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Simple, Rapid, and a Green Derivative ATR-FTIR spectroscopic method for the analysis of Atenolol Loaded Microspheres and its tablet formulations

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ABSTRACT: Developing a non-destructive analytical method to quantify the polymer based analyte is an herculean task. Since there is lacuna in the analysis of drugs in presence of interfering formulation excipients we proposed ATR-FTIR spectroscopic method for the qualitative and quantitative estimation of atenolol in its polymer based microsphere formulations. The current research describes the utility of a validated, simple, rapid, easy-to-implement, and solvent free and green Attenuated total reflection-Fourier transform infrared (ATR-FTIR) spectroscopy method for the quantitative analysis of Atenolol loaded lab-made microspheres and its marketed tablets. This ATR-FTIR spectroscopic analysis is based on the measurement of the absorbance of infrared bands corresponding to the C=O stretching for amide (–$CONH_2$) in the range of 1650-1700cm^{-1} of the carbonyl amide moiety of atenolol. The wave number was selected by derivatisation of the absorbance spectrum to its first, second and third derivative spectrum. The statistical results were compared and correlated with other analytical methods for the quantification of Atenolol. The polymer excipients of the atenolol loaded microsphere and in the commercial tablet preparation did not interfere with the active drug. The linearity was found in the range 0.1 – 1.0 w/w % with r = 0.9821. Precision of the method was assessed by the repeated analysis of Atenolol by inter and inter and Intraday analysis. The results retrieved showed a small standard and relative standard deviation values. The high percentage of recovery of Atenolol in microspheres, and its marketed tablets (99.96, 99.92 and 100.03%w/w) demonstrate the compliance of the accuracy study limits as per the ICH guidelines. The limit of detection (LOD) and limit of quantification (LOQ) values (0.0528 and 0.1599 w/w %, respectively) indicated the high sensitivity of the method. Thus, the developed ATR-FTIR spectroscopic method showed high accuracy and precision, is considered as nondestructive, solvent free, green, low cost and rapid, and can be applied easily for the pharmaceutical quantitative determination of atenolol in their polymer based and tablet formulations.

Keywords: Atenolol, ATR-FTIR spectroscopy, Derivative spectroscopy, Analysis.

INTRODUCTION

Fourier Transform Infrared Spectroscopy is a widely recognized technique for identification and verification of functional groups in compounds, impurities. It is non-contact, non-destructive and no sample preparation is required. This technique has been used to identify several compounds, such as pharmaceuticals, cosmetics and foods, but requires expensive equipment's and mathematical pretreatments. Quantification of some pharmaceutical agents has been reported in the literature using FTIR spectroscopy either by measuring the transmission of analyte in potassium bromide or in chloroform (Bansal *et al.,* 2013; Konoz *et al.,* 2012; Patraa *et al.,* 2010; Matkovic *et al.,* 2005; Bhoomendra Bhongade *et al.,* 2014). Atenolol (ATE), chemically 2-(4-{2-hydroxy-3- [(propan-2-yl) amino] propoxy} phenyl) acetamide, (Indian Pharmacopoeia 1996) (Fig. 1) and Adrenergic beta-1 Receptor Antagonist, is used alone or with chlorthalidone in the management of hypertension, edema and long-term management of patients with angina pectoris (Manaf *et al.,* 2007).

The drug is official in the Indian Pharmacopoeia which describes a UV spectrophotometric method for its assay in tablets. The drug is also official in the United States Pharmacopoeia, which describes high performance liquid chromatographic (HPLC) methods of assay, which are two-stage processes (Marina *et al.* (2009). A wide range of chromatographic techniques, such as HPLC (Ferraro *et al.,* 2002; Mazarevica *et al.,* 2004; Schenk *et al.,* 2007; Veale *et al.,* 2007; Belal *et al.,* 2008; Miller *et al.,* 2010; Baskara *et al.,* 2011; Yilmaz *et al.,* 2012; Kori *et al.,* 2013; Madhusudhan *et al.,* 2018; El-Alfy

et al., 2019; El-Gindy *et al.,* 2019; Sanden *et al.,* 2019; Peleshok *et al.,* 2021) have been used to determine Atenolol. Ultraviolet (UV) Spectrophotometric and HPLC Methods (Goebel and Rolim 2007) in routine analysis. Qualitative and quantitative Forensic Application (Kori *et al.,* 2013) and Spectroscopic Determination (Vaikosen *et al.,* 2020) of atenolol was reported. Furthermore, miscellaneous methods like visible spectroscop (Madhurai *et al.,* 2015), continuous flow injection turbidimetric analysis (Al-Awadie *et al.,* 2014) and kinetic method for estimation of Atenolol (Fadnis and Agarwal 2015) were reported.

Although HPLC, UV spectroscopic and conventional methods are routinely used, these methods require complicated liquid–liquid or liquid–solid extraction steps and/or several complicated clean-up steps. They are time consuming. The kinetic method is less sensitive and involves a heating step, whereas the thermal methods require expensive experimental setup, in addition to being poorly sensitive. But methods for its determination using Infrared Spectroscopic technique were not available.

Hence an attempt was made to develop a simple, rapid and nondestructive method using ATR FT-IR for the routine qualitative and quantitative analysis of Atenolol in pure, polymer based microspheres and tablet formulations.

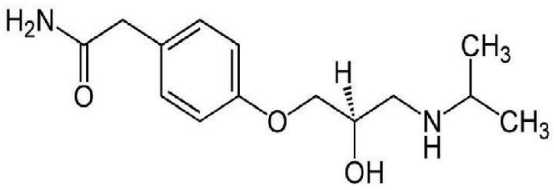

Fig. 1. Structure of Atenolol

MATERIALS AND METHODS

Chemicals and Reagents. Standard sample of Atenolol was obtain as gift sample from Unichem Laboratories, Goa. Potassium bromide (AR Pure), Sodium alginate, and Calcium chloride were obtained from the HiMedia, Mumbai, India.

ATR-FTIR Spectrophotometer Instrumentation. The FTIR analysis was carried out on BRUCKER ALPHA II ATR-FTIR spectrophotometer. FTIR spectra were recorded in the wave number range between 4000 and 650 cm^{-1}, averaging 24 scans per sample using a nominal resolution of 4 cm^{-1}. The IR OPUS software was used for data collection and to analyze the data.

Selection of wavenumber. The absorption spectrum of atenolol API (Fig. 2) was correlated with the standard references and the peak data is tabulated in Table 1. The ideal wavenumber was selected by identifying a uncommon peak from the fingerprint region of atenolol. The overlay ATR-FTIR spectrum of atenolol was derived for various concentration and absorbance peak corresponding to carbonyl amide (-$CONH_2$) in the range of 1650 was selected. Fig. 3 & 4 to derive calibration curve for the determination of linearity range (r^2).

Calibration Curve. Atenolol is mixed with finely powdered IR pure potassium bromide obtains 100mg of total weight. Calibration curves were prepared for five different Atenolol concentrations in the range of 0.1 to 1.0% w/w by diluting appropriate quantity of Atenolol with potassium bromide to get around 100 mg and triturated to ensure sample homogeneity. Each calibration standard was analyzed in the replicates of six. Absorbance corresponding to the C=O NH_2 stretch of amide moiety, which is typically in the range 1630-1650 cm^{-1} was used for the quantification and the average of six measurements was used to obtain the calibration curve. The calibration curve plotting was carried out using OPUS software. The characteristic absorption peaks corresponding to stretching vibrations of different functional groups of Atenolol as shown in Figure 5 and compiled in Table 2.

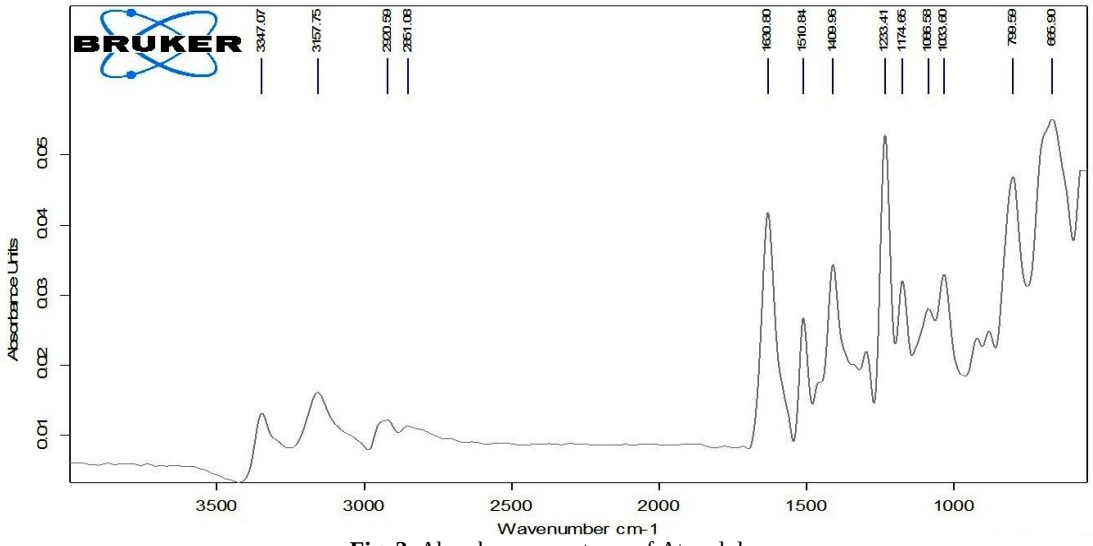

Fig. 2. Absorbance spectrum of Atenolol.

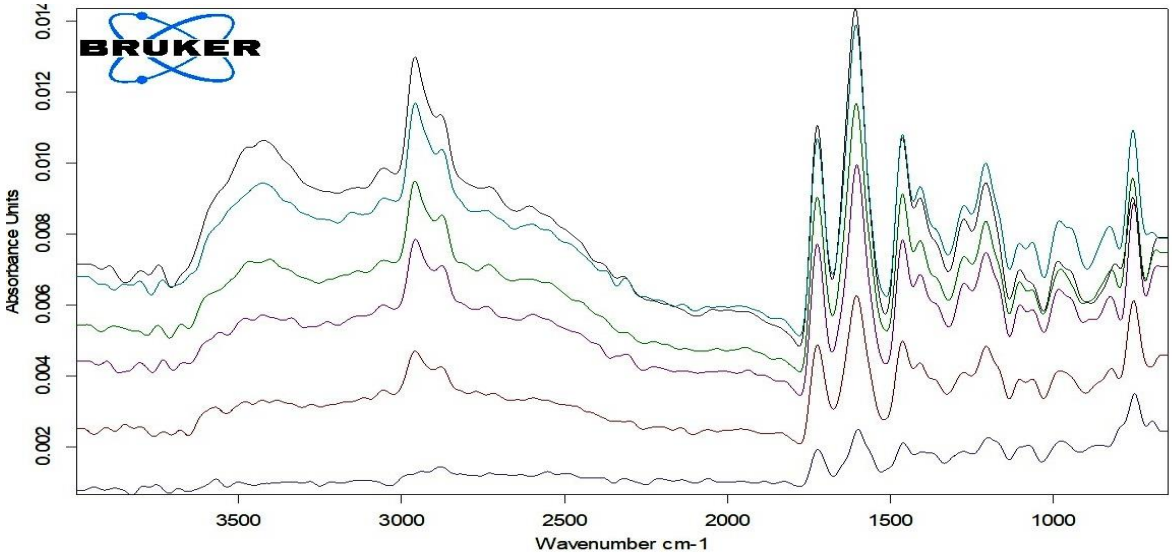

Fig. 3. Overlay Absorbance ATR - FTIR Spectrum of Atenolol.

Formulation of Atenolol loaded Mucoadhesive microspheres. Atenolol loaded mucoadhesive microspheres were prepared by inotropic gelation method. The polymer drug concentration was varied to get three different formulations. Accurately weighed 500mg of atenolol was weighed and dissolved in 50mL of distilled water and it was mixed thoroughly for complete dissolution. 2.5g of Sodium alginate was incorporated to the drug solution and mixed well. The mixture was sonicated for 10 minutes to remove the air bubbles. The drug polymer mixture was dropped using a syringe from a 6 cm distance in to the beaker containing the 5%w/v solution of Calcium chloride to enable gelation with the aid of magnetic stirrer. The wet microspheres are collected, washed and dried at 40ºC in an Oven for 6 hours. The formulated microspheres were saved for further analysis (Dey *et al.*, 2015).

***In-vitro* Mucoadhesive property of Atenolol loaded microspheres.** The prepared microspheres were characterised for the micromeritic properties and the mucoadhesive properties were determined by *in vitro* wash off test. Goat intestine was procured from the local slaughter house and stored in the isotonic solution. The 2×4cm sized intestinal mucosa was stick to a glass slide and a total number of 50 microspheres were placed on the wet intestinal tissue.

Table 1: ATR Absorption peaks of Atenolol.

IR Frequency Band (cm^{-1})	Functional group
3347	-OH
3157	-H-N
2966	$-C-CH_3$
2920	$-CH_2$
2851	-C-H
1630	$-O=C-NH_2$
1614	-Conjugated C=C (aromatic)
799	$-C=CH_2$

Table 2: Linearity studies results.

Concentration (%w/w)	Absorbance
0.1	0.722
0.2	0.855
0.3	1.187
0.4	1.508
0.5	1.917
0.6	2.315
0.7	2.694
0.8	2.963
0.9	3.256
1.0	3.629

Isotonic solution was continuously dropped on the stuck microspheres. The amount of microsphere adhered was noted every 30 minutes and the *in vitro* efficiency was calculated.

ATR-FTIR analytical method validation. The proposed method was validated as per ICH guidelines for specificity, precision, accuracy, and linearity, intermediate precision (ICH Q2A 1995, ICH Q2B 1996).

Specificity. The wavelength selected for analysis was specific for ATE and there was no blank and excipient interference.

Linearity. The linearity of calibration curve was assessed by linear regression. Calibration curves were plotted over the concentration range of 10-70µg/mg for ATE. Each sample was analysed six times and averages were calculated. The calibration curve was constructed by taking concentration on the X- axis and absorbance / area on the Y – axis. The linearity was evaluated by linear regression analysis. This was calculated by the least square regression method. The correlation coefficient and Y- intercept of the calibration curve were calculated. Results obtained for linearity were shown in Fig. 5 and Table 2.

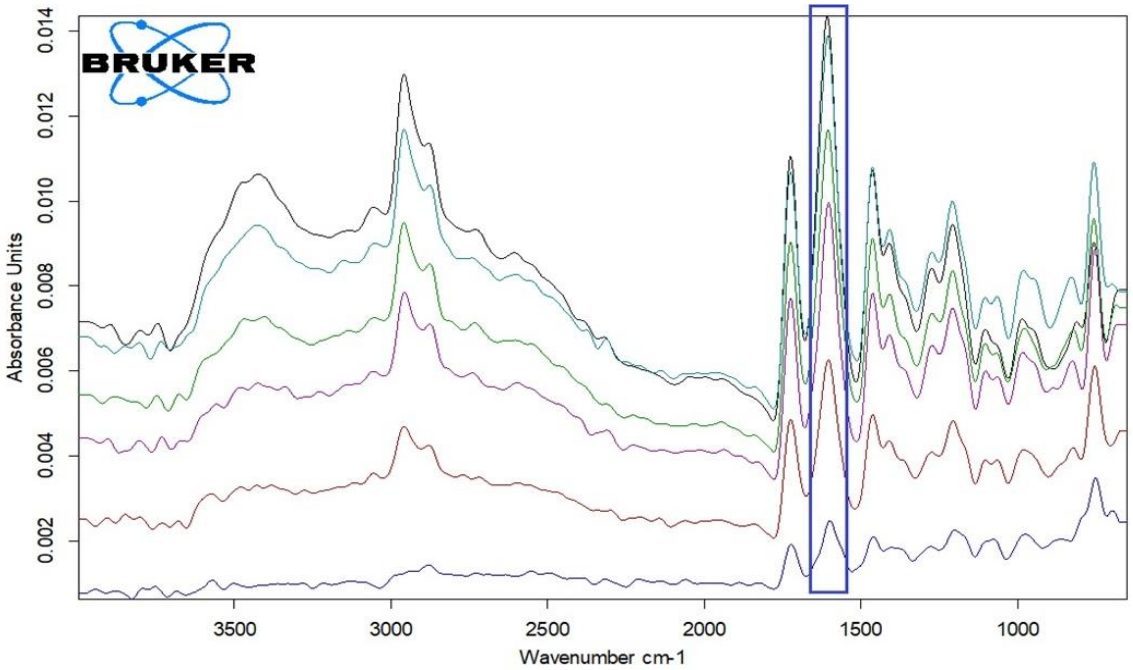

Fig. 4. Overlay Fingerprint region ATR- FTIR Spectrum of Atenolol.

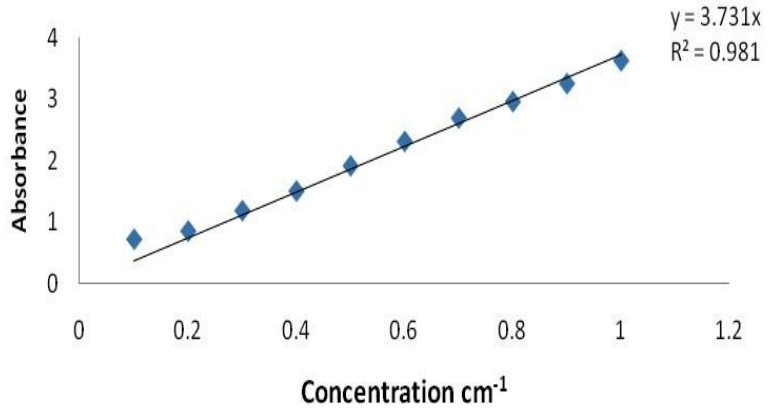

Fig. 5. Calibration curve of Atenolol.

Table 3: Analysis results of Atenolol Formulation.

Sr. No.	Formulations	Formulation Code	Label Claim	Estimated amount	% Drug Content
1.	Atenolol Microspheres	AMS5	50mg	49.82 mg	**99.64**
2.	Atenolol Microsphere	AMS6	50mg	49.98 mg	**99.96**
3.	Atenolol Tablet	AT1	50mg	49.96 mg	**99.92**
4.	Atenolol Tablet	AT2	50mg	50.01 mg	**100.02**

Accuracy. Recovery experiments were conducted at concentration range of 50, 80 and 120% to validate the accuracy of the test method. Each test preparation was prepared in triplicate and the analysis was performed in triplicate. The assay value at the beginning of validation was considered as the true value (100%) for recovery calculations. From the analyzed data, % assay and % recovery were calculated and reported in Table 3.

Precision. Precision studies were conducted to determine the reproducibility of results. The precision of the method was checked by repeated scanning and measurement of the absorbance of the infrared band at 1242 cm^{-1} (n = 6) of 40µg of ATE per mg of KBr without changing the parameters for the method. The repeatability was expressed in terms of relative standard deviation (RSD) and reported in Table 4.

Intermediate Precision. The intraday, inter-day and inter-analyst precision of the proposed methods were performed by analyzing the corresponding responses 6 times on the same day and on 2 different days over a period of 1 week for assay level concentrations of

standard solutions of ATE (40 µg). The results were reported in terms of relative standard deviation (RSD) in table. 5.

Analysis of Marketed Atenolol microspheres and Tablet Formulations. 20 tablets were accurately weighed and triturated and a powder weight equivalent to 0.5%w/w of Atenolol was weighed accurately and mixed finely powdered with IR-pure potassium bromide to get around 100mg. Powders were mixed and ground until obtaining a homogeneous powder. The mixture was made in to a thin transparent pellet by crushing it in mechanical pellet press equipment. Dilutions with potassium bromide were made to give final concentration of 40 µg.

The same procedure was repeated for drug loaded microspheres for sample preparation. The analysis was carried out using six samples which were analyzed in six replicates. The sample absorbance of the atenolol was compared with the standard using the calibration curve parameters. The concentration of active drug is calculated by interpolation method. The determined concentration was subjected to statistical analysis to predict the reliability of the method. The relative standard deviation is determined for each determination and it is considered to be acceptable if it falls below 2%.

The validated analytical method can be carried forward for the routine analysis of drugs loaded in tablets and polymer based dosage forms for the simultaneous qualitative and quantitative analysis.

Table 4: Accuracy test results.

Spiked %	Amount spiked	Amount recovered	% Recovery	Mean	STD	% RSD
50	25	24.79	99.16	99.596	0.4350	0.4367
80	40	39.84	99.60			
120	60	60.02	100.03			

Table 5. Results obtained from Precision studies.

Sample	Assay	%	Mean	STD	% RSD
Atenolol API	49.82 mg	99.64	99.85	0.1684	0.1686
Atenolol microspheres	49.98 mg	99.96			
Atenolol tablet (T_1)	49.96 mg	99.92			
Atenolol tablet(T_2)	50.01 mg	100.02			

Table 6: Results obtained from Intermediate Precision studies.

Tests	Mean	STD	%RSD
Intraday Analysis	99.65	0.3112	0.3122
Interday Analysis	99.92	0.5798	0.5802
Inter-analyst	99.98	0.5020	0.5021
Intra-analyst	99.27	0.3342	0.3366

RESULTS AND DISCUSSION

The method is based in the measurement of absorption of radiation at absorption band C–O stretch of ether (Ar-O-R) centred at 1242 cm^{-1}, which is typically in the range 1274.95 – 1195.87 cm^{-1} because those absorption bonds did not occur in excipients present in atenolol loaded microspheres and its tablet pharmaceutical preparation. The *in vitro* wash off test revaled that 80% of the microspheres adhered to the intestinal mucosa with good stability. The proposed method was validated as per ICH guidelines. The calibration curve was obtained for a series of concentration in the range of 0.1 to 1.0 % w/w and it was found to be linear. The linear regression equation was y = 0.0371x + 0.7633 with correlation coefficient value 0.9812 which were within the acceptance criteria. Specificity was studied for the examination of various excipients present in the tablet dosage form of atenolol. The results indicated that they did not interfere in the assay.

The precision was measured in terms of repeatability, which was determined by sufficient number of sample within the day (intraday) and next consequent three days for inter day precision. For each cases intra-day, interday, interanalyst and intra-analyst % RSD was calculated and was found to be 0.3122 0.5802, 0.5021, 0.3366 and 0.1783 respectively. These values were well within the acceptance limit ± 2.0%. This proves that the precision of the method was sensitive, satisfactory, and good. Accuracy found out by recovery study from prepared samples (three replicates) with standard solution. Recovery was carried out standard addition method at three different levels which is 50%, 100% and 150%.

The % recovery was calculated and was found to be 99.16 to 100.03. This was found to be well within the acceptance criteria of 98 – 102%. This showed that the recovery of atenolol by proposed method was satisfactory. Ruggedness, intermediate precision performed by using six replicate preparations of

standard atenolol which were prepared and analyzed by different analysts or two different days over a period of one week, the % RSD was calculated and it was found to be 0.5020, which was well within the acceptable criteria NMT 2.0%. It was concluded that the analytical technique showed to be rugged and showed good repeatability.

The validated method was applied for the assay of atenolol microspheres, commercial tablets of Atenolol (T_1 and T_2 50mg). The % assay was calculated from standard calibration curve. The assay results for Atenolol API, Atenolol microspheres, its tablet formulations T_1 and T_2 are 99.64 ± 0.10, 99.92 ± 0.24, 99.92± 0.36 and 100.01± 0.24 respectively. It presented good agreement within the labeled content. Thus, the method developed in the present investigation is simple, sensitive, accurate, rugged, rapid and precise. Hence, the developed method can be successfully applied for the estimation of atenolol in bulk and tablet dosage forms.

There were no reported ATR-FTIR methods for the estimation of atenolol loaded polymer based formulations. The HPLC (Elkady *et al.,* 2020; Ekaterina *et al.,* 2021; Vaikosen *et al.,* 2020), and Spectrophotometric (Vaikosen *et al.,* 2020) utilized expensive, hazardous and toxic solvents. Moreover the reported conventional analytical methods were less accurate and non- reproducible (Fadnis and Agarwal 2015). Hence the rapid analysis time with a less technical expertise keeps this proposed method on a high when compared with the reported methods.

CONCLUSIONS

Fourier Transform Infrared Spectroscopy is widely recognized technique has been used to identify several compounds, such as pharmaceuticals, cosmetics and foods, but requires expensive equipments and mathematical pretreatments. The quantization of Atenolol through infrared spectroscopy accomplishes with the requirements of specificity, precision, and accuracy in order to be used as a method for the quality control of polymer based dosage forms and in pharmaceuticals.

The method has been evaluated for linearity, accuracy, precision and ruggedness in order to ascertain the suitability of the analytical method. The method was applied to marketed samples. It has been proved that the method was selective and linear between the concentrations 10 - 70 µg and correlation coefficient value was found to be 0.9989. The developed method was found to be precise as the % RSD value for repeatability and intermediate precision were 0.1783 and 0.1688, which were less than 2.0%. The percentage recovery was found to be 99.76 ± 0.185. The method is very simple, rapid and economic nature, which makes it especially suitable for routine quality control work. We conclude that

Our work was aimed to focus on the implementation of sustainable chemistry by replacing conventional analytical methods developed with the aid of hazardous solvents with our no-solvent green technique without hindering method performance. The future scope of our work is to perform *in vitro* and in vivo real time dissolution analysis to predict the pharmacokinetic behavior of the drug.

Conflict of Interest. The authors don't have any conflict of interest.

Contributions. Author S Ruby designed the research work and drafted the data collection strategy. Annapoorani Arjunan performed the analysis and interpretation of results. Author Kumar M helped in Drafting and Critical revision of the article. Author Bhuvaneswari R helped in the drafting and English correction.

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