RESEARCH ARTICLE

Analytical Method Development and Validation for the Estimation of Palladium Content in Tapentadol Hydrochloride by Atomic Absorption Spectrometer

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ABSTRACT

A validated method for determining the palladium concentration in tapentadol hydrchloride was devised using an atomic absorption spectrophotometer (AAS) with a 0.7 nm slit width and a high speed deuterium lamp (D_2). The integration time was set at 5.0 seconds with a wavelength of 247.6 nm. The system performance characteristics were used to evaluate the system performance. The limits of quantification and detection were determined to be 0.30 and 0.10 mg/l, respectively. The percentage recovery for LoQ level, 50, 100 and 150% levels of spiked concentrations of palladium in tapentadol hydrochloride were found to be 100.09, 100.13, 100.11 and 99.78%, respectively. This article discusses the status of trace elements and heavy metals in bulk pharmaceuticals, as well as AAS method which is convenient and simple that may be used for quality control and standardization of bulk drugs and other related items at the industrial level.

Keywords: Tapentadol, Palladium, AAS, API, Catalyst

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INTRODUCTION

Impurities arise from normal manufacture of pharmaceuticals which are undesirable chemicals. They are not intentionally or unintentionally introduced chemicals. Impurities are possibly toxic and have no therapeutic efficacy.[1] Impurities can appear from numerous phases of the synthetic procedure and sources in drug substances. By-products and intermediates may be carried during synthesis as contaminants into the drug ingredient or act as an impurity source emerging from them. The drug substance may contain impurities which were carried from the starting material. Impurities are categorized as organic impurities, inorganic impurities, and residual solvents by the International Conference on Harmonisation (ICH).[2] Synthetic intermediates, by-products, degradation products and starting materials can all lead to the development of organic impurities. The manufacturing process may produce inorganic impurities, which are typically known and recognized as inorganic salts, catalysts, reagents, heavy metals, charcoal, filter aids and ligands, etc.[3]

According to patent US-8791287-B2, tapentadol hydrochloride was designed and synthesized using the following method. The starting ingredients for the synthesis comprise of stage of alkylation of the ketone to produce the molecule, with strong stereoselectivity because the amino group's substitute, the benzyl group, is present. Palladium was used as a catalyst in this synthesis. The title chemical tapentadol hydrochloride was prepared.[4]

The acceptable levels of palladium (Pd) permitted in the finished drug product specified by ICH Q3D guidelines drives the need to remove Pd from API procedure streams. The limits for the platinum (Pt), including Pd as well as rhodium (Rh), and ruthenium (Ru), are low - 10 µg/g as a dosage form in the drug product., drug ingredient, or excipient. These metals are classified as route-dependent human toxicants (ICH Classification 2b).[5]

Tapentadol (3-((1R,2R)-3-(dimethyl amino)-1-ethyl-2-methylpropyl) phenol hydrochloride) is a non-racemic molecule. $C_{14}H_{23}NO.HCl$ is the molecular formula of tapentadol. Tapentadol has a single molecule with a dual mechanism of action that combines mu-opioid receptor agonism and noradrenaline reuptake inhibition. Tapentadol is a novel, centrally acting analgesic. When related to opioids and

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nonsteroidal anti-inflammatory medications, it has a better side effect profile. Tapentadol is a useful analgesic to treat chronic, neuropathic and acute pain due to its dual mode of action. Tapentadol has a fast half-life and a 32% oral bioavailability after a single dose due to substantial first pass metabolism. The body has a large distribution of tapentadol. After intravenous dosing, the distribution's volume is 540 ± 98 l. Plasma proteins only bound to 20% of the drug. 97% of the dosage of tapentadol is extensively metabolised to inactive metabolites. Tapentadol-O-glucuronide is the key metabolite, and the primary metabolic route involves conjugation with glucuronic acid to form glucuronides. Moreover, CYP2C9, CYP2C19, and CYP2D6 metabolise it into N-desmethyl tapentadol and hydroxyl tapentadol, which are then further metabolised by conjugation. CYP enzymes do not play a chief role in metabolism. The analgesic effect is unrelated to any of the metabolites. None of the CYP isoforms' activity is either repressed or stimulated by tapentadol.[6]

The literature review revealed various analytical methods for estimation of tapentadol hydrochloride in single and combined dosage form concerning UV spectrophotometer,[7-13] capillary electrophoresis,[14] high-pressure thin layer chromatography,[15-17] high pressure liquid chromatography.[18-23] liquid chromatography-mass spectrometry,[24-29] ultra-high-performance liquid chromatography.[30-32] Form the review of literature it was observed that there was no testified process for the estimation of palladium in tapentadol hydrochloride using atomic absorption spectrophotometry. So, the present study aimed to develop a validated analytical method for the palladium content determination in bulk drug by atomic absorption spectrometer as per ICH guidelines.

EXPERIMENTAL

As a gift sample, Tapentadol hydrochloride (Figure 1) was obtained from Symed Labs. Palladium standard purchased from inorganic ventures was used in the study. Nitric acid of carloerba, hydrochloric acid and perchloric acid of fisher scientific were used. Ultrapure water of evoqua was used. An AA-6300 atomic absorption spectrometer from Shimadzu Corporation with completely integrated atomizers was used for the investigation. An interfaced computer controlled the system.

Optimized Conditions

The determination was performed using an atomic absorption spectrophotometer (AAS) with a 0.7 nm slit width and a high speed deuterium lamp (D_2). The integration time was set at 5.0 seconds with a wavelength of 247.6 nm. Table 1 shows the ideal operating conditions for palladium flame atomization.

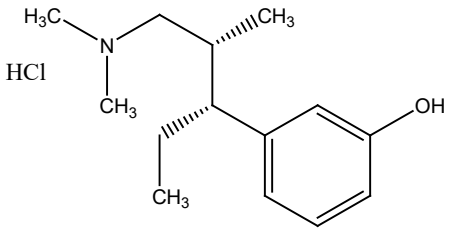

Figure 1: Structure of tapentadol hydrochloride

Table 1: Optimal conditions for atomization of palladium

Element	*Palladium*
Lamp	Palladium hallow cathode lamp
Wavelength	247.6 nm
Slit width	0.7 nm
Lamp current	10 mA
Lamp mode	BGC-D_2
Prespray time	3.0 Sec
Integration time	5.0 Sec
Oxidant flow (l/min)	15.0 l/min
Acetylene flow (l/min)	1.8 l/min
Recommended flame	Air-Acetylene
Burner height	9 mm

Preparation of Standards and Samples

Palladium Standard Stock Solution Preparation

A palladium standard stock solution of 1 mL was transferred (1000 mg/L of palladium) to a 20 mL volumetric flask and combined and diluted with diluent to the volume (i.e., 50.0 mg/L of palladium).

Preparation of Blank Solution

Concentrated nitric acid of 20 mL was transferred to a 2000 mL volumetric flask. Then, diluted up to volume with the ultrapure water and mixed well.

Preparation of Sample Solution

Sample of 1.0012 g was taken into a 20 mL beaker and concentrated nitric acid of 5.0 mL was added and dissolved completely. Then, diluted to volume with the diluent and blended well.

Analytical Validation Parameters

Linearity

A graphical representation of concentration versus absorbance assessed linearity. The measured absorbance was at 247.6 nm depending on total palladium concentration of standard palladium solutions. The analytical curves were built through transferring a certain amount of palladium standard stock solution to a volumetric flask (0.25 to 1.50 mg/L) and made up to the volume with diluents. The linearity of the analytical curve was confirmed through the technique of linear regression.

Specificity

Since the samples were prepared in concentrated nitric acid, a study was carried out to validate the absence of a matrix effect produced by the nitric acid. This was done by analysing four sets of solutions, one 100% palladium standard stock solution, one sample solution, a blank and a 100% spike sample solution.

Sensitivity (LoD and LoQ)

The LoD and LoQ were used to evaluate the performance of an instrument or an analytical process. LoD and LoQ

were computed using ICH guideline Q2R1 "Based on visual Evaluation" palladium-0.10 mg/l (10.0% w. r. t sample concentration) considered as LoD and palladium-0.30 mg/L (30.0% w. r. t sample concentration) considered as LoQ.

Accuracy

The accuracy (%recovery) of *palladium content in* tapentadol hydrochloride was demonstrated by spiking known quantities of standard solution having known palladium concentration into a sample. The various concentrations range from LoQ to 150% level (LoQ, 50, 100, and 150%) of the specification limit. The sample solutions were prepared as three preparations at each level and the palladium content was calculated. The %recovery at each level obtained were also calculated and the results are tabulated.

System Precision

The procedure system precision analyzed the 100% palladium standard solution six times. This established that the system was consistent, and the % RSD for six replicates was calculated.

Intermediate Precision

In intermediate precision the method was checked whether giving the constant result or not by different analysts on different days. Three sample preparations and 100% spike sample six individual preparations were prepared and analysed as per the method, and obtained results were tabulated. The %RSD for the six spike sample preparations and the cumulative %RSD for the different analysts on different days was calculated.

Method Precision

In method precision, the method was checked to determine whether giving the constant results or not. Three sample preparations and 100% spike sample six individual preparations were prepared and analysed as per the method, and obtained results were tabulated. The %RSD for the six spike sample preparations were also calculated. Individual 100% spike sample solution of tapentadol hydrochloride sample were prepared six times and each preparation was aspirated. The palladium content and the %RSD for palladium content in six preparations was calculated.

RESULTS AND DISCUSSION

Linearity

Linearity studies were executed to express the range of the method. The linearity for palladium was established by examining a variety of different amounts of the investigated element. The calibration curves were created using standard aqueous solutions at concentrations ranging from 0.25, 0.50, 1.0, 1.25, 1.5 mg/L. The method was found to be linear for the aforementioned range. The correlation coefficient between the concentration and absorbance of the standard palladium solution was found to be 0.998. The correlation coefficient obtained was within the acceptance criteria. The outcomes of linearity were tabulated in Table 2. Figure 2 shows the calibration curve of palladium.

Table 2: Linearity of palladium

S. No	*Name (mg/l)*	*Obtained average absorbance for three replicates*	*Correlation coefficient*
1	Standard-1 (0.25)	0.0249	
2	Standard-2 (0.50)	0.0503	
3	Standard-3 (1.00)	0.0932	0.998
4	Standard-4 (1.25)	0.1243	
5	Standard-5 (1.50)	0.1498	

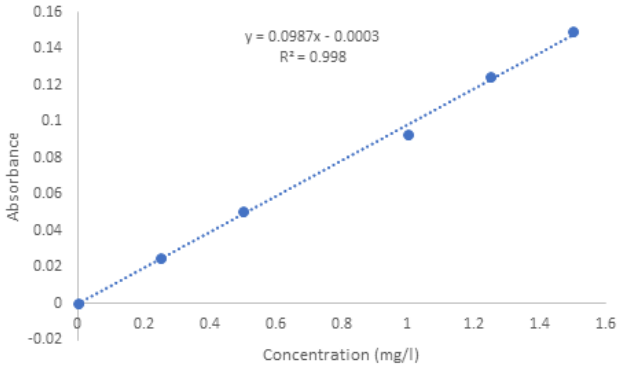

Figure 2: Linearity of palladium

Table 3: Specificity

S. No	*Name*	*Obtained average absorbance*	*Obtained % RSD for three replicates (%)*
1	Blank	-0.0039	-
2	100% Standard solution	0.0952	0.25
3	Sample	0.0081	-
4	100% Spike sample solution	0.1030	0.31

Specificity

The technique was performed on blank, 100% standard solution, sample solution and 100% spiked sample solution. The parameter specificity was defined as the ability to distinguish the palladium signal from the background signal and the matrices signals. The %RSD of absorbance obtained with the solutions were found to be within the acceptable limits. There was no interference from both matrices. The specificity results meet the acceptance criteria and hence the method was found to be specific. The outcomes were tabulated in Table 3.

LoD and LoQ

LoD and LoQ parameters show the sensitivity of the method. LoD and LoQ of the method were computed using ICH guideline Q2R1 "Based on visual evaluation" palladium 0.10 mg/L (10.0% w. r. t sample concentration) considered as LoD and palladium-0.30 mg/l (30.0% w. r. t sample concentration) considered as LoQ.

Table 4: System precision

S. No	*100% Standard solution*	*Absorbance*
1	R-1	0.0971
2	R -2	0.1010
3	R -3	0.0934
4	R-4	0.0987
5	R-5	0.1008
6	R -6	0.0998
Average		0.0985
S. D		0.00287
% RSD		2.92

*R- Replicate

System Precision

The system's precision was validated to show if the instrument response to the palladium standard solution was always reproducible. 100% standard level solution was aspirated in six replicates and the %RSD was calculated. The %RSD for absorbance of palladium standard solution at 100% level from six replicates was found to be 2.92%. The result was found to be within the acceptance criteria. The results of precision at limit of quantification level were tabulated in Table 4.

Method Precision

The method precision validation parameter, defined in percentage relative standard deviation, shows how closely the measurements agree with one another. Precision test was done using six replicates of 100% spike sample solution. The experimental data, with an RSD of 1.70%, demonstrated that the method was precise. Table 5 displays the calculated palladium determination results in the working standard solution together with the relative standard deviation.

Accuracy

The closeness of the true value to the test results achieved by that method was the accuracy of the analytical procedure. The accuracy of the technique was established by spiking known amounts of standard palladium concentrations, i.e., LoQ level, 50,100 and 150% levels into individual tapentadol hydrochloride standard sample solutions. These samples represent three increment levels of 50, 100, and 150%, and each class was aspirated in triplicate. The palladium content in each trail was calculated and establish the % recovery of palladium content in each trail. The result was found to be within the acceptance criteria. The results were tabulated in Table 6.

Intermediate Precision

Variations in between laboratories were articulated by intermediate precision, including various days, analysts, equipment, etc. A precision test was done using six replicates of 100% spike sample solution. The experimental data, with an RSD of 1.70%, demonstrated that the method was precise. Table 7 displays the calculated palladium determination results in the standard working solution together with the relative standard deviation.

Table 5: Method precision results

S. No	*Name*		*Obtained %RSD for three replicates (%)*	*Weight of sample taken (g)*	*Obtained concentration (mg/L)*	*Obtained palladium content (mg/L)*	*Average palladium content (mg/L)*	*% RSD for palladium content (%)*	*Spiked palladium content (w.r.t sample) (mg/L)*	*Obtained recovery (%)*	*Average recovery (%)*	*% RSD for recovery (%)*
1	Sample	P-1	-	1.0023	-0.0036	BDL	BDL	-				
		P-2		1.0036	0.0008	BDL						
		P-3		1.0046	0.0014	BDL						
2	Sample Spiked at 100% Level	P-1	0.42	1.0014	1.0123	10.11	10.15	1.70	10.00	101.09	101.50	1.70
		P-2	0.37	1.0009	1.0234	10.22				102.25		
		P-3	0.69	1.0045	1.0025	9.98				99.80		
		P-4	0.75	1.0031	1.0143	10.11				101.12		
		P-5	0.19	1.0012	1.0471	10.46				104.58		
		P-6	0.47	1.0018	1.0036	10.02				100.18		

*P - Preparation

Table 6: Accuracy results

S. No	*Name*		*Obtained % RSD for three replicates (%)*	*Weight of sample taken (g)*	*Obtained concentration (mg/L)*	*Obtained palladium content (mg/L)*	*Average palladium content (mg/L)*	*% RSD for palladium content (%)*	*Spiked palladium content (w.r.t sample) (mg/L)*	*Obtained recovery (%)*	*Average recovery (%)*	*%RSD for recovery (%)*
1	Sample	P-1	-	1.0011	-0.0009	BDL	BDL	-				
		P-2		1.0003	-0.0481	BDL						
		P-3		1.0012	-0.0351	BDL						
2	Sample Spiked at LoQ Level	P-1	1.14	1.0036	0.3025	3.01	3.00	0.57	3.00	100.47	100.09	0.57
		P-2	0.37	1.0014	0.2987	2.98				99.43		
		P-3	0.98	1.0011	0.3014	3.01				100.36		
3	Sample Spiked at 50% Level	P-1	1.25	1.0014	0.5014	5.01	5.01	0.14	5.00	100.14	100.13	0.14
		P-2	1.39	1.0084	0.5041	5.00				99.98		
		P-3	0.25	1.0008	0.5017	5.01				100.26		
4	Sample Spiked at 100% Level	P-1	1.47	1.0009	1.0014	10.00	10.01	0.10	10.00	100.05	100.11	0.10
		P-2	0.58	1.0001	1.0024	10.02				100.23		
		P-3	0.37	1.0031	1.0036	10.00				100.05		
5	Sample Spiked at 150% Level	P-1	0.64	1.0047	1.5017	14.95	14.97	0.34	15.00	99.65	99.78	0.34
		P-2	0.12	1.0034	1.4981	14.93				99.53		
		P-3	0.37	1.0015	1.5047	15.02				100.16		

*P - Preparation

Table 7: Intermediate precision results

S. No	*Name*		*Obtained %RSD for three replicates (%)*	*Weight of sample taken (g)*	*Obtained concentration (mg/L)*	*Obtained palladium content (mg/L)*	*Average palladium content (mg/L)*	*%RSD for palladium content (%)*	*Spiked palladium content (w.r.t sample) (mg/L)*	*Obtained recovery (%)*	*Average recovery (%)*	*% RSD for recovery (%)*
1	Sample	P-1	-	1.0003	-0.0032	BDL	BDL	-				
		P-2		1.0042	-0.0017	BDL						
		P-3		1.0018	-0.0008	BDL						
2	Sample Spiked at 100% Level	P-1	0.03	1.0014	1.0132	10.12	10.16	1.70	10.00	101.18	101.63	1.70
		P-2	0.08	1.0024	1.0452	10.43				104.27		
		P-3	0.14	1.0001	1.0325	10.32				103.24		
		P-4	0.35	1.0009	1.0012	10.00				100.03		
		P-5	0.25	1.0002	1.0036	10.03				100.34		
		P-6	0.61	1.0014	1.0084	10.07				100.70		

*P - Preparation

CONCLUSION

Tapentadol hydrochloride is a frequently prescribed medication for the treatment of moderate to acute pain. Palladium, which is used as a catalyst in synthesizing tapentadol hydrochloride, can harm humans. Hence it must be measured. This method used a validated simple, precise, and accurate atomic absorption spectroscopy technique to assess palladium as an elemental impurity in tapentadol hydrochloride drug. The maximum acceptable palladium concentration was 10 ppm, in accordance with USP general chapter <232>. The described method provided results that were within acceptable limits. This simple, cost-effective, and exact technique can be used to estimate the palladium content in tapentadol hydrochloride.

CONFLICT OF INTEREST

The authors affirm that they have no known financial or interpersonal conflicts that would have appeared to impact the research presented in this study.

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