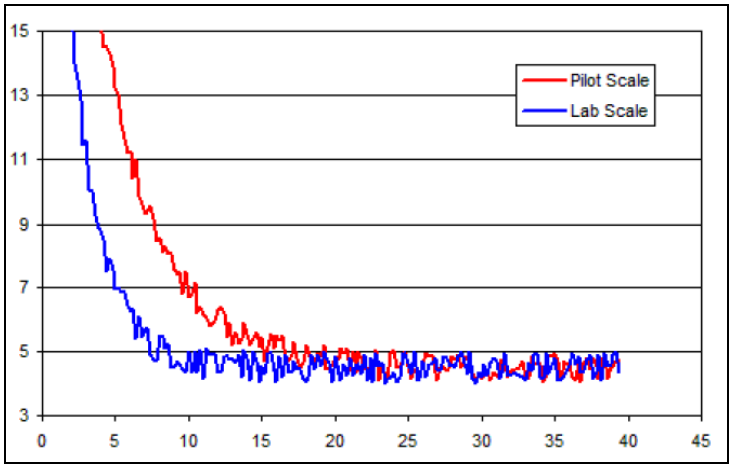

FIGURE 1.2: TARGET PRODUCT PROFILE- BLENDING CONTROL DATA

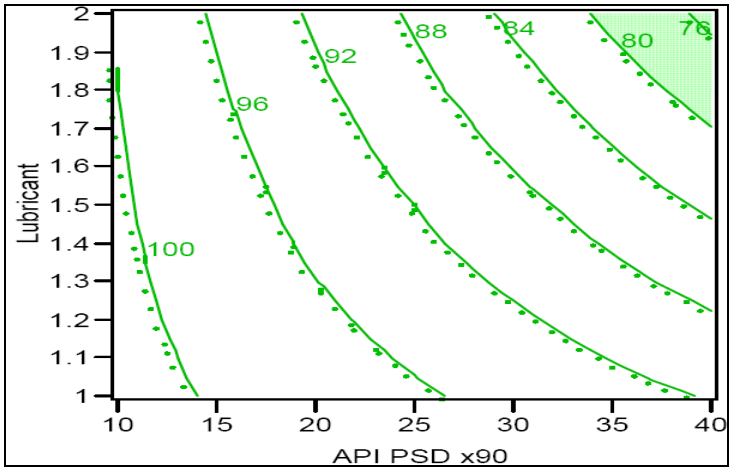

FIGURE 1.3: TARGET PRODUCT PROFILE- CONTOUR PLOT OF DISSOLUTION AT A SET TARGET TABLET HARDNESS

Dissolution profile with Multiple Time Points in Multimedia: To ensure the impact of pH changes on dissolution and release of drug substance for absorption, the percent drug release pattern at different time intervals for different dissolution medias at different pH are presented in **figure 2, 3 and 4**.

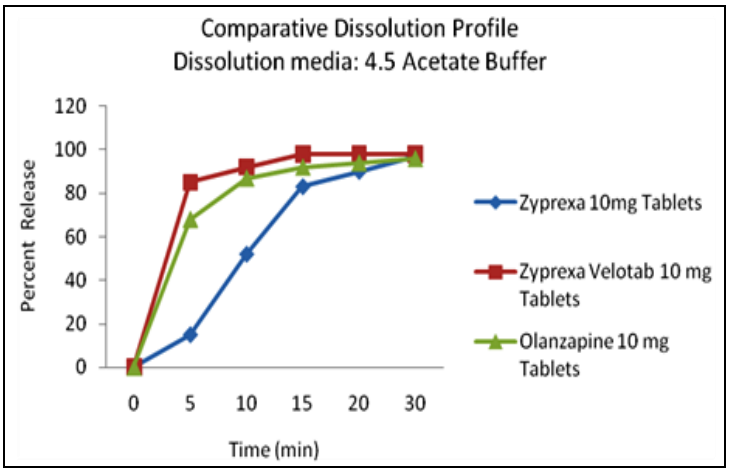

FIGURE 2: COMPARATIVE DISSOLUTION PROFILE, DISSOLUTION MEDIA: pH 4.5 ACETATE BUFFER

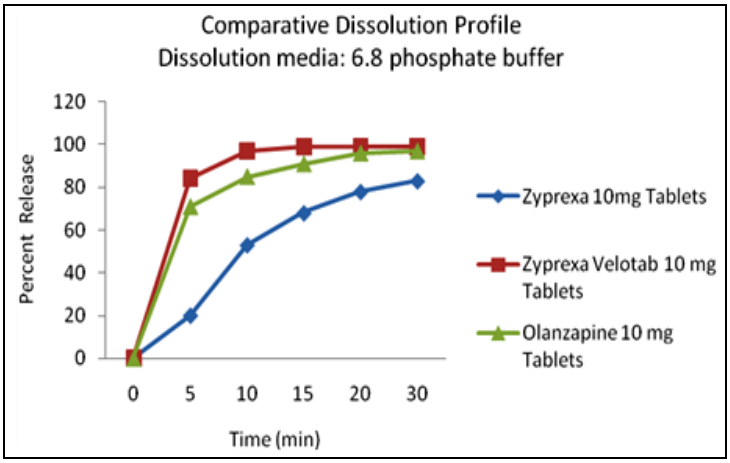

FIGURE 3: COMPARATIVE DISSOLUTION PROFILE, DISSOLUTION MEDIA: pH 6.8 PHOSPHATE BUFFER

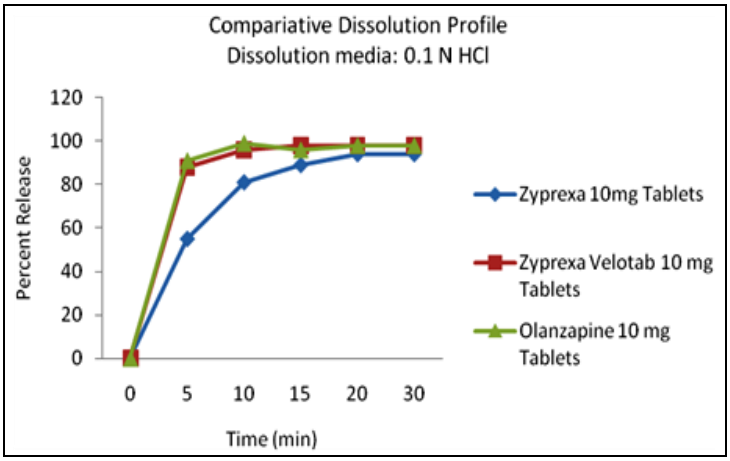

FIGURE 4: COMPARATIVE DISSOLUTION PROFILE, DISSOLUTION MEDIA: 0.1N HCl

Pharmacokinetics: Table 2.1 & 2.2 summarizes the results on the pharmacokinetic parameters (AUC and C_{max}: arithmetic mean ± SD, t_{max}: median, range) after a single 10 mg oral dose of olanzapine (n=26).

TABLE 2.1: TREATMENT COMPARISONS

Parameters		Test [Olanzapine (A)]			Reference 1 [Zyprexa Velotab (B)]			Reference 2 [Zyprexa (C)]		
		Mean	SD	CV (%)	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC_{0-t}	(pg·h/mL)	493316.39	147483.62	29.90	500532.08	142287.80	28.43	497101.97	139667.32	28.10
AUC_{0-inf}	(pg·h/mL)	523710.65	158041.04	30.18	531973.77	153602.01	28.87	530665.42	148954.57	28.07
C_{max}	(pg/mL)	11425.30	3243.33	28.39	11913.34	3011.51	25.28	11824.53	3040.87	25.72
Residual area	(%)	5.63	2.25	39.95	5.77	1.83	31.64	6.22	2.75	44.21
T_{max}	(h)	5.58	2.63	47.17	5.06	2.04	40.38	4.99	1.86	37.34
T_{max*}	(h)	4.51	4.00	-	5.25	2.50	-	5.00	2.39	-
Kel	(h-1)	0.0174	0.0024	14.01	0.0169	0.0019	11.42	0.0170	0.0023	13.55
T½ el	(h)	40.60	5.82	14.32	41.64	4.71	11.31	41.36	5.36	12.96

* Medians and interquartile ranges are presented

TABLE 2.2: TREATMENT COMPARISONS

Statistical Analysis (ANOVA)	Treatment Comparisons	Ratio of LS Means [1]	90 % Geometric C.I.[2]		Intra-Subject CV	Inter-Subject CV
			Lower	Upper		
AUC0-t	Olanzapine (A) vs Zyprexa Velotab (B)	98.04%	94.62%	101.59%	7.64%	30.97%
	Olanzapine (A) vs Zyprexa (C)	98.71%	95.27%	102.28%		
AUC0-inf	Olanzapine (A) vs Zyprexa Velotab (B)	97.88%	94.50%	101.37%	7.55%	31.72%
	Olanzapine (A) vs Zyprexa (C)	98.12%	94.74%	101.63%		
C_{max}	Olanzapine (A) vs Zyprexa Velotab (B)	95.14%	90.96%	99.52%	9.68%	24.29%
	Olanzapine (A) vs Zyprexa (C)	96.01%	91.79%	100.43%		

[1]Calculated using least-squares means (ln-transformed data). [2]90% Geometric Confidence Interval using ln-transformed data

DISCUSSION: The Olanzapine 10 mg Tablets was within the acceptable limits of the United States Pharmacopoeial monograph. The disintegration time less than 15 seconds and rapid dissolution. The results revealed that the Olanzapine 10 mg Tablets had a good dissolution profile. Stress testing was conducted to ensure that the assay and impurity methods are specific and stability indicating. Six months of stability data indicates that all monitored attributes of the Olanzapine 10 mg Tablets fall well within the proposed stability specifications.

All formulations were well tolerated, with no major side effects and no relevant differences in safety profiles were observed between the test formulation and reference formulations. On application of ANOVA to various variables like sequence of dosing, subjects nested within sequences, period of treatment and drug formulations no significant variation were observed for parameters of C_{max}, $AUC_{(0-t)}$, $AUC_{(0-inf)}$. The 90% Confidence Interval calculated for ln-transformed parameters and untransformed parameters of Cmax, and $AUC_{(0-t)}$ $AUC_{(0-inf)}$ values were within the prescribed limit of bioequivalence (80 -125 %).

Based on the statistical results of 90% confidence intervals of log-transformed pharmacokinetic parameters C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$, it is concluded that the test formulation (Olanzapine 10 mg Tablets) was bioequivalent to both references Zyprexa Velotab and Zyprexa under fasting conditions.

CONCLUSION: Based on these results, it can be concluded that the test olanzapine (Treatment A) is bioequivalent to both references Zyprexa Velotab (Treatment B) and Zyprexa (Treatment C) following a 10 mg dose under fasting conditions.

All formulations were well tolerated, with no major side effects and no relevant differences in safety profiles were observed between the preparations, particularly with respect to the number and pattern of adverse events.

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