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# Development and Validation of Reverse Phase HPLC Method for Simultaneous Determination of Ibandronate Sodium and its Related Substances in Tablet Dosage Form

**Jineetkumar B. Gawad[1]*, Pritam S. Jain[2], Sanjay B. Bari[2]**

**[1]*St. John Institute of Pharmacy and Research, Palghar (E) Dist: Thane (M.S) India**
**[2]R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur. Dist: Dhule (M.S) India**

***Corres. Author: gawadjinit@yahoo.com**
**Phone: +91-09028186859**

**Abstract:** A simple, accurate and sensitive liquid chromatographic method has been developed for the simultaneous assay of ibandronate sodium drug substance and the determination of its impurities. The separation was achieved on Allsep™ anion column 150mm×4.6mm, 7µm particle diameter. The mobile phase consisted of 0.2% (v/v) aqueous formic acid with pH 3.1and acetonitrile 95:5% (v/v); flow rate 0.5 ml $min^{-1}$ at ambient temperature. The analytes were monitored by refractive index detector. The drug substance was subjected to stress conditions of hydrolysis, oxidation, photolytic, thermal and humidity degradation. Considerable degradation was achieved only under oxidative conditions. Mass balance was demonstrated in all stress conditions. The method was validated for specificity, precision, linearity, solution stability and accuracy. The average recoveries for impurities and ibandronate were in the range of 99.0–102.0% and the method can be successfully applied for the routine analysis of ibandronate sodium drug substance.

**Keywords:** RP- HPLC; Stability indicating; Ibandronate Sodium; Refractive Index Detection.

## 1. INTRODUCTION:

Ibandronate sodium [(1-hydroxy-3-(methyl pentyl amino) propylidene bisphosphonic acid monosodium monohydrate)] is the sodium salt of ibandronic acid, a synthetic nitrogen-containing bisphosphonate drug. This new third generation bisphosphonate is used to treat patients with bone disease like Paget's disease, malignant hypercalcemia and postmenopausal osteoporosis [1, 2]. For quantification of impurities and assay of ibandronate sodium, few analytical methods have been reported [3–6]. Indirect fluorescence detection was used in a high performance ion exchange chromatographic method based on the formation of the non-fluorescent $Al^{3+}$-ibandronate complex after post-column addition of the fluorescent $Al^{3+}$-morin reagent. Ibandronate was determined by high performance ion exchange chromatography with UV detection at 240nm after complex formation with $Cu^{2+}$ ion [4]. Ibandronate and related impurities (phosphate, phosphite) were determined by capillary zone electrophoretic method within direct detection at 254nm [5], The limit of detection (LOD) values reported for phosphate, phosphite and ibandronate were 5µg$ml^{-1}$, 3µg$ml^{-1}$, and 176µg$ml^{-1}$, linearity ranges were 92–460µg$ml^{-1}$, 24–384µg$ml^{-1}$ and 352–1760µg$ml^{-1}$ [6].

The aim of this study was to develop a simple, sensitive liquid chromatographic method with refractive index detection for the simultaneous determination of ibandronate and all the above listed impurities together.

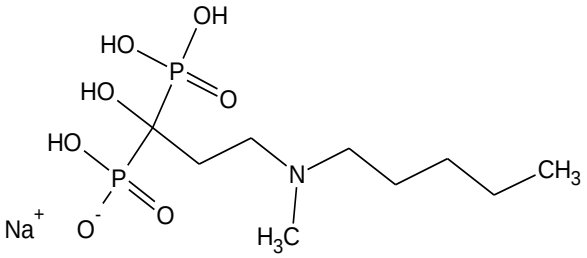


**Fig1. Structure of Ibandronate Sodium**

## 2. EXPERIMENTAL:

### 2.1 REAGENTS, CHEMICALS AND SAMPLES:

The standard and samples of ibandronate sodium drug substance and orthophosphoric acid (Phosphate), phosphorous acid (Phosphite) impurities were procured from Aarti Drugs Ltd, Boisar-Dist: Thane. Analytical reagent (AR grade), formic acid, Ammonia, Sulfuric acid, Sodium hydroxide etc and HPLC grade acetonitrile was procured from Merck, water from mili Q system.

### 2.2 HIGH PERFORMANCE LIQUID CHROMATOGRAPHY:

Agilent HPLC 1200 series chromatograph equipped with binary pump, Refractive Index Detector with data processing capacity was used. Allsep$^{TM}$ anion exchange column (150 mm x 4.6 mm i.d., 7 µm particle size) was used. The pH measurement was performed by using LAB INDIA- PICO controlled pH analyzer equipped with pH electrode. Mobile phase filtration was performed by vacuum pump using 0.45 µm filter paper. The mobile phase was delivered in an isocratic mode at a flow rate of 0.5 ml min$^{-1}$. The injection volume was 20µl and run time was 25 min. As a degasser, PCI Analytics Pathak ultrasonicator was used. Column compartment temperature, 60$^0$C and 35$^0$C for differential refractometer. The retention times of the ibandronate, phosphate and phosphite, peaks are at about 26.79, 24.62, 19.57 min, respectively. The resolution between phosphate and ibandronate peaks and between ibandronate and phosphite peaks, respectively, was not <1.5. Relative standard deviation for the peak areas of the six replicate injections for each impurity peak is not more than 5.0% and that of ibandronate peak is not more than 1.0%.

### 2.3 PREPARATION OF STANDARD AND SAMPLE SOLUTIONS:

#### 2.3.1 PREPARATION OF IMPURITIES STOCK SOLUTION:

Weigh accurately and transfer about 580 mg of orthophosphoric acid (Phosphate) impurity standard and 530 mg of Phosphorous acid (Phosphite) impurity standard to 50 mL volumetric flask. Add about 30 mL of diluents and mix. Dilute to volume with diluents and mix. Dilute 5 mL of solution to 50 mL with diluent.

#### 2.3.2 PREPARATION OF STANDARD SOLUTION:

Weigh accurately and transfer 200 mg of ibandronate sodium monohydrate to 10 mL of volumetric flask. Add about 5 mL diluent and sonicate to dissolve, mix. Allow to equilibrate at room temperature. Add 1 mL of impurities stock solution, dilute to volume with diluent, mix.

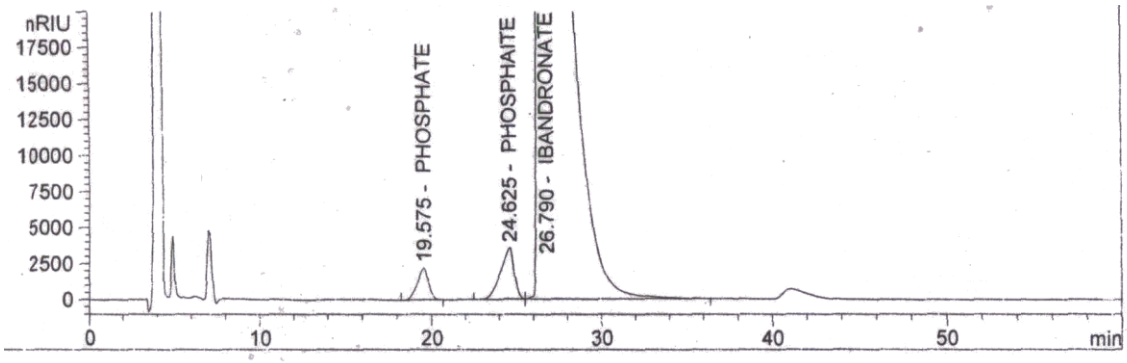


**Fig2. Chromatogram Showing Selected conditions with resolution**

### 2.3.3 PREPARATION OF SAMPLE SOLUTION:

Weigh accurately and transfer tablet powder equivalent to 200 mg of Ibandronic acid to a 10 mL volumetric flask. Add about 5 mL of diluent and sonicate for 10 min with intermittent shaking. Allow to equilibrate to room temperature and dilute to volume with diluent, mix. Centrifuged the solution at 2500 RPM for 5 min. filter the supernatant through 0.45 µm nylon filter discarding first 3 mL of filtrate.

## 2.4 METHOD VALIDATION:

### 2.4.1 SPECIFICITY:

Blank, standard and placebo preparation of ibandronate sodium tablet (54 mg) was prepared. Interference of main drug peak in placebo was checked. Diluent (water) used as a blank.

### 2.4.2 LINEARITY:

Linearity was studied by preparing standard solutions at different concentration levels such as 5, 10, 30, 50, 80, 90, 100, 120, 150 (% levels) for both impurities (phosphate as well as phosphite).

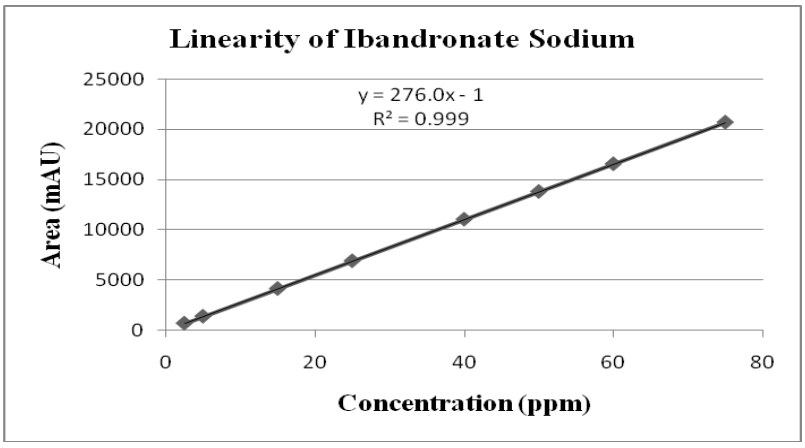


**Fig3.Linearity of Ibandronate Sodium**

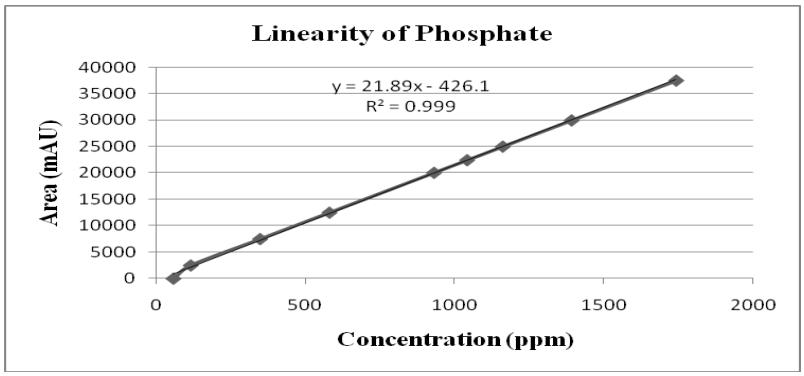


**Fig4.Linearity of Phosphate**

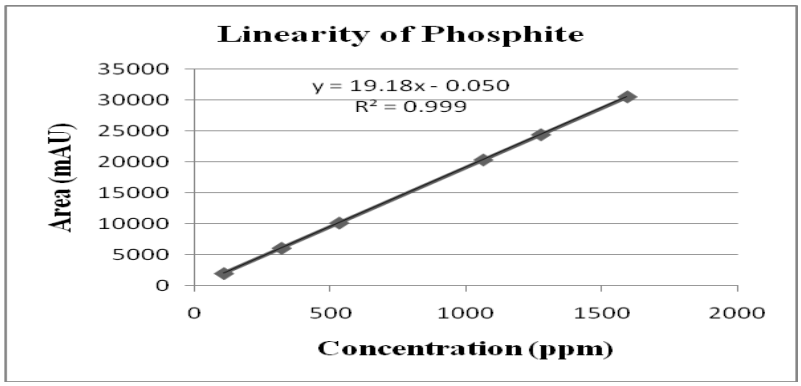


**Fig5.Linearity of Phosphite**

### 2.4.3 ACCURACY:

The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found. It was done by recovery study. Sample solutions were prepared by spiking the impurity at about 50 %, 100 % and 150 %.

### 2.4.4 PRECISION:

### 2.4.4.1 METHOD PRECISION (REPRODUCIBILITY):

Reproducibility expresses the precision between laboratories. Six samples were Prepared and analyzed as per the test method and calculated the % RSD for six injections.

### 2.4.4.2 SYSTEM PRECISION (REPEATABILITY):

Solutions of ibandronate sodium were prepared as per test method and injected for 6 times. Mean, SD and RSD were checked for precision.

### 2.4.5 INTERMEDIATE PRECISION (RUGGEDNESS):

Solutions of ibandronate sodium were prepared as per test method and injected for 6 times. Mean, SD and RSD were checked for precision.

### 2.4.6 ANALYTICAL SOLUTION STABILITY:

The stability of the drug in solution during analysis was determined by repeated analysis of standard and sample. The standard and sample were prepared and injected into HPLC at initial and different time intervals up to 24 hrs.

### 2.5 FORCED DEGRADATION STUDIES:

A sample was stressed at the following conditions and the peak purity was evaluated for Ibandronate Sodium peak.

### 2.5.1 ACID DEGRADATION STUDIES:

10 tablets were weighed. The average weight was determined. Sample powder equivalent to 100 mg of Ibandronate sodium was transferred in to a 100 ml volumetric flask. About 50 ml diluent was added and sonicated for 10mins. Added 5 ml of 5M HCl and kept at 80°C on water bath for 5 hrs. Then solution was allowed to cool at room temperature, 5 ml of 5M NaOH solution was added, for neutralization, and volume was made up to the mark with diluent and mixed properly. These solutions were centrifuged and subsequent solutions were collected. A 10 µl of these solutions were injected into LC, under optimized chromatographic conditions**.**

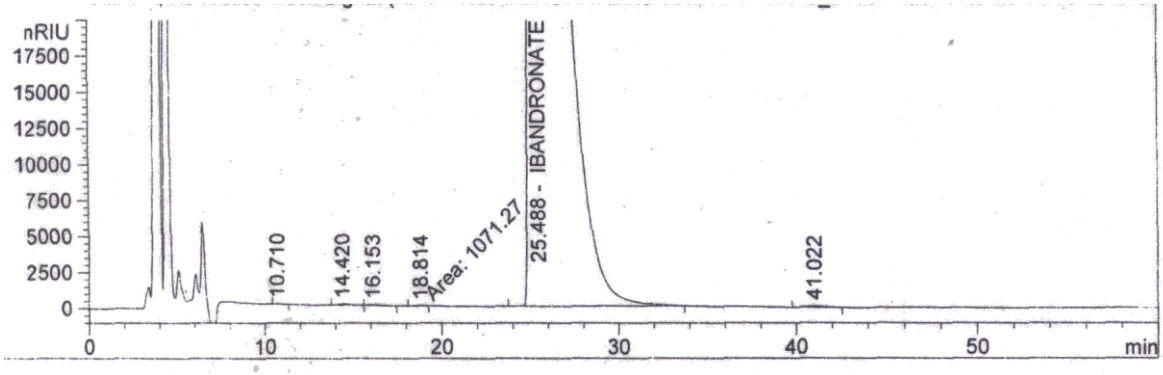


**Fig6. Chromatogram Showing Acid Stress Sample**

### 2.5.2 ALKALI DEGRADATION STUDIES:

10 tablets were weighed. The average weight was determined. Sample powder equivalent to 100 mg of Ibandronate sodium was transferred in to a 100 ml volumetric flask. About 50 ml diluent was added and sonicated for 10mins. Added 5 ml of 5M NaOH and kept at 80°C on water bath for 5 hrs. Then solution was allowed to cool at room temperature, 5 ml of 5M HCL solution was added, for neutralization, and volume was made up to the mark with diluent and mixed properly. These solutions were centrifuged and subsequent solutions were collected. A 10 µl of these solutions were injected into LC, under optimized chromatographic conditions.

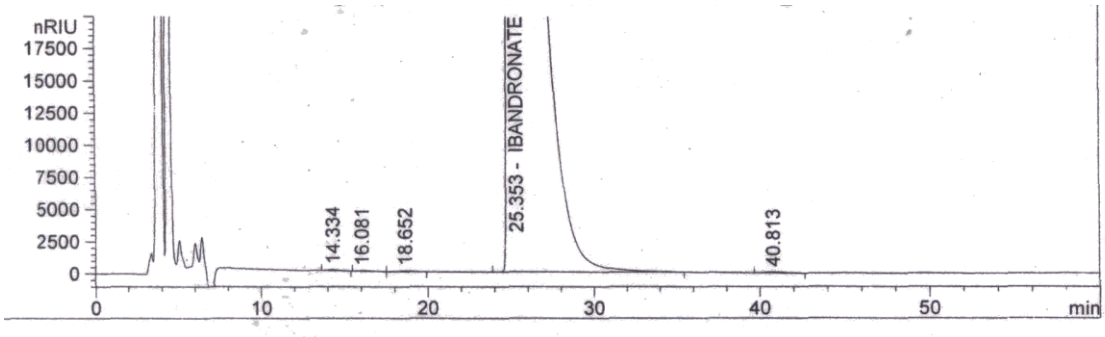


**Fig7. Chromatogram Showing Base Stressed Sample**

### 2.5.3 OXIDATION STUDIES:

Weighed and determined average weight of 10tablets. Weighed and transferred sample powder equivalent to 100 mg of Ibandronate sodium in to a 100 ml volumetric flask. About 50 ml diluent was added and sonicated for 10mins. 5 ml of 3% $H_2O_2$ was added and kept at 80°C for 5 hrs, equilibrated to room temperature and made up to volume with diluent and mixed. This solution was centrifuged and supernatant solution was collected. A 10 µl of this solution was injected into LC, under optimized chromatographic conditions.

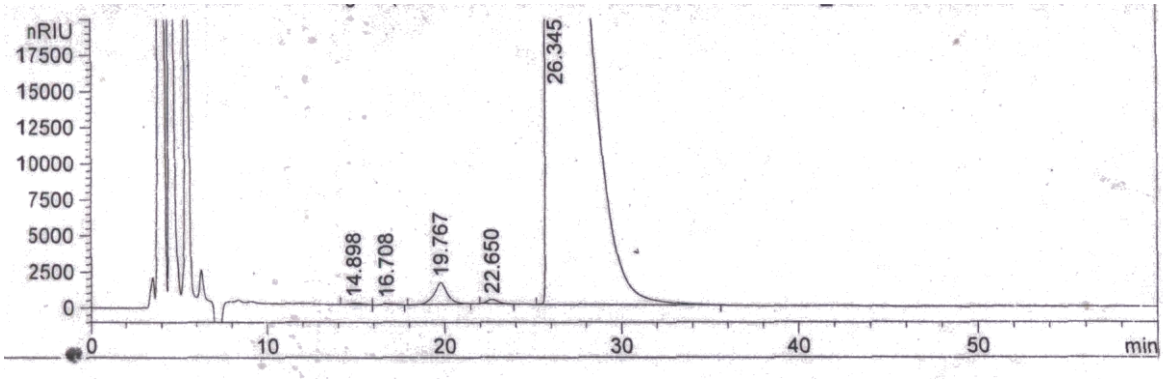


**Fig8. Chromatogram Showing Oxidised Sample**

### 2.5.4 TEMPERATURE STRESS STUDIES/ DRY HEAT INDUCED-DEGRADATION:

Crushed tablet content was heated at 105°C, for 24 hrs and allowed to cool to room temperature. Weighed and transferred sample powder equivalent to 100 mg of Ibandronate sodium in to a 100 ml volumetric flask, 75 ml of diluent was added and sonicated for 10mins and volume was made up to the mark with diluent and mixed. This solution was centrifuged and supernatant solution was collected. A 10 µl of this solution was injected into LC, under optimized chromatographic conditions.

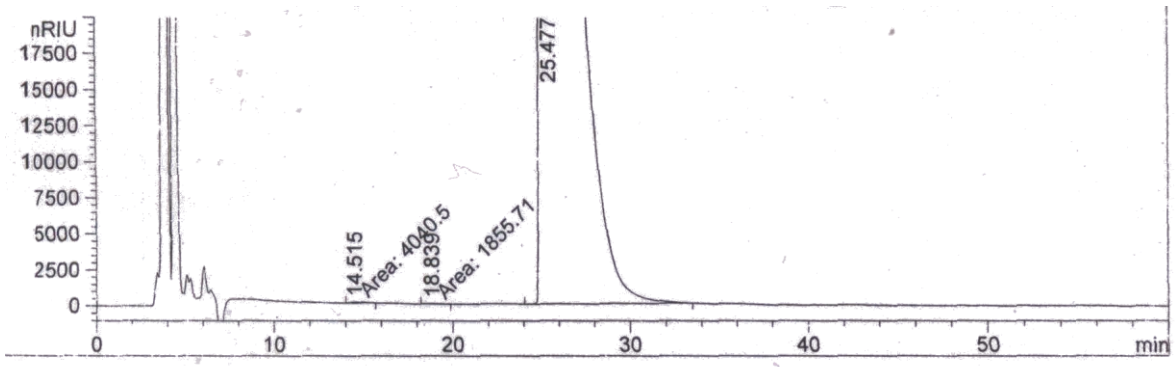


**Fig9. Chromatogram Showing Thermal/ Heat Treated Sample**

### 2.5.5 HUMIDITY DEGRADATION:

Tablet was kept in 40°C/75% Rh chamber for 24 hrs. Weighed and transferred sample powder equivalent to 100 mg of Ibandronate sodium in to a 100 ml volumetric flask, about 75 ml of diluent was added and sonicated for 10mins and made up to volume with diluent and mixed. This solution was centrifuged and supernatant solution was collected. A 10 µl of this solution was injected into LC, under optimized chromatographic conditions.

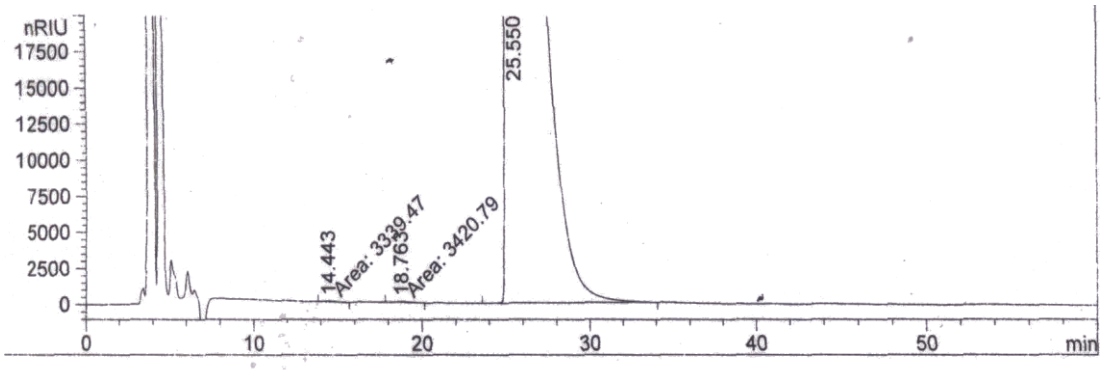


**Fig10. Chromatogram Showing Humidity Sample**

### 2.5.6 PHOTOSTABILITY STUDIES:

Crushed tablet powder was kept in the photo stability chamber and exposed to, as per ICH guidelines. Weighed and transferred sample powder equivalent to 100 mg of Ibandronate sodium in to a 100 ml volumetric flask, about 75 ml of diluent was added and sonicated for 10mins and made up to volume with diluent and mixed. This solution was centrifuged and supernatant solution was collected. A 10 µl of this solution was injected into LC, under optimized chromatographic conditions.

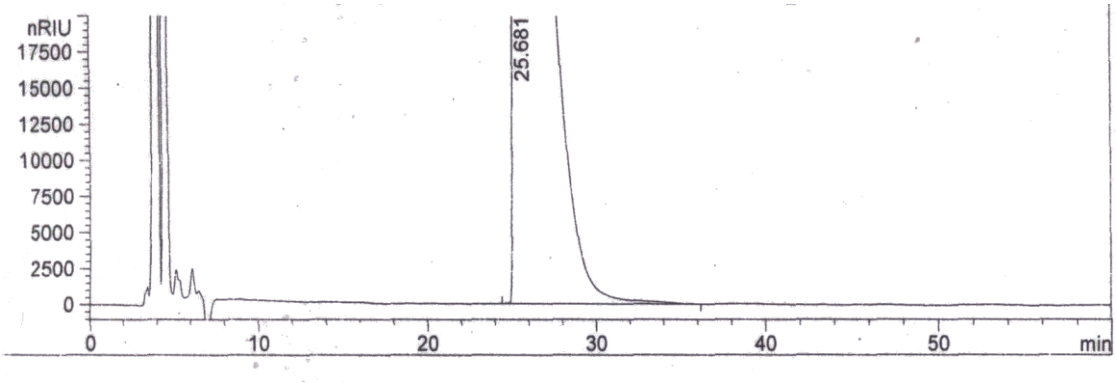


**Fig11. Chromatogram Showing UV Treated Sample**

## 3. RESULTS AND DISCUSSION:

### 3.1 METHOD DEVELOPMENT AND OPTIMIZATION:

As there is no chromophore present in ibandronate sodium, there was no possibility for UV or fluorescence detection and no suitable groups are present for derivatization. Ibandronate and its impurities are ionic; for this reason water was chosen as diluents. Preliminary experiments were carried out Using Inertsil ODS column with buffer pH 5.0: ACN (90:10v/v) analytes were not sufficiently separated while on Zorbax SB CN column resolution was not achieved. Separation was achieved on Allsep $^{TM}$ anion (Alltech Associates Inc.) 150mm×4.6mm, 7_mparticle diameter column, with 0.2% (v/v) aqueous formic acid (with pH 3.1) as mobile phase. In 0.1% (v/v) aqueous formic acid condition, ibandronate and phosphite peaks merged as well as late elution of analytes was observed. Satisfactory separation was achieved with 0.2% (v/v) aqueous formic acid with reasonable retention times of analytes. For better resolution between analytes, trials were performed with 0.1% (v/v) aqueous formic acid using acetonitrile as organic modifiers. With acetonitrile, broad peak shapes and poor base line were observed, For better peak shapes and good resolution, several trials were performed with 0.1% (v/v) aqueous formic acid using acetonitrile in 2%, 5%, 10% and 20% (v/v) concentrations. Satisfactory separation and good peak shapes were achieved within a reasonable time using a

mobile phase of 95:5% (v/v) mixture of0.1% (v/v) aqueous formic acid and acetone with a flow rate of 0.5 ml $min^{-1}$. The effect of column temperature on separation was studied at different temperatures ranging from $35^0$C to $65^0$C. Ambient temperature was found to be optimal from the point of view of both resolution and peak shape.

### 3.1 METHOD VALIDATION:

#### 3.1.1 SPECIFICITY:

For specificity of the assay of ibandronate the possible interference of diluent and impurities, phosphate and phosphite was studied. It was found that their peaks did not interfere with the ibandronate peak and are well resolved. chloride-free water as diluent.

#### 3.1.2 LINEARITY:

The linearity of refractive index detector response of ibandronate and its impurities at different concentrations were studied in the range 2.5-75 $\mu gml^{-1}$ for ibandronate and 58-1740 $\mu gml^{-1}$, 53-1590 $\mu gml^{-1}$ for phosphate, phosphite respectively. The data was subjected to statistical analysis using a linear-regression model. The regression equations for phosphate, phosphite impurities are y = 21.89x-1, y=19.18x-0.050 respectively. The statistical parameters slope and correlation coefficient values were calculated.

**Table1. Linearity of Ibandronate sodium**

| % | Conc. | Area |
|---|---|---|
| 5 | 2.5 | 690.05 |
| 10 | 5 | 1380.1 |
| 30 | 15 | 4140.3 |
| 50 | 25 | 6900.5 |
| 80 | 40 | 11040.8 |
| 100 | 50 | 13801 |
| 120 | 60 | 16561.2 |
| 150 | 75 | 20701.5 |

**Table2. Linearity of phosphate**

| % Level | Conc. | Area |
|---|---|---|
| 5 | 58 | 0 |
| 10 | 116 | 2499.2 |
| 30 | 348 | 7497.6 |
| 50 | 580 | 12496 |
| 80 | 930 | 20036.69 |
| 90 | 1040.4 | 22415.24 |
| 100 | 1160 | 24992 |
| 120 | 1390.2 | 29951.62 |

**Table3. Linearity of phosphite**

| % Level | Conc. | Area |
|---|---|---|
| 5 | 53 | 0 |
| 10 | 106 | 2033 |
| 30 | 318 | 6099.3 |
| 50 | 530 | 10165.5 |
| 100 | 1060 | 20331 |
| 120 | 1272 | 24397.2 |
| 150 | 1590 | 30496.5 |

**Table4. Statistical Data of Ibandronate Sodium**

| Statistical Parameters | Phosphate | Phosphite | Ibandronate |
|---|---|---|---|
| Correlation Coefficient | 0.99 | 0.99 | 0.99 |
| Slope | 21.54 | 19.18 | 276.0 |
| Concentration Range (ppm) | 58-1740 | 53-1590 | 2.5-75 |
| LOD ($\mu gml^{-1}$) | 58 | 53 | 2.5 |
| LOQ ($\mu gml^{-1}$) | 116 | 106 | 5 |

#### 3.1.3 ACCURACY:

Accuracy of method was determined by recovery experiments using standard addition technique. Recoveries were determined by spiking the impurities at 3 different levels i.e. 50% 100% 150% into IBN sodium (with respect to 0.5% level). Similarly recovery experiment was carried out ranging from 50% to 150% of Ibandronate sodium (with respect to test).

**Table5. Accuracy data of Ibandronate sodium**

| **Sr. No.** | **Phosphate** | | | **Phosphite** | | |
|---|---|---|---|---|---|---|
| Levels | 50% | 100% | 150% | 50% | 100% | 150% |
| Added (%w/w) | 0.27 | 0.58 | 0.65 | 0.25 | 0.53 | 0.67 |
| Recovered (%w/w) | 0.26 | 0.55 | 0.63 | 0.24 | 0.52 | 0.65 |
| Recovery % | 99.7 | 98.1 | 98.7 | 99.9 | 99.9 | 99.2 |
| % RSD | 1.4 | 1.2 | 1.7 | 0.9 | 1.4 | 2.0 |

### 3.1.4 PRECISION:

The precision was the study of the method using repeatability and reproducibility (ruggedness). The performance of the method was evaluated with replicate injections of standard and sample solutions. Standard solution was analyzed six times for checking the performance of the system under the chromatographic conditions on the day tested (System precision). Repeatability was the intra-day variation (Method precision) and the intermediate precision was the inter-day variation (Ruggedness). The repeatability and reproducibility of the method was studied by analyzing six sample solutions separately by adding impurities at known concentration levels. The ruggedness of the method was defined as the degree of reproducibility obtained by the analysis of the same sample (which is used in the Method precision) under a variety of conditions using different series of column, with different analyst on different day by preparing new standards and new mobile phase.

**Table6. Method Precision (Reproducibility)**

| | **Ibandronate** | **Phosphate** | **Phosphite** |
|---|---|---|---|
| **Method Precision** | | | |
| 1 | 101.2 | 0.531 | 0.492 |
| 2 | 100.0 | 0.530 | 0.487 |
| 3 | 100.9 | 0.529 | 0.490 |
| 4 | 101.7 | 0.535 | 0.510 |
| 5 | 100.9 | 0.538 | 0.501 |
| 6 | 101.8 | 0.532 | 0.509 |
| Average | 101.08 | 0.532 | 0.498 |
| SD | 0.44 | 0.4 | 0.21 |
| %RSD | 0.4 | 0.8 | 2.0 |

**Table7. System Precision (Repeatability)**

| | **Ibandronate** | **Phosphate** | **Phosphite** |
|---|---|---|---|
| **System Precision** | | | |
| 1 | 117.212 | 1.910 | 4.323 |
| 2 | 121.253 | 1.875 | 4.290 |
| 3 | 121.290 | 1.868 | 4.351 |
| 4 | 119.581 | 1.941 | 4.303 |
| 5 | 121.206 | 1.902 | 4.324 |
| 6 | 120.049 | 1.989 | 4.332 |
| Average | 120.098 | 1.914 | 4.320 |
| SD | 1.5862 | 0.045 | 0.021 |
| %RSD | 0.8 | 1.52 | 2.0 |

**Table8. Reproducibility (Ruggedness)**

| | **Ibandronate** | **Phosphate** | **Phosphite** |
|---|---|---|---|
| **Reproducibility** | | | |
| 1 | 99.0 | 0.489 | 0.501 |
| 2 | 99.2 | 0.487 | 0.496 |
| 3 | 99.5 | 0.490 | 0.498 |
| 4 | 98.9 | 0.488 | 0.489 |
| 5 | 99.7 | 0.485 | 0.504 |
| 6 | 99.1 | 0.490 | 0.507 |
| Average | 99.23 | 0.488 | 0.499 |
| SD | 0.24 | 0.06 | 0.05 |
| %RSD | 0.2 | 1.2 | 1.0 |

### 3.1.5 SOLUTION STABILITY:

The sample solution was prepared by the addition of impurities with known concentration level into ibandronate sodium drug substance. The stability of the solution was tested by recording and comparing the chromatograms freshly prepared and at different intervals up to 24 h at ambient temperature. The results indicate that the sample solution was stable for up to 24 h at ambient temperature.

### 3.2 RESULTS OF FORCED DEGRADATION STUDIES:

The stability indicating nature of the method was evaluated by performing forced degradation studies as per International Conference on Harmonization (ICH) hydrolytic, photolytic, thermal and oxidative stress testing [9]. Ibandronate sodium was found stable at all conditions except in oxidative degradation. Drug substance peak was homogeneous and pure under the stress conditions; there was no interference observed for ibandronate peak from other peaks. In hydrogen peroxide degradation experiments interference was found at the retention time of phosphate peak.

**Table9. Evaluation of Forced Degradation Studies**

| Type of Degradation | Degradation Condition | Degradation (%w/w) | Degradation of Impurity (%w/w) |
|---|---|---|---|
| Sample as such | - | - | - |
| Acid hydrolysis | 5M 5 mL HCl/85 $^0$C/5 Hrs | Nil | Nil |
| Base degradation | 5M 5 mL NaOH/85 $^0$C/5 Hrs | Nil | Nil |
| Oxidation degradation | 3% 5mL $H_2O_2$/85 $^0$C/5 Hrs | 14.9 | 15.35 |
| Thermal degradation | 105$^0$C/ 24 Hrs | 0.1 | 0.1 |
| Humidity degradation | 40$^0$C/75% 24 Hrs | 0.3 | Nil |
| Photolytic degradation | 10 K Lux/ 24 Hrs | Nil | Nil |

### 4. CONCLUSION:

A simple, reproducible, specific and stability indicating RP-HPLC method was developed for separation of related substances of ibandronate sodium in pharmaceutical dosage form.

The developed method was validated as per ICH guidelines for relative retention factor, linearity, precision, solution stability and ruggedness. From the degradation studies, it can be concluded that IBN Na was well separated from all process impurities. Phosphite was increased in oxidation, hence it can be concluded that degradation product of phosphite was found to be process impurity. Ibandronate Sodium sample is relatively stable in Acid, Base, humidity, thermal and UV. The developed method could separate the drug from its process impurities and degradation products and hence found to be specific for Ibandronate Sodium.

Hence, we conclude that degradation product of phosphite is process impurity of Ibandronate Sodium.

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