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Original Article

LC-MS/MS Analytical Method Development and Validation for Determining Vinamidinium HexafluoroPhosphate Impurity in Etoricoxib

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ABSTRACT

Background and Aim: Process impurities may adversely affect the efficacy, excellent quality, and safety of pharmaceutical drugs. Ultimately, the purpose of this research work was to develop and validate a LC-MS/MS-based method for determining the Vinamidinium hexafluorophosphate impurity (VHP) in Etoricoxib in a simple, specific, accurate, and precise manner. **Materials and Methods:** To elute the Vinamidinium hexafluorophosphate impurity in Etoricoxib at a flow rate of 0.5mL/min within 20.0 min of runtime, a Symmetry Shield RP18, 5µm column with a 150 x 3.9 mm internal diameter was utilized in binary gradient mode. The buffer solution, which contained formic acid (0.1%) and acetonitrile (100%), as well as a diluent solution of acetonitrile (50%) and water (50%), was used to achieve the chromatographic separation. A triple quadrupole mass spectrometer (Shimadzu LC/MS/MS 8040) in Multiple Reaction Monitoring (MRM) mode was needed to monitor the results. **Results and Discussion:** The method's linearity was evaluated at levels from 25% to 150%, and the R^2 value was discovered to be 0.99. Sensitivity values of 0.04µg/g (LOD) and 0.13µg/g (LOQ) were established. The recovery of impurity levels of Vinamidinium hexafluorophosphate ranges from 70.0% to 130%. Linearity, specificity, accuracy, LOD, LOQ, and precision of the method were all validated. Within the assay variability limitations, it was found that the intra- and inter-day precision values were 0.67%, and 0.58%, respectively. **Conclusion:** According to ICH and FDA specifications, the optimized method was validated. The developed method was found to be appropriate for quantifying Vinamidinium hexafluorophosphate in Etoricoxib by employing LC-MS.

Keywords: Vinamidinium Hexafluorophosphate (VHP), Etoricoxib (ETC), International Conference on Harmonization, LC-MS/MS.

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INTRODUCTION

The COX-2 inhibitor Etoricoxib is used to treat osteoarthritis and rheumatoid arthritis. A variety of selective cyclooxygenase II (COX-2) inhibitors have recently entered the Nonsteroidal Anti-Inflammatory Drug (NSAID) market.[1-3] Because typical NSAIDs, such as ibuprofen and aspirin, COX-1 as well as COX-2 enzymes are both inhibited, the vast majority of the population has a great potential for using these COX-2 inhibitors.[4] The COX-1 enzyme conveyed in more or lesstotal tissues in human, has been set up to perform a vital part in gastrointestinal and kidney homeostasis, but the COX-2 enzyme is not being unless activated by a provocative act and an inflammatory event. Therefore, long-term usage of conventional NSAIDs might cause stomach ulcers and bleeding as side effects.[5] Etoricoxib, anextremelyparticularly COX-2 inhibitor, was established to conveymore safety problems with conventional NSAIDs although also treating the pain of inflammatory illnesses likeosteo-and rheumatoid arthritis.[6] Vinamidinium Hexafluorophosphate (Figure 1) is one of the raw materials used in the synthesis of Etoricoxib and may be carried forward as an impurity in the Etoricoxib process. (CAS Number: 291756-76-8, Molecular Formula: $C_7H_{14}ClN_2F_6P$, Molecular Weight: 306.62).[7]

Impurities, particularly drug substance related impurities such as those caused by **Degradation** (DRIs) and **Process** (PRIs), can have a hostile impact on the safety, excellent quality, and efficiency of pharmaceutical drugs.[8] The control of impurities in pharmaceuticals is subject to current international regulatory regulations, which were examined. Many researchers have identified the LC-MS method, as an apt method for the analysis of impurities in pharmaceuticals. The proposal includes an algorithm for identifying impurities using LC-MS/MS, as well

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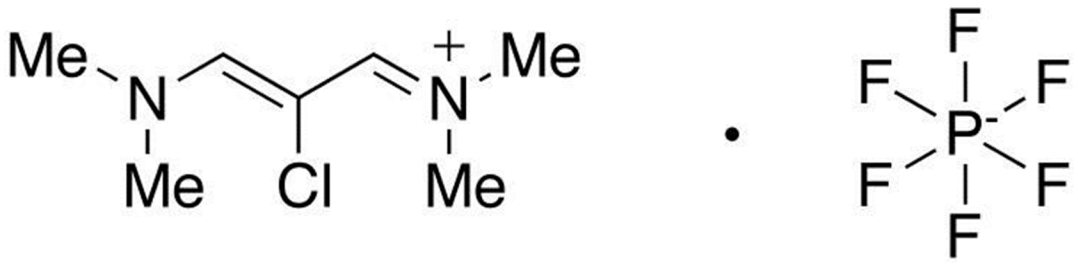

Figure 1: Structure of Vinamidinium Hexafluorophosphate.

as a method for developing analytical methods, in addition to acceptance criteria for DRIs and PRIs in compliance with ICH regulations. Based on the literature reports on impurity identification for ETC in human plasma by HPLC-MS/MS,[9-13] HPLC,[14] and spectrophotometric.[15] Furthermore, by using UPLC-ICP-MS, ETC was found in inflammatory arthritis patients' serum and synovial fluid.[16] Robert Hartman *et al.*, (2003) thirteen PRIs and three major DRIs were reported,[14] and S. Venugopal *et al.*, (2011) three PRIs and DRIs also reported in ETC.[17] Different analytical techniques were reported for the quantification of this drug and the impurities arising during its manufacturing process.[18-21] However, no LC-MS/MS approach for determining the process impurity Vinamidinium Hexafluorophosphate was disclosed. Finally, we will work on establishing a suitable method for detecting impurities by employing LC-MS/MS. In the meantime, the verification procedure for validating reliability in identification results will be evaluated. Hence, at present, the aim is to describe a LC-MS/MS method for the quantification of the process impurity Vinamidinium Hexafluorophosphate in Etoricoxib.

MATERIALS AND METHODS

Chemicals and Reagents

Acetonitrile, Formic acid, Methanol, Vinamidinium hexafluorophosphate, Etoricoxib, HPLC Grade Water was used.

Instrumentation

Shimadzu LC/MS/MS 8040 system well fitted out with a Symmetry Shield RP18, column having 150 x 3.9 mm internal diameter 5µm column.

VHP-Impurity's Chromatographic Conditions

The mobile phase is a combination of two solutions, A: 0.1% Formic acid (HCOOH) in water and B: Acetonitrile (100%) with a 25.0µ Linjection volume, the mobile phase flow rate was 0.5mL/min. Under these circumstances, the retention time of Vinamidinium Hexafluorophosphate was about 1.7 with a run time of 20.0 min., with a column maintained at 45°C along with the auto sampler temperature at 15°C by utilizing the Symmetry Shield RP18, C_{18}, 50 × 3.9 mm id, 5µm.

Solution Preparations

Formic acid Solution (0.1%v/v)

Pipette 0.1mL formic acid into a measuring cylinder filled with 100mL of water. The contents were properly mixed before being transferred to a reagent vial andkept at ambient temperature. After being prepared, this solution must be utilized within three days.

Mobile Phase

220mL of Acetonitrile and 780mL of Formic acid in water (0.1%v/v) were measured in a measuring cylinder, then transferred to a reagent bottle and thoroughly mixed. At room temperature. This solution was utilized within three days after being prepared.

Auto sampler rinsing solution

A measuring cylinder was used to measure 500mL of methanol and 500mL of water. After being transferred to a reagent bottle, the mixture was thoroughly mixed. Kept at ambient temperature.

Drug (Etoricoxib) standard stock solution

Etoricoxib standard was accurately weighed to obtain 400.0mg of Etoricoxib, and a proper volume of diluent was added to yield desired absolute concentration of Etoricoxib. The solution was kept in the refrigerator at 53°C. Utilize the solution within a week of preparing it.

Impurity (Vinamidinium Hexafluorophosphate) standard stock solution

Vinamidinium Hexafluorophosphate impurity was properly weighed (10mg) and transferred to a 10.0mL volumetric flask, in which it was dissolved, diluted to volume with diluent and thoroughly mixed.

(Vinamidinium Hexafluorophosphate) Impurity standard solutionandard stockd diluted to the volume with diluent and mixed well.

In a 10mL volumetric flask, 0.1mL of the previously mentioned Vinamidinium Hexafluorophosphate impurity was accurately weighed, transferred, and thoroughly dissolved before being fully combined.

Vinamidinium HexafluorophosphateImpurity solution

0.5mL of above (Vinamidinium Hexafluorophosphate) Impurity standard solution, was transferred in (10.0mL) volumetric flask, dissolved, and then thoroughly diluted to the volume with diluent.

RESULTS AND DISCUSSION

Method Development and Optimization

The literature provided some physical and chemical properties of Vinamidinium Hexafluorophosphate impurity and Etoricoxib. The analytical method was created in order to determine initial LC-MS/MS technique chromatographic conditions such as MS-spectra, stationary phase, mobile phase, and sample preparation procedure. On behalf of this sole purpose, a numerous series of trials were executed by changing the ratio of take account oftrials. Optimize the chromatographic conditions using Shield RP18, C_{18}, 150 × 3.9mm id,5µm through gradient elution. Table 1 summarizes the method optimization results. The mobile phase is a combination was previously described. Under these conditions, the retention time of Vinamidinium Hexafluorophosphate impurity was about 1.7 min, and Shimadzu's Lab Solution Software 5.60 SP2D was used to capture the chromatograms.

Table 1: VHP's final optimized chromatographic conditions.

Condition	Results
Mobile phase	A:-Formic acid in water, 0.1%v/v,B:-Acetonitrile 100%. [Mobile phase A-78%:Mobile phase B-22%].
Diluents	Methanol: Water (50:50).
Column	Shield RP18, C_{18}, 150 × 3.9 mm id,5µm.
Column Temp.	45°C.
Wavelength	252nm.
Injection Volume	25.0µL.
Run time	20.0 min.
Flow rate	0.5 mL/min.
Parameters	VHP.
Ion Source	Electro Spray Ionization.
Polarity	Polarity Positive.
Collision Energy	(CE) -10.
Parent Ion	306.6.
Dwell Time(m-sec)	50.
Source Dependent Parameters.	
Drying Gas Flow	15.0 L/min.
Corona Discharge	4.5.
Heat Block Temperature	500°C.
DL Temperature	300°C.
Nebulizing Gas Flow	3.0 L/min.

Method Validation

According to FDA and ICH regulations, the LC-MS/MS method for VHP-impurity was validated as well as the validation parameters included specificity, precision, range, linearity, sensitivity, accuracy, and robustness.

Specificity and Linearity

The method's specificity was confirmed by injecting 25.0µL solutions of blank, standard, sample, and placebo separately. LC-parameters was summarized in Table 1. Direct VHP-impurity standard solutions were made by diluting the standard stock solution with the diluent in various concentrations of Vinamidinium Hexafluorophosphate LOQ%-150% in order to assess the linearity and range of this VHP-impurity's analytical method. A linear equation was obtained from the regression analysis, and the goodness-of-fit (R^2) was established 0.99, which corresponds to the target concentration. The same circumstances were used to examine three replicate injections from each concentration. The calibration curve's linearity was assessed using a linear regression analysis adopting the least squares method.

Sensitivity and Accuracy

The S/N ratio was employed to estimate the sensitivity of Vinamidinium Hexafluorophosphate. The LOD is the concentration that yields an S/N ratio of approximately 3:1, whereas the LOQ provides a S/N ratio of approximately 10:1 with an a % RSD (n = 3) of less than 10%. The LOD's were 0.04 µg/g for Vinamidinium Hexafluorophosphate and the LOQ`s was 0.12µg/g respectively. Recovery studies of VHP-impurity at three concentration levels 50%, 100%, and 150% were used to assess the analytical method's accuracy. Each concentration was injected separately. For each of the three replicate samples, the percentage recovery of Vinamidinium Hexafluorophosphate added and RSD were calculated.

Precision and Robustness

Six measurements of the VHP-impurity standard solution at 100% concentration were taken on the same day to establish system precision. On the same day, six assays of the VHP-impurity sample solution at 100% concentration levels were done to determine the method's precision. To assess repeatability, the RSD of the obtained results was determined. The method's robustness was validated by performing minor and purposeful adjustments to the experimental conditions. The attained data for each and every case was analyzed by calculating the percent RSD and the percent of recovery.

Table 2: Linearity results of Vinamidinium Hexafluorophosphate.

Level	Conc. (ppb) w.r.to sample (VHP) dilution	Area
25%	125	141587.28
50%	250	215452.28
100%	500	345099.28
125%	625	419395.28
150%	750	493860.28
Correlation coefficient (R^2)		1.000
Intercept		72416.91
Slope		557.03

Method Validation

Specificity

The HPLC chromatograms of the diluent and standard solution were compared with each other to determine the specificity of Vinamidinium Hexafluorophosphate and the corresponding chromatograms of VHP are shown in Figures 2 and 3. No co-eluting peaks are visible, as they can be seen at the retention time of Vinamidinium Hexafluorophosphate interference. The obtained results showed that the analyte peak was pure, confirming the method's specificity.

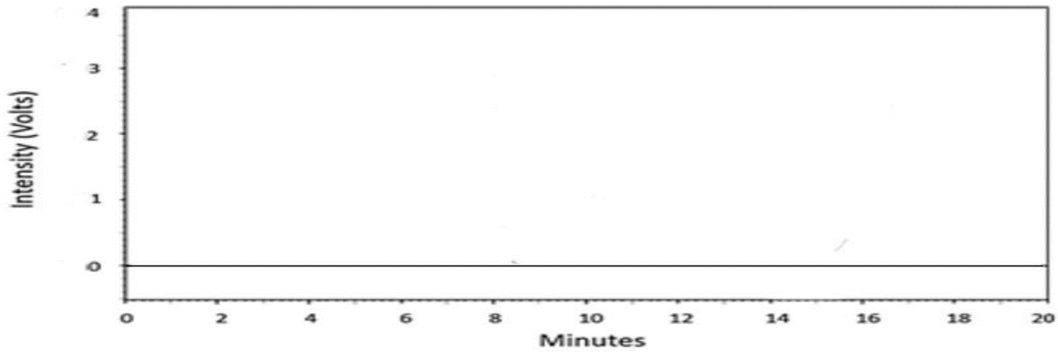

Figure2: Blank chromatogram of VHP.

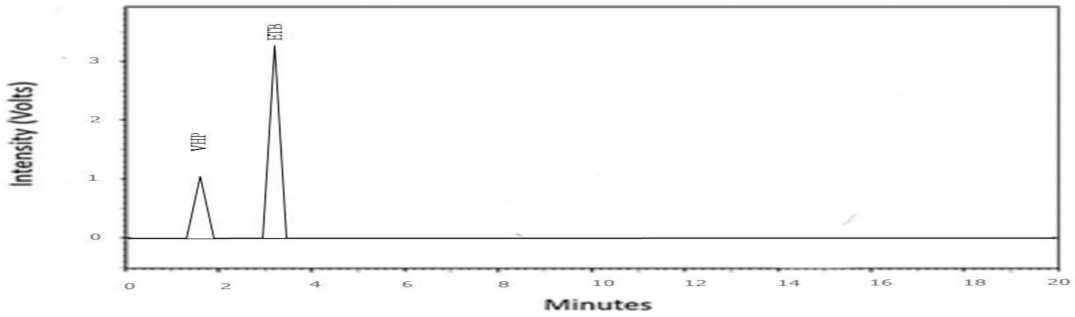

Figure 3: VHP-impurity's and Etoricoxib specificity chromatogram.

Table 3: Recovery results of Vinamidinium Hexafluorophosphate.

Accuracy Level	Wt. of sample (mg)	Area found	Amount added	Amount recovered (ng/mL)	% Recovery
50%	400.10	240636	250.620	323.504	129.1
50%	396.01	243422	250.620	323.904	129.2
50%	396.52	242638	250.620	323.277	129.0
100%	400.55	399894	501.240	538.210	107.4
100%	400.60	402739	501.240	542.107	108.2
100%	400.56	403784	501.240	543.459	108.4
150%	397.13	543681	751.859	725.483	96.5
150%	399.58	535446	751.859	718.902	95.6
150%	399.49	536461	751.859	720.103	95.8

Table 4: **Temperature variations in the column of VHP-LC Method.**

IMP Name	Variation in column temperature 45°C (+ 5°C)		Flow rate variations in VHP-LC Method 0.5mL/Min.(+0.1mL/Min.)		Variation in mobile phase composition A-78%:B-22%(+ 2%)	
	Column Temp.: 40°C	Column Temp.: 50°C	Flow rate: 0.4mL/Min.	Flow: 0.6mL/Min.	(A-76%: B-24%)	(A-80%: B-20%)
	Area	Area	Area	Area	Area	Area
VHP-P-1	111947	111841	110971	112075	112989	112081
VHP-P-2	110094	113094	111841	111843	113856	113089
VHP-P-3	110127	112711	112712	111611	110723	114097
VHP-P-4	111069	112154	113580	111382	113590	115105
VHP-P-5	112585	112585	114454	111153	114457	116113
VHP-P-6	111019	111274	111326	115921	111324	117121
AVERAGE	111140.1	112276.50	112480.67	112330.83	112823.17	114601.00
STDEV	987.85	657.56	1354.81	1788.77	1483.91	1885.80
%RSD	0.88	0.59	1.20	1.59	1.32	1.65

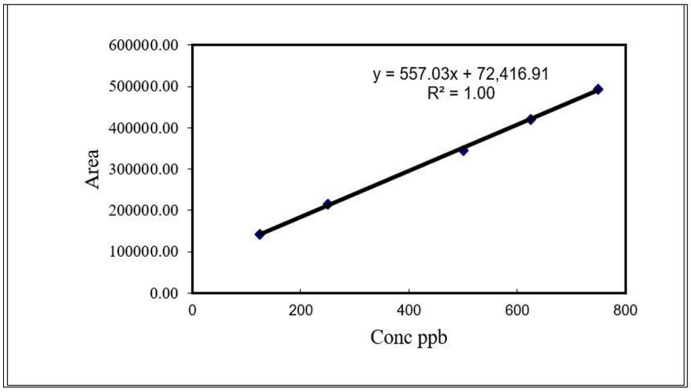

Figure 4: Linearity Graph for Vinamidinium Hexafluorophosphate.

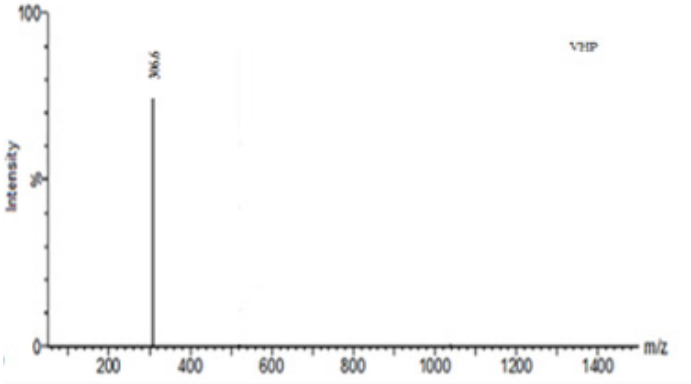

Figure 5: Mass spectrum of VHP.

Linearity and range

Herein, an analytical method's linearity is well-expound as the technique's capacity to produce results from tests that are directly proportional to VHP-impurity analyte concentration within a specified range. The calibration graph was created by plotting the mean peak area from the HPLC against the appropriate concentrations. The linearity study results (Figure 4 and Table 2) revealed a linear connection between Vinamidinium Hexafluorophosphate concentrations ranging from 25% to 150%. The regression study indicated a linear equation with a goodness-of-fit (R^2) of 0.99, showing a linear relationship between analyte concentration and area under the peak.

Limit of detection and limit of quantification (LOD and LOQ)

The Limit of Quantification (LOQ) is the lowest quantity of VHP-impurity analyte in an Etoricoxib sample that is capable of being quantitatively determined with apt precision, as opposed to the LOD, which is the lowest amount of VHP-impurity analyte in an Etoricoxib sample that can be detected but not essentially quantitated. The results of LOD and LOQ were 0.04µg/g and 0.13µg/g, respectively.

Accuracy

The percent recoveries of the samples were used to assess accuracy. The mean of the percent recoveries was found to be 95.6–129.29% for Vinamidinium Hexafluorophosphate (Table 3). The results of the percentage recovery showing that the method is appropriate for routine VHP-impurity analysis.

Precision

For the sake of a method's precision, it is "the closeness of agreement between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions," and the aforementioned precision is usually conveyed as the %RSD. The repeatability (0.67%) and ruggedness (0.58%) results demonstrate that the procedure is exact within tolerable limitations. The %RSD was calculated for

each solution; all of the values are within acceptable limits. The acceptable precision for the %RSD was less than 2.0%.

Robustness

The analytical method's robustness was evaluated by examining the effect of slight changes in the proposed method under LC conditions. The results of these conditions (Table 4) were robust within tolerable ranges. In all modifications, the % RSD is within the permitted range of not more than 2.0%. Figure 5 shows the VHP mass result, i.e., 306.62 *M/z.*

Batch analysis

The three batch analysis was carried out in accordance with the method of analysis used in the quality control for the determination of etoricoxib API. But they were not in a detectable range (specification limit:NMT 12.5 ppm). The vinamidinium hexafluorophosphate impurity in 3 batches of Etoricoxib was determined by LC-MS, and the results were found to be well within the limit.

CONCLUSION

The present LC-MS/MS approach used for determining the process-related impurity Vinamidinium Hexafluorophosphate in Etoricoxib, the suggested method was sensitive, accurate, and reproducible. All parameters, like accuracy, linearity, specificity, and robustness, were validated and determined to meet the acceptance criteria. The observed %RSD values are less than 2.0 percent for all parameters, confirming that the method is validated. The analytical development and validation of a new LC-MS/MS technique encompasses the range of drug analysis techniques that are currently available, increases sensitivity with additional potential applications, and enables quality control lab analysts to choose the best technique in accordance with the primary investigation. Furthermore, mass detection improves detection selectivity, particularly when used in MRM mode, and the technology is well suited for future use in pharmaceutical dosage forms and pharmacokinetic studies**.**

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

ABBREVIATIONS

VHP: Vinamidinium Hexafluorophosphate; **FDA:** Food and Drug Administration; **ICH:** International Conference on Harmonization; **ETC:** Etoricoxib; **COX:** Cyclooxygenase; **NSAID:** Nonsteroidal anti-inflammatory drug.

SUMMARY

Our study provided evidence that the process impurity Vinamidinium Hexafluorophosphate in Etoricoxib identified usingdeveloped using LC-MS/MS. The analytical development and validation of a new LC-MS/MS technique will cover the entire range of drug analysis presently in use which improve sensitivity with more potential applications. Hence, the quality control lab analysts can adapted this method in accordance with the primary quires.

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