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Simple and Novel Zero and First Order Spectrophotometry- AUC methods for Determination of Fimasartan Potassium Trihydrate in Bulk and *in-house* Tablets

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Abstract

Fimasartan potassium trihydrate is chemically, 2-butyl-5-dimethyl amino thiocarbonyl methyl-6-methyl-3-[2'-(1*H*-tetrazol-5-yl) biphenyl-4-yl] methyl] pyrimidin-4(3H)-one potassium trihydrate. Precise and commercial UV-Spectrophotometric methods have been developed using water as a solvent. All five methods of UV-Spectrophotometry based upon Zero Order and First Order derivative Spectrophotometry have been established considering amplitude and Area under Curve of the spectrum. Fimasartan exhibits maximum absorbance at 261 nm when dissolved in water. In all four methods, Fimasartan obeyed linearity in the concentration range of 3-21 µg/mL with correlation coefficient (r2 >0.999). The % amount of drug estimated in the developed methods was found to be good agreement with label claimed in *in-house* tablet formulation. All the methods were validated as per International council on Harmonization (ICH) guidelines. All these proposed methods were proved to be linear, accurate, precise and rugged and also adequately sensitive.

Keywords: Fimasartan potassium trihydrate, UV-Spectrophotometry; first order derivative; Area Under Curve.

Introduction:

Fimasartan potassium trihydrate (FPT) is chemically, 2-butyl-5-dimethyl amino thio carbonyl methyl-6-methyl-3-[[2'-(1H-tetrazol-5-yl) bi-phenyl-4-yl] methyl] pyrimidin-4(3*H*)-one potassium trihydrate (Fig 1). In September 2010 Fimasartan was used under the brand name Kanrab approved by Korean Food Drug Administration (KFDA) and established by Boryung Pharmaceuticals. [1-4]

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Hypertension is the main reason for cardiovascular and renal diseases with high morbidity and The renin-angiotensin system (RAS) [5] is a chief controller of blood pressure and fluid-electrolyte homeostasis, the participation of RAS in several extreme cardiovascular conditions having hypertension [6], for the treatment of this condition and also angiotensin I and angiotensin II inhibiting used the several drugs and methods including Losartan [7], Telmisartan [8], and Irbesartan [9] etc.

Derivative spectroscopy uses first or higher derivatives of absorbance with respect to wavelength for qualitative analysis and for quantification [10, 11]. Derivatisations of spectra are simplest method for increasing selectivity and remove spectral interference's [12, 13]. AUC is calculation of integrated value of area with respect to the wavelength between the two selected wavelengths $\lambda 1$ and $\lambda 2$. [13, 14]

In literature study, several analytical methods such as UPLC, HPLC stability study have been described; Fimasartan is not official in IP, BP and USP. The objective of the existing work is to develop modest, quick and cost-effective, Zero, first Order Derivative spectrophotometry method by using the area under curve methods for the estimation of Fimasartan potassium trihydrate in bulk and *in house* tablet form. The estimated methods are economy and modest than HPLC method. It might be a substitute to the HPLC methods for routine analysis, HPLC are time consuming and tedious method.

Experimental Work:

Materials and Methods:

Chemicals:

Fimasartan potassium trihydrate supplied as a gift sample by Ajanta Pharmaceuticals Ltd, Mumbai, and *in house* tablets. R.O. water was used for the development spectrum.

Instrumentation

A double beam UV-VIS spectrophotometer (UV-2450 Shimadzu, Japan) linked to a computer loaded with spectra manager software UV Probe 2.21 with 10 mm quartz cells was used. The spectra were acquired with the instrumental parameters as follows: wavelength range 400– 200 nm and having scan speed: medium; sampling interval: 1.0 nm; spectral slit width: 1nm. An electronic balance (Model Shimadzu AUX 120) was used for weighing purpose.

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Preparation of Stock standard solution and Determination of wavelength

The stock standard solution was prepared by dissolving 10 mg of FPT in 100 mL of water to acquire a concentration of 100 µg/mL. The working standards were prepared by dilution of the stock standard solution. An appropriate concentration of 9 µg/mL from stock standard solution was prepared and scanned in the UV-visible range 400–200 nm; for "Method A" Absorbance of Zero order spectrum was determined at 261 nm (Fig 2) while for "Method B" AUC of Zero order spectrum was selected between range 249.60 to 269.40 nm (Fig 3). In "Method C" maximum amplitude of First order derivative spectrum was recorded at 280.60 nm (Fig 4) while in "Method D" AUC of First order derivative spectrum was selected between range of 270.60 to 289.60 nm (Fig 5).

Validation of Method

Accuracy

The accuracy of all methods was evaluated by measurement of % recovery. To the pre-analyzed sample solutions (9 μg/mL), known amounts of stock standard solutions were added at three different levels, such as 80%, 100%, and 120%, sample was reanalyzed and % recovery was calculated.

Precision

Precision of the methods was studied as intra-day and inter-day variations. For "methods A, B, C, and D" precision was determined by analyzing the 9, 12, and 15 μg/mL of FPT solutions as intra-day and inter-day variations.

Sensitivity:

The sensitivity of measurements of FPT by the use of proposed methods was estimated in terms of limit of detection (LOD) and limit of quantification (LOQ) which were calculated using formulae "LOQ = 10 $\times N/B$" and "LOD = 3.3 $\times N/B$," where "N" is standard deviation of the absorbance, or amplitudes or AUC of the FPT (n = 3), taken as a measure of noise, and "B" is the slope of the corresponding calibration curve.

Ruggedness:

Ruggedness of all proposed method was determined by analyzing 12 μg/mL concentration of by two different analysts using similar operational and environmental conditions.

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Analysis of *in-house* Tablets

To determine the content of *in-house* prepared tablets of FPT, twenty tablets were weighed and powdered. An amount of powdered drug equivalent of 10 mg of FPT has weighed accurately, transferred into 100 mL volumetric flask containing 50 mL of water, sonicated for 20 min, and the solution was diluted up to 100 mL with the same solvent and filtered through Whatman filter paper (No. 41). From the filtrate, measured volume was taken and diluted with water to get the final concentration of 12 μg/mL for all the methods. The responses were measured as described above and concentrations in the sample were determined from respective linearity equation.

Result and Discussion

Method Validation

Linearity

A linear relationship should be evaluated across the range of the analytical procedure. For method A, B, C and D linearity study, seven solutions at different concentrations (3, 6, 9, 12, 15, 18, and 21 µg/mL).The correlation coefficient, y-intercept, slope of the regression line, and residual sum of squares should be submitted. A plot of the data should be included. In addition, an analysis of the deviation of the actual data points from the regression line may also be helpful for evaluating linearity. Optical characteristics in Table 1

Accuracy

The solutions were reanalyzed by proposed methods; results of recovery studies are reported in Table 3. The % RSD values that were determined and found to be less than 2 indicate that the method is accurate.

Precision

The precision of the developed methods was expressed in terms of % relative standard deviation % RSD. These results showed reproducibility of the assay. The % RSD values were found to be less than 2. Results are shown in Table 3

Sensitivity

The LOD and LOQ for Fimasartan potassium trihydrate were found to be "Method A (0.14 μg, 0.33μg), B (0.59 μg, 1.81μg), C (0.57 μg, 1.75μg), and D (0.58 μg, 1.77μg),"

Ruggedness

Ruggedness was determined for solutions of Fimasartan potassium trihydrate .The results are in acceptable range that is % RSD values less than 2 for all the methods as shown in Table 3

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Analysis of *in-house* Tablets

The amounts of Fimasartan potassium Trihydrate estimated from *in-house* tablets using methods A, B, C, and D were found to be 99.32%, 100.18%, 99.61%, and 99.81%, respectively. The % amount estimated from tablet formulation indicates that there is no interference from excipients present in it. The results was found in table 2

Conclusion

All four methods were developed for the determination of Fimasartan potassium Trihydrate based on different analytical techniques, UV- spectrophotometric derivative, and AUC methods. The methods were validated and found to be simple, sensitive, accurate, and precise. Hence, the methods can be used successfully for routine analysis of pharmaceutical dosage form of Fimasartan potassium Trihydrate. The proposed spectrophotometric methods will not be substituted to the existing known methods available for the analysis of Fimasartan potassium Trihydrate. However, it can serve as an option where advanced instruments (e.g., UV-Visible Spectroscopic and HPLC methods) are not available for routine analysis.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Table 1: Optical Characteristics of fimasartan

Parameters	Method A	Method B	Method C	Method D
Beer-Lambert's range (µg/mL)	03-21	03-21	03-21	03-21
λ max (nm)/Wavelength range (nm)	260	246.60 – 269.40	280.60	270.60 – 289.60
Slope	0.0484	0.0649	0.0163	0.0706
Intercept	0.0015	0.0282	0.0022	0.0397
Correlation coefficient	0.999	0.999	0.999	0.998

Table 2: Analysis of *in-house* Tablets

Methods	% Amount found	%RSD
A	99.40	0.72
B	99.17	1.37
C	99.77	0.64
D	99.20	1.36

Table 3: Validation Parameters

		Methods			
Parameters		A	B	C	D
Accuracy (% Recovery)	80 %	99.11	98.96	100.85	100.31
	100 %	100.66	100.19	99.84	100.11
	120 %	99.53	99.84	100.48	99.33
Precision (% RSD) (n=3)	**Intra-day**	0.815	0.886	0.5214	0.951
	Inter-day	0.62	1.29	1.13	1.13
Ruggedness (% RSD)	**Analyst I**	1.15	0.72	1.01	0.66
	Analyst II	1.00	0.60	1.64	0.73
Limit of Detection		0.14	0.59	0.57	0.58
Limit of Quantification		0.43	1.81	1.75	1.77

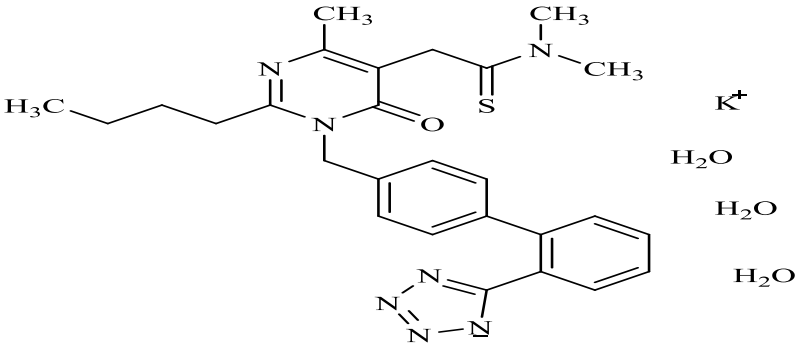

Fig 1: Chemical Structure of Fimasartan potassium trihydrate

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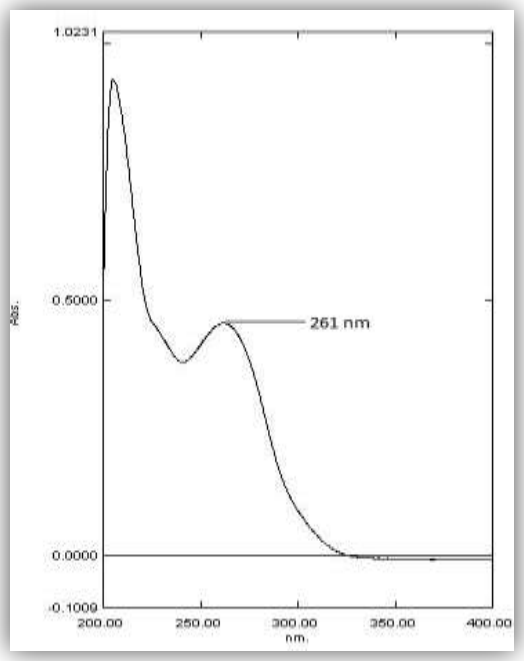

Fig 2

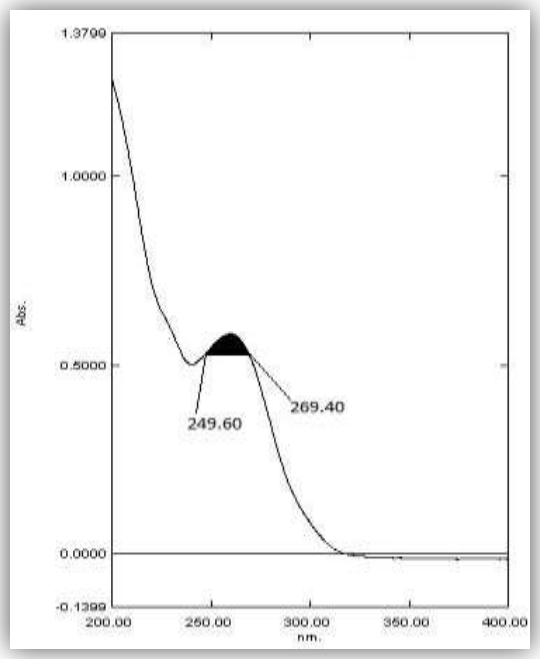

Fig 3

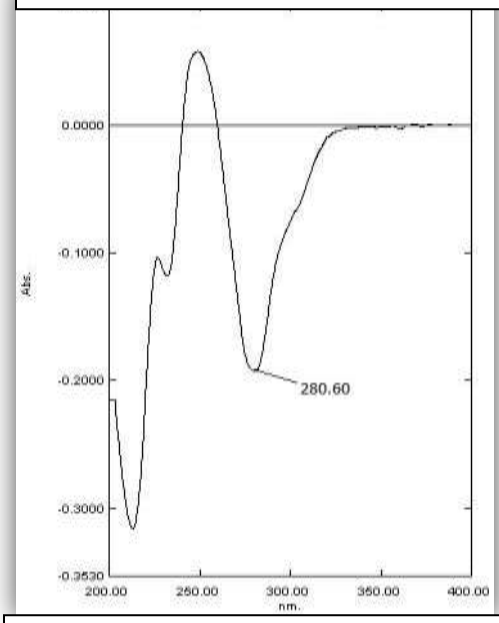

Fig 4

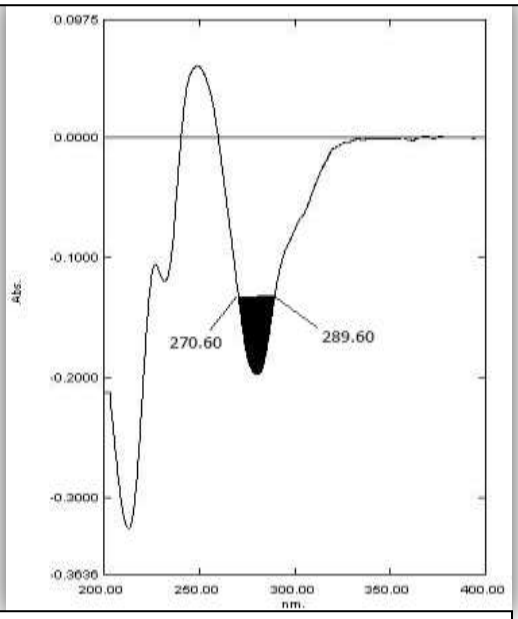

Fig 5

Fig 2 Zero Order spectrum of fimasartan potassium trihydrate, Fig 3 Zero order spectrum showing AUC between selected wavelengths, Fig 4 First order derivative spectrum, and Fig 5 first order derivative spectrum showing AUC between selected wavelengths.