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COMPARATIVE BIOAVAILABILITY ANALYSIS OF ORAL ALENDRONATE SODIUM FORMULATIONS IN PAKISTAN

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Abstract

Alendronate sodium, a bisphosphonate drug, is used to treat osteoporosis and other bone diseases. The present study was designed to conduct comparative bioavailability analysis of oral formulations of alendronate sodium through an open-label, randomized, 2-sequence, 2-period crossover study. Healthy adult male Pakistani volunteers received a single 70mg dose of the test or reference formulation of alendronate sodium followed by a 7 day washout period. Plasma drug concentrations were determined using a validated HPLC-post column fluorescence derivatization method. AUC_{0-t}, $AUC_{0-\infty}$, C_{max} and T_{max} were determined by non-compartmental

analysis and were found within the permitted range of 80% to 125% set by the US Food and Drug Administration (FDA). Results show that both in vitro and in vivo assays of all test brands were within the specification of the US Pharmacopoeial limits and were statistically bioequivalent. No adverse events were reported in this study.

Key words: Alendronate, bioavailability, bioequivalence, pharmacokinetic parameters, HPLC

Abbreviations: PK-Pharmacokinetic parameter, C_{max} -maximum plasma concentration, T_{max} - time to reach maximum plasma concentration, AUC-area under curve, $t_{1/2}$-half life, k_e- elimination rate constant.

1. Introduction

In recent years, the provision of quality health care is receiving global interest and medicines have become a core component of health care system to cater health care needs of patients (1-3). In some countries, up to 60% of total health care expenditure is allocated to the cost of medicines (4) which can be controlled with rational and judicious use of medicines. An essential cost reduction measure is to encourage the prescription of low-cost generics. The generic drugs have captured more than 65% of the global pharmaceutical market (5, 6). Average prescription spending in the United States topped 286 billion in 2007, prompting calls for greater generic drug use to reduce costs without sacrificing quality. Generic drugs account for 66% of prescriptions filled in the US but less than 13% of the cost (7). The importance of generic drugs in health care has made it crucial to consistently monitor their pharmaceutical quality and in-vivo performance since these are alternative to innovator products in the market (8). Alendronate sodium (sodium [4-amino-1-hydroxybutylidene] bisphosphonate) is prescribed for the management of bone diseases such as osteoporosis, hypercalcemia, and Paget's disease (9).

Alendronic acid is released immediately in solution and irritate mucosal lining during deglutition. As a consequence, it can cause esophagitis. Thus, it is administered orally as tablets in its monosodium salt form to prevent esophagitis (10, 11). Moreover, it should be taken in morning with a glass of water at least 30min before food and the patient should avoid lying down during that time.. The fast release of alendronic acid exhibits a potential health risk, which should be kept as low as possible (12).

Alendronate sodium is selectively accumulated in the bone, and its oral absorption is <1% of the administered dose in the fasted state (13). It is reported that about 40% of an oral dose is excreted within 8-12 hours, while the remaining is gradually released from the bone, depending on the rate of bone turnover, and is eventually eliminated in the urine (14). It is an effective inhibitor of osteoclast and bone resorption. The plasma half-life of alendronate is 1.7-1.8 hours in healthy individuals (13, 14, 15). An increasing number of generic alendronate formulations have become available. Although expected to have the same tolerability and efficacy, head-to head comparison of generic and brand alendronate was never performed. A study compared the tolerability and efficacy of generic and brand alendronate and found no significant differences in overall tolerance between treatment groups (16). It was also found that the level of bone turnover markers were significantly decreased over 12 weeks of follow-up for generic and branded alendronate. Generic caused significantly higher abdominal pain scores. Therefore, generic alendronate may not have the same tolerability and efficacy as branded alendronate in the first weeks after starting treatment in patients with a recent fracture. Patients who were previously stable on doses of brand alendronate experienced an increase in adverse events causing discontinuation after introduction of automatic substitution to generic alendronate (17).

In Pakistan, currently multiple pharmaceutical formulations containing alendronic acid are manufactured and marketed by many local pharmaceutical companies with varied prices and may differ in their quality towards the innovator product (18). In line of this, the objectives of the present study were to conduct in-vitro and in-vivo studies of oral formulations of alendronate sodium 70mg. The research was conducted according to standard specifications of United States Pharmacopoeia (USP) and an open-label, randomized, two-period cross over comparison in Pakistani male adult volunteers was done to compare bioavailability and pharmacokinetic parameters (PK) of leading brands with generic product. This study will help the policy makers in guiding various Government and private institutions to buy good quality and cheap generic alendronate sodium in order to cater the demands of patients suffering from osteoporosis and will also save a lot of foreign exchange incurred on medicines. It will also help boosting the confidence of the medical professionals to prescribe locally manufactured drugs and also aid the local industry to export to neighboring countries to earn foreign exchange as well.

2. Subjects and Methods

2.1 *In-Vitro* Analysis

A total of ten leading brands of alendronate sodium 70mg tablets available in the market were purchased, i.e., brand leader and generic; and were tested according to standard USP methods. The samples were tested for their in-vitro characteristic, i.e., physical and chemical parameters, disintegration time and dissolution percentage (19). In-vitro tests were performed according to USP30 guidelines. The dissolution test was performed by Paddle method (dissolution apparatus ERWEKA DT6, GmbH, Germany) with following parameters: water as medium; speed 50rpm; dissolution medium volume 900ml, time 15min, temperature $37.0 \pm 0.5^\circ C$. Disintegration test

(ERWEKA ZT3-A, GmbH, Germany) was also performed according to the specifications of USP30.

Assay for to quantify alendronate was conducted based on USP monograph for alendronic acid tablets. Alendronic acid tablets contain an amount of alendronate sodium equivalent to 90-110% of the labeled amount. Briefly, after mixing standard/test solution with sodium citrate dihydrate diluent and borate buffer for 3min, 0.05% 9-fluorenylmethyl chloroformate solution was agitated with previous mixture for 30 seconds. The resultant mixture was allowed to stand for 25min at room temperature and then centrifuged after adding methylene chloride for 5min. Upper layer was analyzed by high performance liquid chromatographic (HPLC) and amount of alendronate in test/standard sample was estimated by comparing the chromatogram peaks of respective samples with calibration standards. Same method was used to determine percentage of active in dissolution test (19).

2.2 *In-Vivo* Analysis

2.2.1 Study Design

In-vivo studies were materialized through open-label, randomized, 2-sequence, 2-period crossover study in healthy male adult population to compare their bioavailability and PK parameters of the brand leader with generic product. The studies were carried out at Drugs Control and Traditional Medicines Division (DCTM), National Institute of Health (NIH), Islamabad, Pakistan.

2.2.2 Subjects

Healthy Pakistani adult male subjects were eligible to be enrolled in the study. Inclusion criteria consisted of unremarkable results on medical history, physical examination, and clinical laboratory tests (vital signs, serum chemistry and hematology, and urinalysis). Subjects with HIV

or hepatitis B were excluded from the study. Concurrent medications and the consumption of alcohol were not allowed from 2 weeks before administration of the first dose until the end of the study period. Subjects were informed about the aims and risks of the study, and written informed consent was obtained from all volunteers before screening. The study protocol was approved by the board of studies of Sargodha University, Sargodha, Pakistan and DCTM, NIH, Islamabad, Pakistan. All protocols were in accordance with the revised Declaration of Helsinki (20) and the Good Clinical Practice guidelines (21). All the drugs used for bioequivalence studies were procured from market and reference standard of alendronate sodium for the study was provided by M/S MSD (OBS), Pakistan. All chemicals used in the study were from Sigma/Merck (analytical or HPLC grade). Distilled water was used wherever required in the study.

2.2.3 Blood sampling and sample processing

24 healthy adult male volunteers were randomly assigned to receive a single 70mg dose of test or reference formulation of alendronate sodium, administered with 240ml of water, followed by a 7 day washout period and subsequent administration of alternate formulation. Drugs were administered after 12 hour overnight fast. Serial blood samples were collected and adverse events, if any, were monitored by a clinical investigator via observation, personal interview, and measurement of vital signs (blood pressure, heart rate and body temperature) over a 7h period (at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, and 7 hours) after drug administration. After collection, the blood sample was immediately centrifuged (Cat. No. 9527-16, Abbott Diagnostics Centrifuge machine) at 4000rpm for 15min and separated plasma was frozen (UNI-TRAP UT-50L refrigeration system) at -20˚C in eppendorf tubes until analysis.

Plasma alendronate sodium concentrations were determined using a validated HPLC-post column fluorescence derivatization method, with visible detection in the range of 2 to 100 ng/ml

and lower limit of quantification set at 2 ng/ml (22, 23). PK properties including AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$, and the elimination constant (k_e) were determined by non-compartmental analysis. The formulations were considered bioequivalent if 90% CI ratios for C_{max} and AUC were within predetermined interval of 80% to 125% that is the regulatory definition set by US Food and Drug Administration (24).

2.2.4 Standard curve

Stock solution of alendronate sodium in a concentration of 1mg/ml was prepared in mobile phase (buffer solution: acetonitrile: methanol, 75: 20: 5). The stock solution was then diluted to 100μg/ml with methanol to make a working stock solution. From this working stock solution, calibration standards were prepared in plasma in concentrations of 1, 2, 3, 4, 5, 6, 7, 9, 10, 12 and 15μg/ml (Figure 1).

2.2.5 Extraction and assay of alendronate from plasma

Stored frozen plasma was thawed and 200μg of plasma was vortexed (Model MA-1, Torika) 1ml methanol in eppendorf tube for 2 minutes. The sample was then centrifuged (Cat. No. 9527-16, Abbott Diagnostics Centrifuge machine) at 10000rpm for 10 minutes and 800μl of the supernatant was separated in another tube. The sample was dried in a vacuum oven (VOS-300, EYELA) and the residue left after drying was reconstituted with 200μl of mobile phase that was composed of buffer solution (14.7g Sodium citrate dihydrate and 7.05g anhydrous disodium hydrogen phosphate, pH 8) acetonitrile, and methanol in ratio 75: 20: 5. 100μl of sample was injected into the HPLC system (LC-9A; Column: L-21, 4.1 x 250mm, 5μ particle size; temperature 35^0C) for analysis (19). Mobile phase was set to flow through sample at the rate of 1ml/min. Analyte detection was done with a Fluorescence detector (LC 9A, Shimadzu, Japan). The fluorometric detector was operated at 260 nm (excitation) and 310 nm (emission). Amount

of alendronate in plasma was estimated from calibration curve by recording the chromatogram and measuring the responses for the major peaks.

2.2.6 Pharmacokinetic and Statistical Analysis

A non-compartmental pharmacokinetic model was used to determine the pharmacokinetic (PK) parameters of alendronate sodium. The PK parameters i.e., $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow \infty}$, C_{max}, T_{max}, $t_{1/2}$ were determined using Minitab® 16 (Minitab, Inc., USA) for each of the volunteers for both the drugs. Both the AUC and AUMC were calculated using the trapezoidal rule, more specifically the AUMC was calculated by constructing the area under the concentration (C) times time (T) versus time (T) curve (C.T vs. T). The mean residence time (MRT) for the drugs was calculated as MRT = AUMC/AUC. Statistical comparisons between pharmacokinetic parameters of the two products were analyzed by two-way ANOVA with $p < 0.05$ for statistical significance. Data was presented as mean±SD of multiple values.

The first-order terminal elimination rate constant (Kel) was determined by linear regression using points describing the elimination phase on a log-linear plot. The Cmax and Tmax parameters were obtained directly from the curves. The areas under the curve for alendronate plasma concentration versus time for 0–t (AUC_{0-t}) were calculated by applying the linear trapezoidal method.

 The 90% confidence intervals of the test/reference ratio of C_{max}, $AUC_{0\rightarrow t}$ and $AUC_{0\rightarrow \infty}$ were determined using log transformed data. The bioequivalence between the two formulations was accepted if 90% CI of the log transformed C_{max}, $AUC_{0\rightarrow t}$ and $AUC_{0\rightarrow \infty}$ of test was within 80-125% of the original product (19).

3. Results

3.1 *In-Vitro* Parameters

The chemical assay, disintegration time and dissolution rate of all test brands were found within the specifications of USP (Table 1). The brand leader FOSAMAX® from MSD, Pakistan and the one having best dissolution rate were selected for bioequivalence studies.

3.2 *In-Vivo* Parameters

Among the 24 volunteers enrolled in the study, no serious adverse event was found throughout the study period. There was insignificant difference in all analyzed pharmacokinetic parameters among all brands of alendronate sodium. The demographic parameters of subjects were as follows: mean age 23.5±3.5 years (range 21–29 years); mean height 175.4±3.8cm (range 152.0–173.0cm); and mean weight 68±4.8kg (range 64–76 kg).

3.2.1 Alendronate sodium quantification in plasma

The analytical method for alendronate sodium quantification in plasma samples had good specificity, sensitivity, linearity, precision, and accuracy over the entire range of clinically significant and therapeutically achievable plasma concentrations, thereby enabling its use in bioequivalence trials. The linearity was observed within the range of 1 to 100 ng/ml (alendronate sodium; $y = 45579x + 21172$, $r2 = 0.988$; x = plasma concentration, y = peak area ratio) (Figure 1). The intra-day precision ranged from 0.29% to 1.78%, whereas intra-day accuracy ranged from 97.9% to 100.9%. Inter-day precision ranged from 0.82% to 1.56%, whereas inter-day accuracy ranged from 98.30% to 102.6%. The amount extracted of alendronate sodium was determined in pentaplicates. The mean absolute recovery was 92.82%, whereas the relative recovery ranged from 94.9% to 101.2%.

Pharmacokinetic parameters were determined from the plasma level-time curve drawn for either of the drugs in each volunteer (annex.1), . The results of ANOVA revealed that C_{max}, ln C_{max}, T_{max}, AUC, ln AUC_{0-t}, $AUC_{0-\infty}$, and ln $AUC_{0-\infty}$ were statistically insignificant for effect subject, period and treatment. Statistical analysis of the pharmacokinetic parameters of the test and reference drug are presented in table 2. The geometric mean ratio (90% CI) of these parameters along with the results of bioequivalence test are presented in table 3. Since, 90% CI for all parameters was within the predefined bioequivalence acceptance limits (80-125% of the originator); therefore, the test and reference formulations were considered bioequivalent. Hence, Osteopor® could be concluded as having comparable pharmacokinetic profiles with Fosamax®.

3.2.2 Tolerability

Both formulations of alendronate sodium 70mg were well tolerated by all volunteers. No clinical undesirable events were observed throughout the study and for up to two week after the study.

Table 1: In-vitro analysis of various brands of alendronate sodium (70mg)

S. No.	Brand (70mg)	Manufacturer	Batch No	Mfg Date	Expiry Date	Avg. Wt	% Assay	Amount of active substance (mg)	D-Time (min)	% Dissolution
1	BONAFIDE	Medisure	004	12/12	12/14	0.330 ±0.21	95.6	66.92	11	81.4
2	BONATE	Wilshire	007	9/11	8/13	0.216 ±0.14	96.6	67.6	13	80.1
3	BONGARD	PharmEvo	9N033	12/09	12/11	0.205±0.26	101.7	71.2	11	86.6
4	FOSAMAX	OBS Pharma	NM 22110	10/09	10/12	0.746±0.42	100.2	70.1	12	90.2
5	ORTHONATE	Schazoo	Ont 013	Jan, 2012	Jan 2014	0.442±0.09	100.3	70.21	8	82.4
6	OSTEOPOR	Werrick	1414	12/09	12/11	0.553±0.24	101.7	71.2	10	94.4
7	REVENTA-70	Getz	051T 24	12/12	12/14	0.201±0.18	101.5	71.05	8	88.6
8	ALENDRATE	Global	051	01/12	01/14	0.335±0.06	101.7	71.19	2	80.6
9	OSTIM	Genome	003	05/12	05/14	0.445±0.18	100.1	70.07	7	84.8
10	DRATE	SJG Fazal Ellahee	2251T	08/12	08/12	0.566±0.12	99.7%	69.8	9	82.6

D-Time = disintegration time; average weight of tables is expressed in mean±SD. % active is determined with assay limit of 90-110%. Dissolution assay limit is 80%. All tests are according to USP.

Table 2. Statistical analysis of pharmacokinetic parameters for test and reference drug in 1st and 2nd periods.

Pharmacokinetic Profile	Statistical Analysis									
	Test Drug					Reference Drug				
	Mean	SD	SE	Min	Max	Mean	SD	SE	Min	Max
AUC_{0-t} (ng.hr/ml)	112.17	8.26	1.72	99.00	131.00	116.39	6.97	1.45	105.00	131.00
AUC_{0-inf} (ng.hr/ml)	117.09	17.65	3.68	73.00	150.00	119.04	9.05	1.89	105.00	137.00
K_e (l/h)	0.25	0.11	0.02	0.10	0.57	0.37	0.16	0.03	0.11	0.75
MRT (h)	2.78	0.55	0.11	1.90	3.50	2.66	0.82	0.17	0.97	3.78
$t_{1/2\_e}$ (h)	1.92	0.61	0.13	0.81	3.08	1.85	0.45	0.09	1.19	2.83
C_{max} (ng/ml)	49.5	6.86	1.43	41.47	67.7	58.22	8.98	1.13	43.87	79.99
T_{max} (h)	1.00*			0.75	1.5	1.00*			0.75	1.5

AUC= area under curve; ke= elimination rate constant; MRT= mean residence time; t1/2_a= absorption half life; Cmax= maximum plasma concentration; Tmax= time to reach maximum plasma concentration; *median values were calculated

Table 3. Pharmacokinetic parameters of test and reference drugs.

Parameter	Test	Reference	Standard		Observed		Within Equivalent Limit	
			Lower	Upper	Lower	Upper	Lower	Upper
ln AUC_{0-t} (h.ng/ml)	4.72 ± 0.07	4.75 ± 0.10	80%	125%	0.967	1.04	Yes	Yes
ln AUC_{0-inf} (h.ngm/l)	4.72 ± 0.04	4.78 ± 0.09	80%	125%	0.969	1.04	Yes	Yes
ln C_{max} (ng/ml)	3.90 ± 0.07	4.06 ± 0.08	80%	125%	0.962	1.06	Yes	Yes
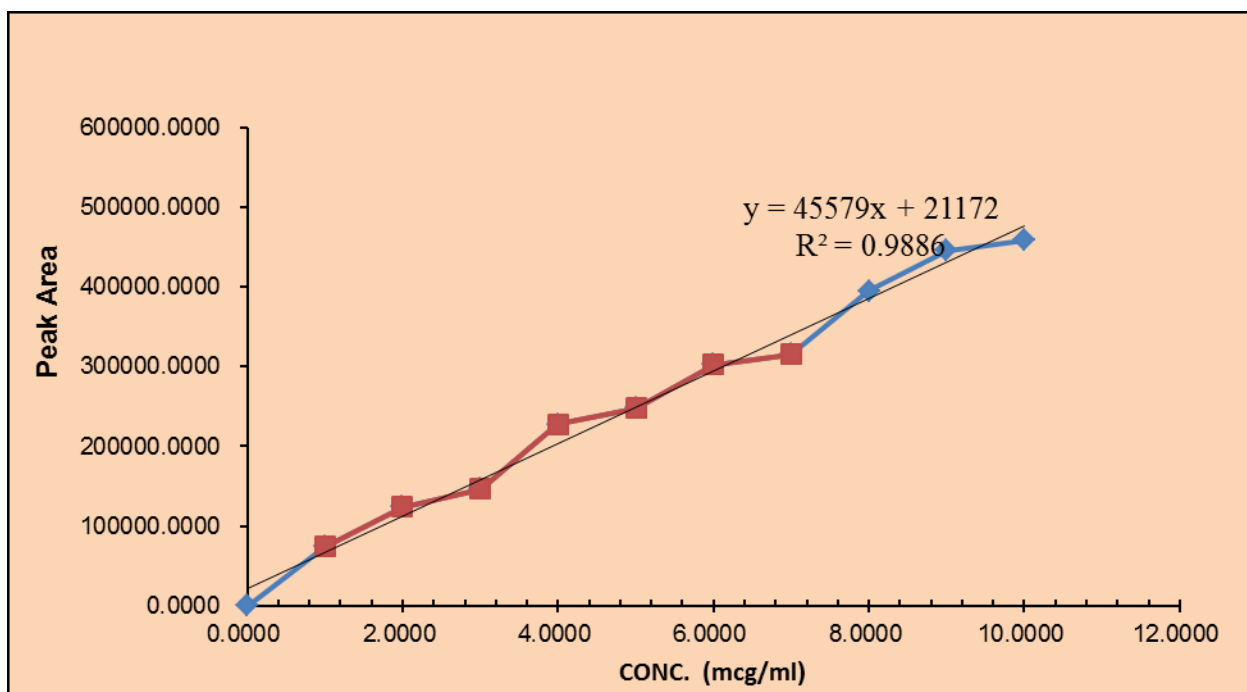
Figure 1: AUC standard curve for alendronate sodium
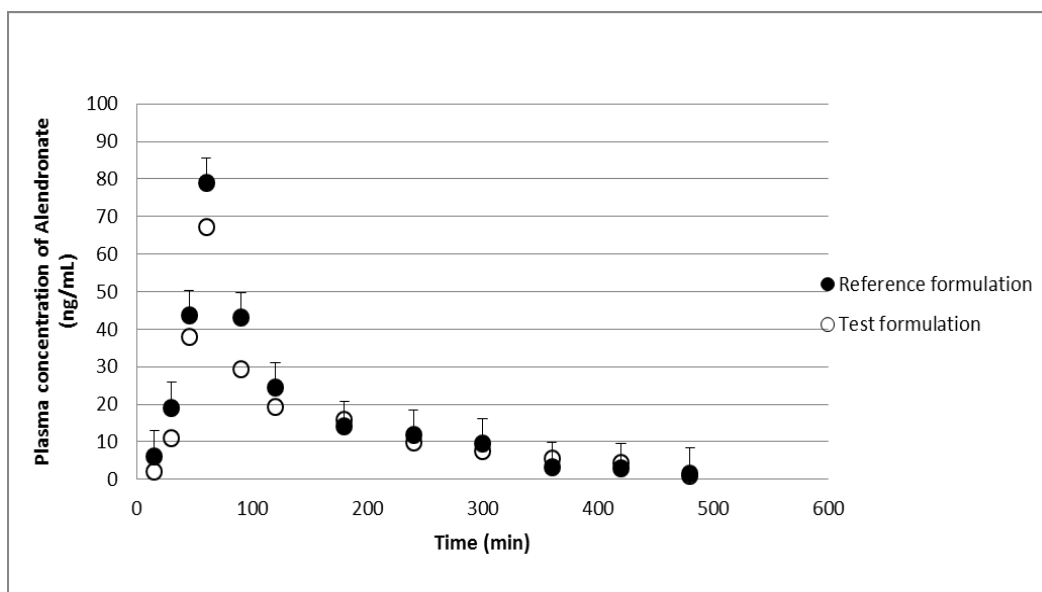
Figure 2. Plasma concentration-time plots of alendronate Sodium. The plot is obtained after a single oral dose (70mg) of reference

and test formulation in healthy volunteers (N=24). No statistical significant difference was recorded. Data is presented as mean values.

4. Discussion

The appearance of off-patent generic drugs in the world's pharmaceutical market is a highly interesting fact from the socio-economic point of view and can bring about an increased efficiency in health systems and increase the percentage of population benefitting from a medical care plan (25). The World Health Organization has reported various copies of substandard quality of original pharmaceutical products (26). The substandard drugs contain low quality ingredients or lack the specified ingredient altogether. Moreover, even when the definite ingredient is present, in some cases, it does not dissolve satisfactorily or the amount is improper (27). It was recognized some 50 years ago that unless an oral dosage form (pill or tablet) disintegrates into small aggregates, it can not be efficiently absorbed by the body (28). However, a switch from disintegration testing to dissolution testing is due to the fact that only tablet disintegration does not ensure its availability in solution form for absorption. Today, disintegration is typically conducted as an in-process test during tablet manufacture. Thus, in present study, dissolution and disintegration tests of all brands of alendronic acid tablets analyzed were rapid, complete and conformed to the established USP30 specifications (Table 1) ensuring adequate drug absorption from the generic products. However, the generic products of alendronic acid tablets are approved based on the results of single-dose bioavailability studies in healthy subjects which is not an adequate test to establish similar disintegration characteristics (29). In United States, if a drug substance and a drug product monograph exist in USP, the generic version is expected to conform to these established quality specifications. The generic version is also required to use the same salt form of the active ingredient, as the salt form can affect the inherent solubility and subsequent absorption of the active ingredient. Thus, alendronic acid must also be formulated as sodium salt. There is currently a USP monograph for alendronate

sodium (active substance) and for alendronic acid tablets (19) and unless stated otherwise the generic form should conform to these standards. In our study, all generics and brands tested conformed to USP standards (Table 1). Recently, a study has shown that for all drug categories investigated, the patients who experienced a generic switch did not have more concerns about their index medicine than patients who did not switch and patients having high confidence in the health-care system showed less concern (30).

Generic versions of alendronate have been reported to be bioequivalent to branded alendronate (22, 23). The development of a brand name formulation requires the demonstration of its pharmacokinetics, efficacy and tolerability in both healthy subjects and in the target patient population. However, the development of the generic equivalent requires only the demonstration of its bioequivalence with the brand name product in healthy subjects (31). WHO guidelines state that 18 to 24 healthy male and female volunteers aged 18 to 55 years of normal body weight should be used in a crossover study design to determine whether bioequivalence is achieved between two formulations (21). It is assumed that bioequivalence demonstrated in crossover studies performed in this typically younger and healthier population would be equivalent to that observed in the patient population. It is further supposed that this bioequivalence would translate into comparable clinical efficacy and tolerance; however, evidence to support the existence of a well-defined relationship between these parameters is lacking (32). These differences have fostered concern as to whether bioequivalence, as ascertained in crossover studies of healthy adults, should be used to make claims of comparable clinical effectiveness and tolerability in patients who are older and often have numerous underlying disorders or diseases. Further, older individuals tend to have greater difficulty in swallowing pills (orientation of pill in mouth) and have reduced GI motility as compared to younger individuals. These differences may increase

the exposure time of the alendronate tablet to the upper GI tract which could then increase the probability of alendronate exposure to the esophagus in older adults.

Much dissimilarity exists between brand and generic alendronate including: disintegration time, bio-adhesion to the esophagus, patient compliance to treatment, adverse event prevalence, and conservation of bone mineral density. Generic forms of alendronate warrant closer clinical study before their credibility for clinical usefulness and acceptability of brand. Differences in the excipient composition between the brand and generic formulations of alendronate may alter the bioavailability of the generic alendronate to bone if this substitution changes the behaviour of the tablet such that the alendronate tablet becomes more easily bound to food or drink and unavailable for absorption in the gut (33).

Since, the bioavailability of alendronate is low and dosing requirements are strict; therefore, any characteristic of the tablet that changes the speed of delivery of alendronate, such as time required for disintegration or dissolution, can have important implications on drug effectiveness or tolerance. For regulatory approval, explicit dissolution parameters are required to allow for the generic substitution of brand alendronate; however, there are no specifications for the required disintegration characteristics of the generic forms.

It has been reported (29) that the dissolution and disintegration rates of a number of generic formulations of alendronate from Canada, Netherlands, Germany, and United Kingdom were compared to United States manufactured brand risedronate and alendronate. All of the generics tested had an acceptable dissolution rate as compared to brand alendronate. Commercially available oral tablets designed to dissolve in mouth without water prior to swallowing were

purposefully included to act as disintegration comparators. Six of the 26 generic versions of alendronate tested had disintegration times that were comparable to oral tablets disintegrating in mouth.

Furthermore, substantial evidence indicates that many generic formulations of alendronate are more poorly tolerated than the proprietary preparations resulting in ominously poorer adherence and efficacy (34). Reduced effectiveness may result from faster disintegration times of many generics that increase the likelihood of adherence of particulate matter to the esophageal mucosa. Unfortunately, market authorisation, based on the bioequivalence of generics with a proprietary formulation, does not take into account the potential concerns about safety. Poor adherence of many generic products has implications for guideline development, cost-effectiveness and impact of treatment on the burden of disease. The impact of generic bisphosphonates requires formal testing to re-evaluate their role in the management of osteoporosis.

The majority of generic versions of alendronate disintegrate faster or slower than brand alendronate, whereas dissolution times are largely similar between brand and generic alendronate. Moreover, a qualitative study had shown two general themes: first, complications in recognizing the substituted medicine and second, lack of confidence in the identical effect of the substitutable medicines (35). Previous interview and questionnaire based analysis have shown that some patients felt anxious and insecure about generic substitution and furthermore expressed uncertainty with regard to inferior quality of the generic drugs compared with the original products. Moreover, side effects were experienced by some users of generic drugs (35, 36, 37).

The Drug Regulatory Authority (DRAP) of Pakistan has not made it mandatory requirement for marketing a generic in Pakistan with bioequivalence studies, nevertheless, bioequivalence studies have been carried out in recent years either for the purpose of quality enhancement or as a marketing tool (38, 39). We are aware of the fact that there are strict guidelines in Europe and USA for marketing authorization of oral (small molecule) generics to ensure good quality and enhance their utilization. This is recognized as the first step to enhance the use of generics versus originators and patented products in a class. Without such legislation and subsequently its implementation in its true letter and spirit, there will always be concerns with the quality of generics especially the one that are locally produced. It will also be difficult to promote low priced generics in Pakistan. There is a dire need to revisit the drug policy of DRAP to promote and encourage the prescribing of low cost generics with highest quality, especially with generics priced at 2% to 10% of pre-patent loss prices as established in some (5, 6, 40). Our study is a step towards this goal.

5. Conclusions

It is concluded that in the present study in healthy male Pakistani volunteers, no statistically significant differences in AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were found between the test and reference formulations of alendronate sodium. The single 70-mg dose of these formulations met the regulatory criteria for bioequivalence and all test brands were within the acceptable quality limits.

Conflict of Interest

The study was carried out for educational purposes and the authors have declared no conflict of interest.

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Annexure 1

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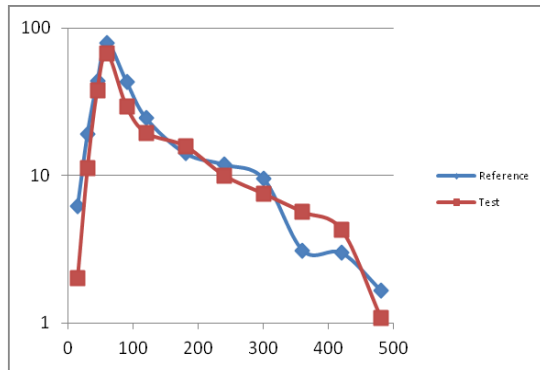
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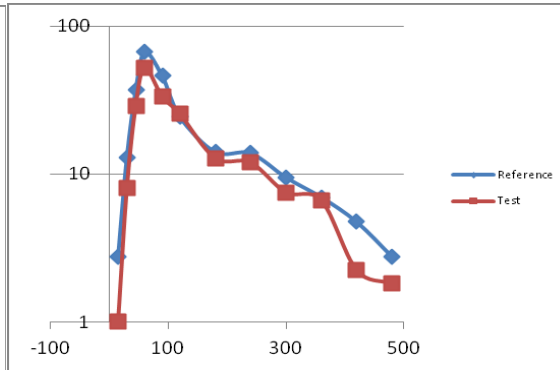
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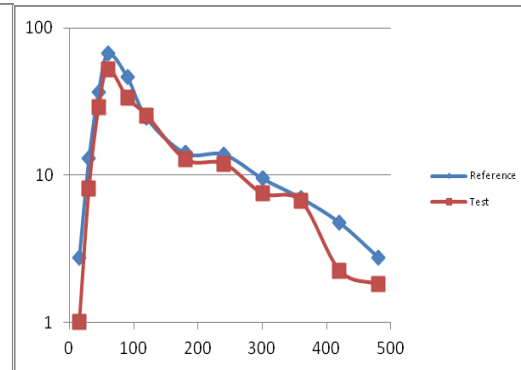
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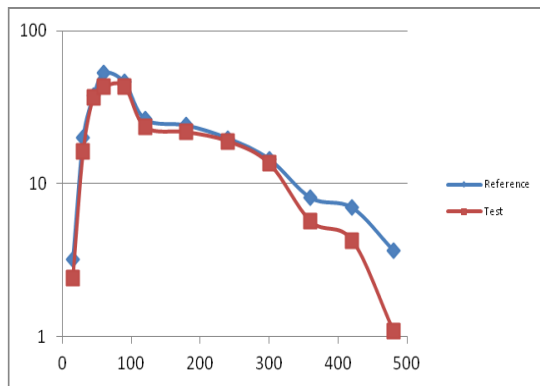
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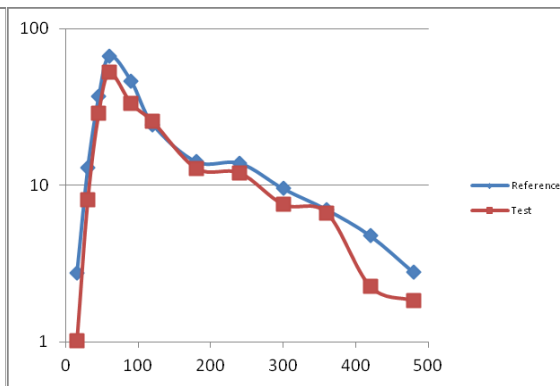
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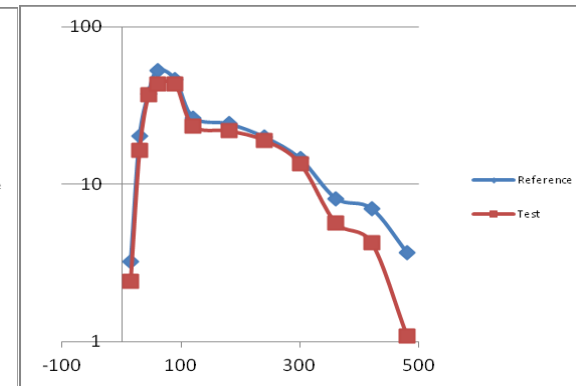
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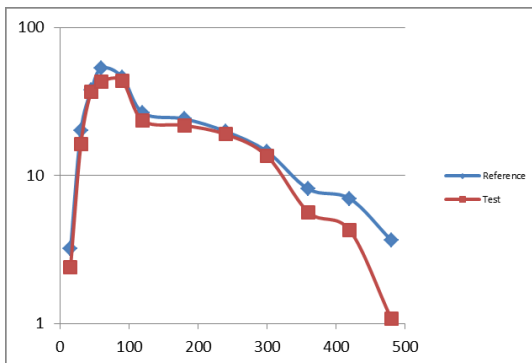
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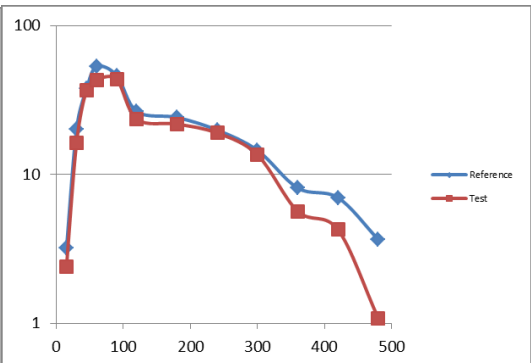
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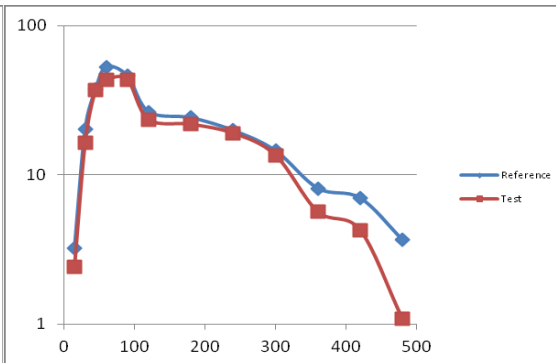
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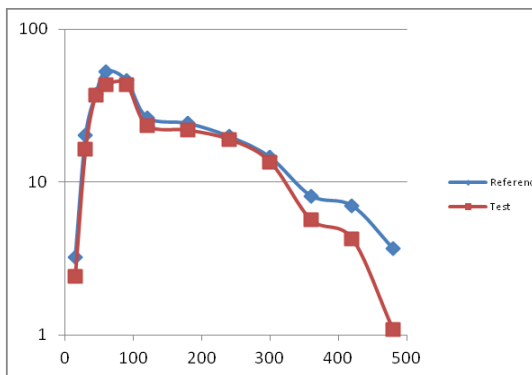
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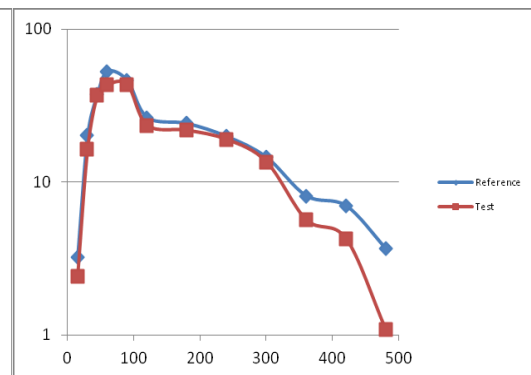
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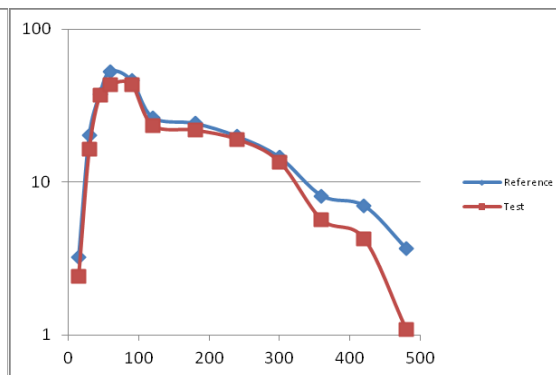
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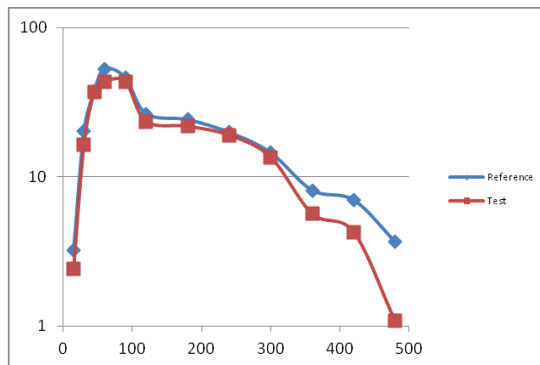
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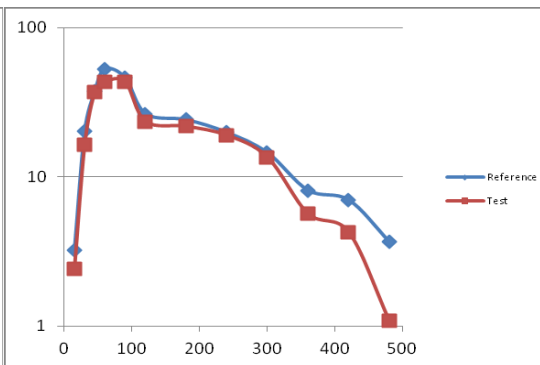
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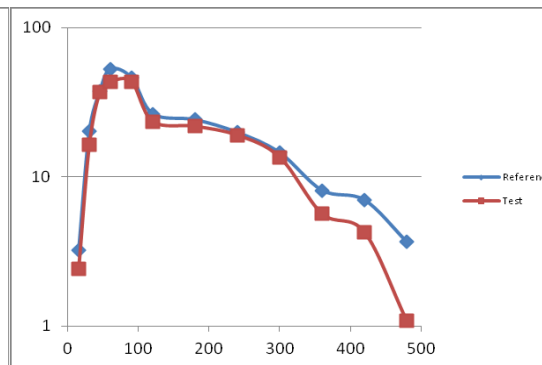
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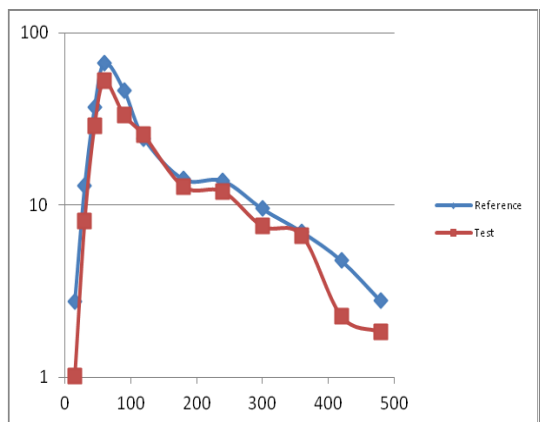
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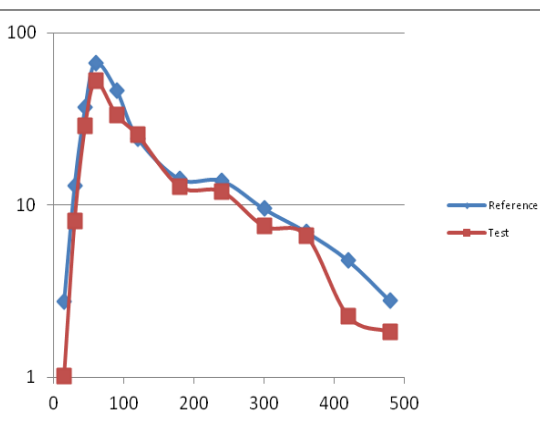
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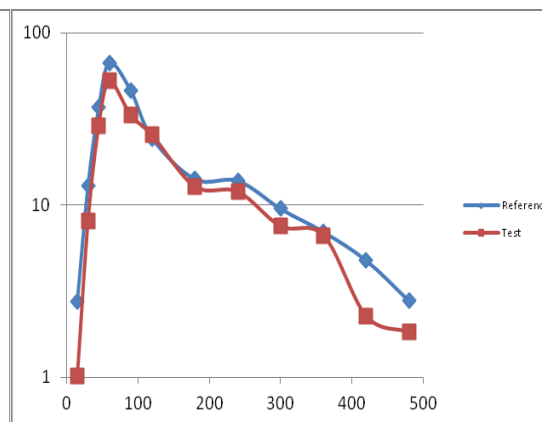
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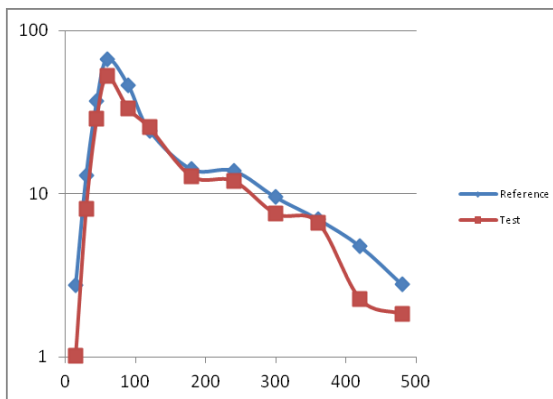
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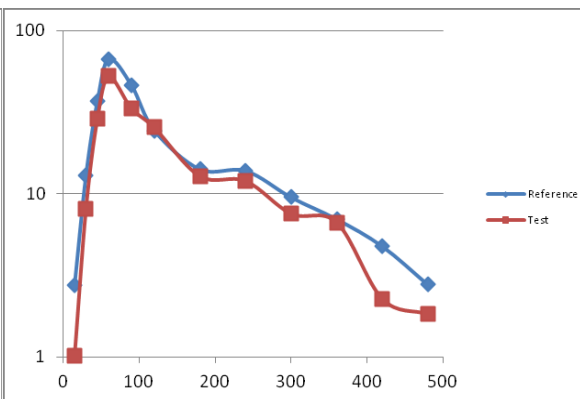
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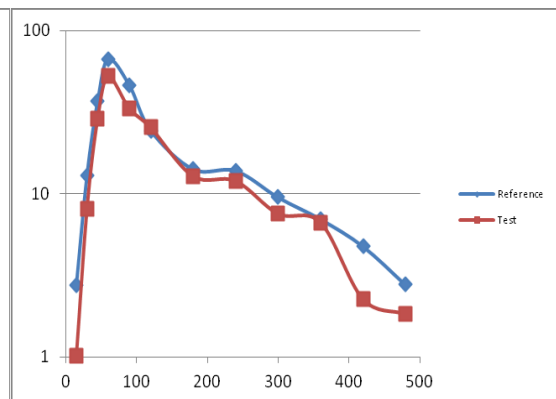
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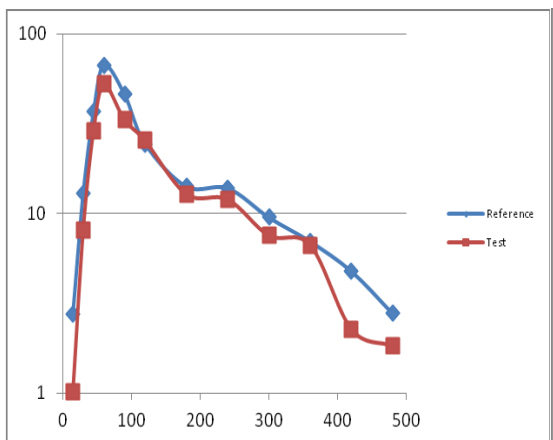
Volunteer 23

Volunteer 24