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DEVELOPMENT AND VALIDATION OF DILTIAZEM HYDROCHLORIDE IN NEW ANALYTICAL BY USING UV-SPECTROPHOTOMETRIC METHOD

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ABSTRACT

A novel and simple Zero order derivative spectroscopic method was developed and validated of Diltiazem hydrochloride an absorption maximum at 236nm using distilled water. The Linearity was found to be in the concentration range of 2-10µg/ml and the correlation coefficient was found to be 0.999 and it has showed good linearity, reproducibility, precision in this concentration range. The regression equation was found to be Y = 0.568x + 0.009. The % recovery values were found to be within 100.8-101.37% showed that the method was accurate. The LOD and LOQ were found to be 0.00871 and 0.02640µg/ml respectively. The %RSD values were found to be less than 2. The developed method was validated according to ICH guidelines for linearity, accuracy, precision and ruggedness. Limit of detection and limit of quantitation. The developed method was successfully applied for the quantitative estimation of Diltiazem hydrochloride.

KEYWORDS

Diltiazem hydrochloride, Zero order derivative spectroscopy, Water linearity, Precision, Reproducibility and Accuracy.

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INTRODUCTION

Diltiazem hydrochloride

Diltiazem is an oral and parenteral non-dihydropyridine calcium channel blocker. It is useful in many clinical scenarios as an antihypertensive, anti-arrhythmic, and as anti-anginal[1]. FDA approved indications are atrial arrhythmia, Hypertension, Paroxysmal supraventricular tachycardia, Chronic stable angina, Angina due to coronary artery spasm (Prinzmetal's or variant angina)[2].

Diltiazem is a non-dihydropyridine calcium channel blocker (CCB). Therapeutic effects occur through various mechanisms. Primarily, Diltiazem inhibits the inflow of calcium ions into the cardiac, smooth muscles during depolarization. Reduced intracellular calcium concentrations equate to increased smooth muscle relaxation resulting in arterial vasodilation and, therefore, decreased blood pressure[3].

In the United States, Diltiazem is an FDA-approved as an oral and intravenous formulation. Compounded topical preparations of Diltiazem are used off-label[4,5].

Diltiazem is teratogenic in animals and only limited data in humans exist; thus, its use is only recommended in pregnancy if the potential benefit justifies the potential risk to the fetus[6]. Diltiazem is excreted in human milk. Based on current data, amount of Diltiazem ingested by the infant are small. However, due to serious adverse reactions, if Diltiazem is deemed essential, the clinician should suggest an alternative method of infant feeding[7].

Common adverse effects of Diltiazem therapy include peripheral edema, bradycardia, dizziness, headache, and fatigue[8].

Diltiazem is extensively metabolized through the CYP450 system and requires careful medication profile review. Concomitant use alongside potent CYP450 inhibitors may increase Diltiazem concentrations leading to adverse effects even at clinically recommended doses[9].

Diltiazem is indicated for the treatment of arrhythmias and, consequently, the potential to worsen or create new arrhythmias such as extrasystole and AV block[10].

Diltiazem has been widely used in practice for many clinical indications. Proper dosage and frequency are essential to enhance patient care and improve the outcomes. Diltiazem possesses negative inotropic effects and is generally avoided in patients with congestive heart failure and diltiazem is also on the Beers Criteria[11].

MATERIAL AND METHODS

Instrument

UV-visible double beam spectrophotometer, SHIMADZU (model UV-1800) with UV probe software. All weights were taken on analytical balance.

Chemicals

Diltiazem hydrochloride drug was obtained as a gift sample from INM research private limited.

Solvent

Water

Selection of analytical wavelength

Appropriate dilutions were prepared for drug from the standard stock solution and the solution was scanned in the wavelength range of 200-400nm. The absorption spectra thus obtained were derivatized from zero order method. It shows maximum absorbance at 236nm was shown in Figure No.2.

Preparation of standard stock solution

Accurately weigh 100mg of Diltiazem hydrochloride was transferred into 100ml volumetric flask and diluted with purified water upto the mark (stoke solution 1) From this pipette out 10ml in to 100ml volumetric flask and diluted with water up tomark (stock solution 2), from this solution pipette out 2, 4, 6, 8 and 10ml into 10ml individual volumetric flask and add water up to the mark, this gives 2, 4, 6, 8 and 10.µg/ml concentrations.

Method validation

The above method is validated according to the ICH guidelines.

RESULTS AND DISCUSSION

Method: zero order derivatives spectroscopy

Linearity

The linearity of analytical method is its ability to elicit test results that are directly proportional to the concentration of analyte in sample within a given range, the linearity of the method was demonstrated over the concentration range of 2-10µg/ml of the target concentration. Aliquots of 2, 4, 6, 8 and 10µg/ml are prepared from Stock solution-II; calibration curve was plotted and presented.

Range

The range of analytical method is the interval between the upper and lower levels of analytet hat have been demonstrated to be determined with in a suitable level of precision, accuracy and linearity.

Sensitivity

The sensitivity of the proposed method for the measurement of Diltiazem hydrochloride was estimated in terms of Limit of Detection (LOD) and Limit of Quantification (LOQ). The LOD and LOQ were calculated by using the average of the slope and SD of the intercept. The mean slope value and SD of the intercept were obtained after plotting six calibration curves. The LOD and LOQ which are calculated are reported.

Precision

The precision of an analytical method is the degree of agreement among individual test results when the method is applied repeatedly to multiple samplings of homogenous samples. It provides an indication of any random error results and was expressed as coefficient of variation (CV).

Accuracy

Accuracy is the closeness of the test results obtained by the method to the true value. To study the accuracy, Recovery studies were carried out at three different levels i.e. 50%, 100% and 150% by adding standard drug solution to the sample solution. The% recovery was calculated and reported.

Ruggedness

The solutions were prepared and analyzed with change in the analytical conditions like different laboratory conditions and different analyst and are presented in Tables.

Table No.1: Results of calibration curve at 236nm for Diltiazem hydrochloride by zero order spectroscopy

S.No	Concentration in µg/ml	Absorbance ± Standard Deviation*
1	0	0
2	2	0.131±0.000577
3	4	0.241±0.001
4	6	0.356±0.001528
5	8	0.465±0.000208
6	10	0.572±0.002

*Average of six determinations.

Table No.2: Optimum condition, optical characteristics and statistical data of the regression equation in UV method

S.No	Optimized conditions	Diltiazem hydrochloride
1	Range (µg/ml)	2-10
2	Λmax (nm)	236
3	Regression Equation	Y = 0.568x + 0.009
4	Slope (b)	0.0568
5	Intercept (a)	0.009
6	Correlation Coefficient (r2)	0.999
7	Sandell's equation	0.0168
8	Limit of detection (µg/ml)	0.0087
9	Limit of quantification (µg/ml)	0.0264

**Average of six determinations

Table No.3: Determination of precision results for Diltiazem hydrochloride at 236nm by zero order derivative spectroscopy

S.No	Concentration (µg/ml)	Intra-day Absorbance ±SD**	%RSD	Inter-day Absorbance ±SD**	%RSD
1	2	0.131±0.00057	0.44	0.131±0.0011	0.83
2	4	0.241±0.001	0.41	0.242±0.001	0.63
3	6	0.356±0.0015	0.42	0.356±0.00057	0.28
4	8	0.465±0.0020	0.44	0.465±0.0011	0.44
5	10	0.567±0.002	0.34	0.567±0.0015	0.26

**Average of six determinations

Table No.4: Determination of LOD and LOQ results for Diltiazem hydrochloride by Zero order derivative spectroscopy

S.No	Parameters	Values
1	SD of Intercepts*	0.0015
2	Average of Slopes*	0.568
3	LOD (3.3×SD of Intercepts/average of slopes)	0.00871
4	LOQ (10×SD of Intercepts/average of slopes)	0.02640

*Mean value obtained from 6 calibration curves

Table No.5: Determination of accuracy results for Diltiazem hydrochloride by Zero order derivative spectroscopy

S.No	Drug	Spiked levels %	Amount of sample (µg/ml)	Amount of standard (µg/ml)	Amount recovered	% Recovery ±SD**	%RSD
1	Diltiazem hydrochloride	50	4	2	6.07	101.1% ±0.02616	0.02616
		100	4	4	8.11	100.37% ±0.036056	0.0355
		150	4	6	10.08	100.80% ±0.035119	0.03484

**Average of six determination

Table No.6: Ruggedness results for Diltiazem hydrochloride at 236nm by zero order derivative spectroscopy

S.No	Analysts	Analyst-1	Analyst-2
1	Mean absorbance	0.356	0.3563
2	Standard deviation	0.000577	0.002082
3	%RSD	0.16207	0.58433

**Average of six determinations

Figure No.1: Chemical structure of Diltiazem hydrochloride

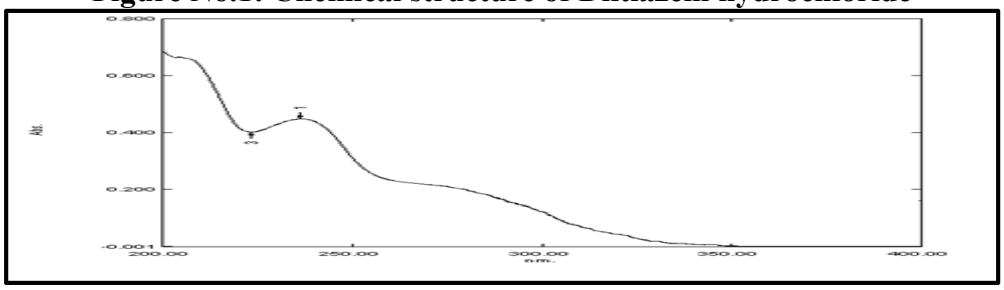

Figure No.2: Zero order spectrum of Diltiazem hydrochloride at 236nm

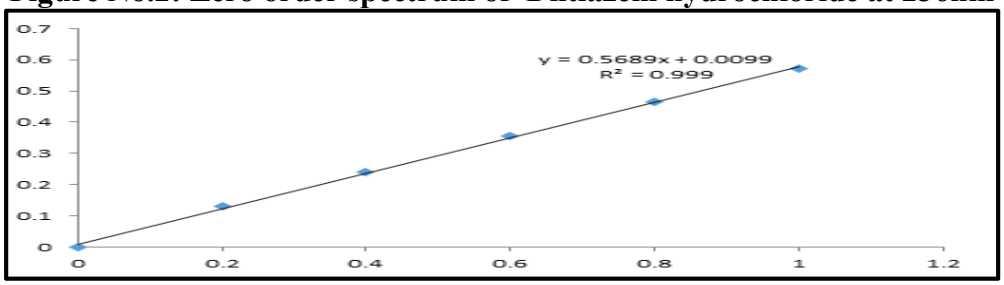

Figure No.3: Calibration curve of Diltiazem hydrochloride

CONCLUSION

From the above it can be concluded that all validation parameters (precision, accuracy, linearity, LOQ, LOD, Ruggedness) met the predetermined acceptance criteria as mentioned in ICH guidelines. The developed spectrophotometric method is simple, rapid, accurate, and precise of Diltiazem hydrochloride.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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