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Overview of the Analysis Methods of Atenolol in Pharmaceutical Preparations and Biological Matrices During 2000 - 2020

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Abstract

Atenolol is one of the most widely used beta-blocker antihypertensive drugs. Therefore, atenolol levels' determination is essential for quality control, either as raw material, in pharmaceutical preparations, biological fluids, or mixtures. Information search on atenolol level determination was conducted through Google Scholar with the keywords "atenolol," "determination," "pharmaceutical preparation," "biological matrix," "mixture." The results showed that atenolol levels could be determined by titrimetric, spectrophotometric, high-performance liquid chromatography, gas chromatography, and electrometry methods. Therefore, it can be concluded that atenolol in the form of raw material can be determined by titrimetric method, spectrophotometry, high-performance liquid chromatography, gas chromatography, and electrometry. Atenolol in pharmaceutical dosage forms can be determined by spectrophotometric methods, high-performance liquid chromatography, gas chromatography, and electrometry. Atenolol in biological fluids can be determined by the high-performance liquid chromatography method. In contrast, atenolol in mixtures with other substances can be determined using the high-performance liquid chromatography method.

Keywords: Atenolol, assay, pharmaceutical preparations, biological matrix, mixtures

1. Introduction

Most of the results of randomized controlled trials (RCTs) on beta-blockers as initial therapy for hypertension carry a high risk of bias. Atenolol is the most widely used beta-blocker. Current evidence suggests that starting hypertension treatment with beta-blockers leads to modest reductions in cardiovascular disease (CVD) and little or no effect on mortality. The impact of these beta-blockers is lower than other antihypertensive drugs.[1] Atenolol contains not less than 98.0 % and not more than 102.0 %, $C_{14}H_{22}N_2O_3$, calculated against the dry matter. Atenolol is a white or almost white powder, odorless. Melting temperature ranges from 146 - 148 ^oC, crystallizes from ethyl acetate. Atenolol is soluble in methanol; relatively difficult to dissolve in ethanol; difficult to dissolve in water and isopropanol. The chemical name for atenolol is 2- [p- [2-Hydroxy-3-(isopropylamine) propoxy] phenyl] acetamide, molecular weight 266.34, and its structure, as shown in Figure 1.[2]

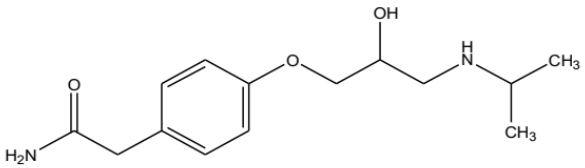

Figure 1: Structure of atenolol

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Several methods have been reported related to atenolol analysis in pure compounds and pharmaceutical preparations, and biological fluids. To date, many analytical methods have been developed for the quantitative determination of atenolol levels.

2. Research Methods

2.1 Data collection

In compiling this article, the technique used is a literature study by finding sources or literature in official books and international journals in the last 20 years (2000-2020). The keywords used for data search were "atenolol analysis," "pharmaceutical preparations," and "biological matrix." This review article's primary reference searches are through trusted websites such as Science Direct, NCBI, ResearchGate, Google Scholar, and other published and trustworthy journals.

3. Atenolol Analysis Methods

3.1 Titrimetric method

A titrimetric method, using chloramine-T (CAT), has been developed for the determination of atenolol (ATN) in bulk drugs and tablets. The titrimetric process involves the oxidation of the drug with an excess of CAT measured in an acid medium, followed by the determination of residual oxidants by iodometric back titration. Titrimetry can be applied in the 3-20 mg range. A selection of experimental conditions, which provide maximum accuracy, precision, and sensitivity, is discussed. Common excipients and additives found in tablet preparations do not interfere. The proposed method is successfully applied for the determination of drugs in tablets. Recovery ranged from 96.43 to 103.74 %. Parallel decisions further established the technique's utility and accuracy by the official Indian Pharmacopoeia method and recovery studies. The reaction scheme between atenolol and chloramine-T is shown in Figure 2.[3]

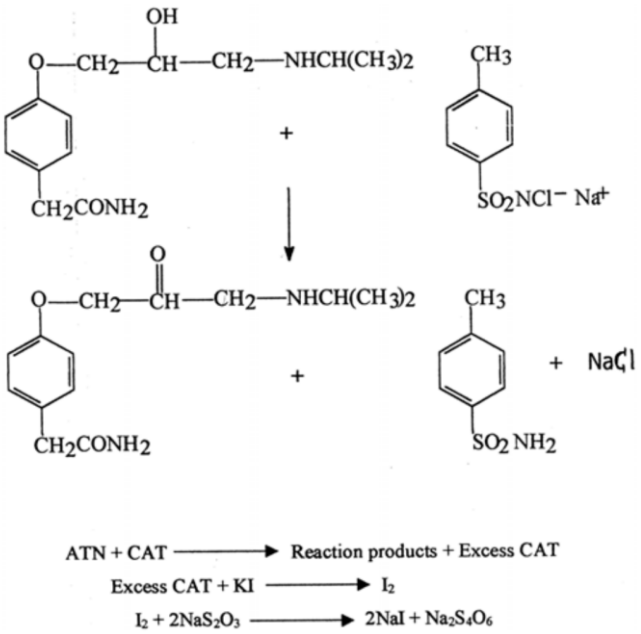

Figure 2: Schematic reaction of atenolol with chloramine-T

3.2 Visible spectrophotometric method

Two spectrophotometric methods, using two dyes, methanyl yellow and indigo carmine, have been developed to determine atenolol (ATN) in bulk and tablet drugs. In the spectrophotometric method, ATN is oxidized by a known excess chloramine-T (CAT) in an acidic medium followed by the determination of the unreacted oxidant by reacting with a fixed amount of methanyl yellow (Method A) or indigo carmine (Method B) and

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measuring the increase in absorbance at 530 or 610 nm. Beer's law is adhered to over a range of spectrophotometry concentrations, 1-12 µg/mL (Method A), and 2.5 - 20.0 µg/mL (Method B). The molar absorptivity values calculated from Beer's law data were 1.19×10^4 L/mol/cm (Method A) and 6.65×10^3 L/mol/cm (Method B), and the corresponding Sandell sensitivity values were 0.022 and 0.040 µg/cm^2. Common excipients and additives found in tablet preparations do not interfere. The proposed method is successfully applied for the determination of drugs in tablets. Recovery ranged from 96.43 to 103.74 %. Parallel determinations further established the method's utility and accuracy by the official Indian Pharmacopoeia method and recovery studies.[3]

A simple kinetic procedure is described for the determination of atenolol in its dosage form. This procedure is based on coupling the drug with 4-chloro-7-nitrobenzo-2-oxa-1,3-diazole in a borate buffer pH 8 at boiling temperature for a fixed time of 30 minutes and then measuring the absorbance of the solution. the reaction product at 460 nm. The absorbance-concentration plots were square in the range of 5–50 µg/mL with a minimum detection limit of 1.3 µg (4.9×10^{-6} M). Determination of atenolol using the fixed concentration and rate constant method is also feasible with the obtained calibration equations, but the fixed time method has proven to be more applicable. The procedure was successfully applied to commercial tablets, and statistical analysis showed that the results were better than those obtained by official methods. Possible interruptions to the introduction of several co-formulated drugs and the effects of sensitizers and surfactants on the proposed method's performance were also studied.[4]

A simple analytical method for calculating atenolol in pharmaceutical formulations by diffuse reflectance spectroscopy is described. This method is based on the reaction, on the filter paper's surface, between the drug and p-chloranil to produce a colored compound. The best reaction conditions were obtained with 20 µL of atenolol solution and 20 µL p-chloranil. All reflectance measurements were carried out at 550 nm, and the linear range was from 1.13×10^{-2} to 7.88×10^{-2} mol/L ($r = 0.9992$). The detection limit is 2.80×10^{-3} mol/L. The proposed method was successfully applied to the analysis of various commercial brands of pharmaceutical formulations. The results obtained with the proposed method were by those obtained using the British Pharmacopoeia method.[5]

Three fast, selective, and sensitive spectrophotometric methods have been proposed for the quantitative determination of atenolol (ATN) in pure form and pharmaceutical formulations. The method is based on the complexation reaction of ATN charge transfer as an n-electron donor with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), 2,4-dinitrophenol (DNP), and 2,4,6 -trinitrophenol (picric acid; PA) as a π acceptor that produces radical anion species that are very colorful. Colored products were quantified spectrophotometrically at 590 nm with DDQ (method A) and 420 nm with DNP (method B) and PA (method C). Under optimized experimental conditions, Beer's law was adhered to over a concentration range of 3 - 48, 2 - 24, and 1.5 - 18 µg/mL of ATN for method A, method B, and method C. Molar absorptivity, Sandell sensitivity, limits of detection and quantification were also reported. The effect of reaction media, reaction time, and reagent concentration on the sensitivity and stability of the complexes formed has been investigated. The proposed method has been successfully applied to ATN's determination in pure and commercial tablets with good accuracy and precision. Statistical comparisons of the results were performed using Student's t-test and F-ratio at the 95% confidence level. The results showed no significant difference between the reference and the proposed method in accuracy and precision. Furthermore, the accuracy and reliability of the method were confirmed by recovery studies via standard addition techniques.[6]

A simple, fast, accurate, and precise spectrophotometric method is proposed to determine atenolol both in pure form and in pharmaceutical formulations. This method is based on the oxidation of atenolol with chromate in 1 N H_2SO_4 acid medium. The remaining amount of oxidizing agent is then reacted with indigo carmine dye in the oxalate as a catalyst, increasing dye absorbance, which is proportional to the determinant amount of atenolol, which is then measured at 610 nm. Beer's law is adhered to in a concentration range of 30-1500 µg/25 mL with a molar absorptivity of 0.73×10^4 L/mol/cm, a Sandell sensitivity index of 0.364 µg/cm^2, and a relative standard deviation of ± 0.263 to ± 0.376 % depending on the concentration level. The limits of detection (LOD) and limits of quantification (LOQ) were 0.3259 and 1.0863 µg/mL, respectively. The

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proposed method has been successfully applied to the determination of atenolol in pure and pharmaceutical preparations.[7]

A simple and fast spectrophotometric method has been developed for the determination of atenolol in bulk and tablets. This method forms a yellow ion-pair complex between Atenolol and Bromocresol green in 1, 2-dichloroethane medium. The maximum absorption of the complex was found to be 414 nm. Different parameters affecting the reaction are optimized, such as solvent effect, time, reagent concentration, correlation ratio, etc. The complex formed was measured spectrophotometrically at maximum absorption. The linearity range was 2.66–26.63 µg/mL. The regression analysis showed a good correlation coefficient of R^2 = 0.9999. The limits of detection (LOD) and limits of quantification (LOQ) were 0.22 µg/mL and 0.66 µg/mL. The mean recovery percentage was found (97.23-101.53) % for atenolol. The method was successfully applied to atenolol's determination in pharmaceutical tablet formulations in six Syrian pharmaceutical brands: (Tenormin MPI 100, Tenormin MPI 50, Hypoten UNIPHARMA 100, Hypoten UNIPHARMA 50, Normoten BARAKAT 100, and Normoten BARAKAT 50). The proposed method is simple, direct, sensitive, and does not require any extraction process. Thus, this method can be directly applied to quality control and routine analysis.[8]

3.3 Ultraviolet spectrophotometric method

A fast and sensitive UV spectrophotometric method for routine control of atenolol in tablets was developed. The UV spectrophotometric method was carried out at 226 nm, and the samples were prepared with sodium acetate solution. Linearity shows a correlation coefficient of 0.9986. The proposed way is simple, fast, precise, accurate, and sensitive, and can be used for routine quality control in pharmaceuticals.[9]

3.4 Potentiometric method

An ion-selective membrane electrode for the drug atenolol, based on incorporating the associated atenolol phosphotungstate ion in the PVC coating membrane and acetophenone as a plasticizer, was constructed. The effect of membrane composition, temperature, electrode conditioning time, pH of the test solution, and foreign ions on the electrode performance was investigated. The inversion and selectivity, and the response time of the electrodes have been studied. The drug electrode showed a Nernstain response in the $5 \times 10^{-7} - 1 \times 10^{-2}$ M concentration range and was found to be highly selective, precise, and usable in the pH range 3-6. This sensor shows fast response time (approx. 8 seconds), low detection limit (1×10^{-7} M), long service life (> 2 months, 2 hours a day), and good stability. The standard electrode potentials, E°, are determined at 10, 20, 30, 40, and 50 °C and are used to calculate the isothermal temperature coefficient (dE°/dT) of the electrodes. Temperatures higher than 50 °C significantly affect the electrode performance. The electrode has been successfully applied to atenolol determination both in pure and pharmaceutical preparations using potentiometric resolution.[10]

3.5 High-performance liquid chromatography method

The rapid and sensitive RP-HPLC method with UV detection for simple control of atenolol in tablets was developed. Chromatography was performed with a mobile phase containing a 10 mM mixture of ammonium acetate buffer (pH 7.0) and acetonitrile (80:20 v/v). The sample was injected onto a Purospher RP-18 column (250 mm x 4.6 mm, 5 µm). The flow rate is 0.8 mL/min. Samples were detected at 275 nm. The assay is linear in the range of 125 to 375 µg/mL with a very significant correlation coefficient (r = 0.9999) for this method. The accuracy is 99.80 %. The proposed way is simple, fast, precise, accurate, and sensitive, and can be used for routine quality control in pharmaceuticals.[9]

The use of bloodstain collection cards was investigated to obtain small-volume samples to measure therapeutic drugs to assess treatment adherence. The high-resolution liquid chromatography-mass spectrometry method (LC-HRMS), based on accurate mass measurements to fill target analyte ratios, was used to ascertain the specificity of atenolol in dry blood spot (DBS) samples. Working methods are developed and validated. For sample preparation, DBS whole blood spiked with the analyte was used to produce 30 µL of blood spot on the specimen collection card. The 5 mm discs were cut from dried blood stains and extracted using methanol: water (60:40, v/v) containing the internal standard, atenolol. The extract was vortexed, sonicated, and then centrifuged. Gradient chromatographic elution was achieved using an Ascentis Express C18 column 100 mm x 2.1 mm, a mobile phase flow rate of 0.2 mL/min, and a column oven temperature at 30 °C. The detection of MS was carried out in electrospray positive ion mode for target ions at m/z accurate masses of 267.1703 for atenolol and 274.2143 for IS. The efficiency of drug extraction from the spike blood spots was 96 ± 5 %, and

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the drug was stable in DBS for at least ten weeks. The LC-HRMS method developed is linear in the tested calibration range of 25-1500 ng/mL. The validation shows the accuracy (relative error) and precision (coefficient of variation) values are within predetermined limits of ≤ 15% at all concentrations with quantification limits. 25 ng/mL. Factors that could potentially influence drug quantification measures such as matrix effect, blood volume used on collection cards, and the impact of different sampling cards were investigated. The developed LC-HRMS method was applied to the blood spots on a sampling card taken from healthy adult volunteers who were previously given 50 mg of atenolol tablets. A DBS concentration-time profile was obtained for atenolol. Blood sample for analysis requiring only a micro-volume (30 µL), the developed DBS-based test can assess patient adherence to atenolol.[11]

3.6 Gas chromatography method

Analytical procedures were developed and validated for the determination of atenolol in human plasma. Atenolol and metoprolol (internal standard) were extracted from human plasma with a mixture of chloroform and butanol at alkaline pH. The extract was derivatized with N-methyl-N-(trimethylsilyl) trifluoroacetamide and analyzed by GC-MS. Linear calibration curve over a concentration range of 15-250 ng/mL. The intra- and inter-day precision values for atenolol in human plasma are less than 7.4, and the accuracy (relative error) is better than 6.4%. Atenolol recovery from human plasma reached an average of 90.46 %. The limits for detection (LOD) and quantitation (LOQ) of atenolol were 5.0 and 15 ng/mL. This method was successfully applied to six hypertensive patients who had been given 50 mg of atenolol oral tablet.[12]

3.7 Flow injection analysis method

A simple, fast and sensitive method for analyzing atenolol in pure and pharmaceutical preparations as an alternative analytical procedure was developed with continuous flow injection analysis via turbidimetry ($T180^{o}$) and the effect of scattered light two opposite positions ($2N90^{o}$). This method is based on a white precipitate formation for ion-pair compounds by phosphomolybdic acid with atenolol in an aqueous medium. The deposition is measured through the incident light's attenuation, and the scattering of the incident light in two opposite directions, i.e., the $+90^{o}$ angle and the -90^{o} angle, are measured. Chemical and physical parameters are investigated. Atenolol linearity ranges from (0.1-11) mmol/L, with a correlation coefficient of r = 0.9938, lower limit of detection (LOD) 0.05 mmol/L (3SB) (S/N = 3) for n = 13 and relative standard deviation for 7 mmol/L of Atenolol solution was lower than 3 % (n = 7). The method has been applied successfully for the determination of atenolol in three pharmaceutical drugs. Comparisons were made between the newly developed analytical method and the classical method (UV spectrophotometry at a wavelength of 274 nm) analysis using the standard addition method through the t-test. It shows no significant difference at α = 0.05 (95 % confidence) between the two methods. Therefore, the newly developed method can be accepted as an alternative method for Atenolol analysis, apart from comparing the official values and the calculated values for the two methods.[13]

3.8 Electrochemical method

Graphite-polyurethane composites were evaluated as alternative electrodes in the determination of atenolol (ATN) in pharmaceutical formulations. Using the differential pulse voltammetry (DPV) procedure, linear analytical curves were observed in the range 4-100 µmol/L with LOD = 3.16 µmol/L, without the need for surface updating between successive processes, with a gain between 95.5 and 108 %. Other antihypertensive drug disorders were observed, but not from the components of ordinary tablets. The results of the proposed method agree with HPLC, with a 95 % confidence level.[14]

Indium tin oxide (ITO) modified gold nanoparticle electrodes have been used for the determination of atenolol (ATN) in drug and urine formulations by differential pulse voltammetry (DPV). Compared to bare ITO electrodes, the nanogold-modified electrodes showed a less positive shift of the oxidation potential and a marked increase in ATN's current response. Linear calibration curves were obtained in the range of 0.5 µM to 1.0 mM in a 1.0 M phosphate buffer solution (pH 7.2) with a correlation coefficient of 0.9965. The detection limit for atenolol in standard solutions (pH 7.2) is estimated at 0.13 µM. The recovery rate ranges from 95.7 % to 105.2 %. This method's practical analytic usefulness is illustrated by the quantitative determination of ATN in several commercially available pharmaceutical and urine formulations, without pretreatment.[15]

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C60 modified glass carbon electrodes have exhibited excellent electrocatalytic activity against atenolol oxidation for their voltammetric determination at physiological pH. The overpotential reduction associated with atenolol oxidation indicates the electrocatalytic properties of the electrodes. Atenolol determination was carried out at pH 7.2 at the modified electrode, and a well-defined oxidation peak was observed to be 1040 mV versus the Ag / AgCl electrode for atenolol oxidation. A calibration plot with good co-linearity with a correlation coefficient of 0.997 is obtained in the atenolol concentration range of 0.25–1.5 mM, and the method sensitivity was found to be 8.58 µA/mM. The detection limit was found to be 0.16 mM. The method developed can be applied for the determination of atenolol in pharmaceutical preparations and urine samples. The modified electrode showed good surface coverage (~85 %) with C60.[16]

3.9 Electrophoresis method

The capillary zone electrophoresis method is optimized for the determination of β-insulating atenolol in plasma. The separation was carried out in uncoated silica capillaries measuring 58.5 cm (sufficient length 50 cm) x 75 µm ID, and detection was at 194 nm. The buffer (concentration and pH) effect, injection time, applied voltage, and plasma cleaning procedure were studied. Atenolol determination was achieved in less than 3 minutes, using an electrolyte of 50 mM H_3BO_3 - 50 mM $Na_2B_4O_7$ (50:50, v/v) pH 9, injected hydrodynamically for 4 seconds at 50 mbar, and applying a voltage of +25 kV. This method was used to determine atenolol in the plasma of nine hypertensive patients (male and female, aged 39 to 73 years). The atenolol concentrations found varied from 30 to 585 ng/mL.[17]

4. Methods of Analysis for Atenolol in Mixtures

4.1 A mixture of atenolol and amlodipine

A new simple, precise, fast, and selective thin layer chromatography (HPTLC) method has been developed for the simultaneous determination of atenolol (ATL) and amlodipine (AMLO) in tablets. Using methylene chloride: methanol: ammonia solution (25 % NH) (8.8: 1.3: 0.1; v/v) as the mobile phase and Merck HPTLC plates (0.2 mm thickness) coated with silica gel $60F_{254}$ on aluminum sheets as the stationary phase. The detection was carried out densitometry using a UV detector at 230 nm. The retention factors for ATL and AMLO were 0.33 and 0.75, respectively. Linear calibration curves in the range 10-500 µg ml for both. The ATL and AMLO tests were 49.87 mg per tablet (relative standard deviation (RSD, 1.3 %) and 4.90 mg per tablet (RSD, 1.38 %) for the brand I, and 49.27 mg per tablet. (RSD, 1.12 %) and 4.98 mg per tablet (RSD, 1.42 %) for brand II, respectively. The recovery percentages of ATL and AMLO for brands I and II were 99.06 and 99.30 %, and 99.27 and 99.15 %, respectively.[18]

A simple, fast, and precise method was developed for the simultaneous quantitative determination of atenolol and amlodipine in combined pharmaceutical dosage forms. This method is based on High-Performance Liquid Chromatography (HPLC) on reverse phase column, shim-pack CLC, ODS (C18), 4.6 mm × 25 cm & 0.5 µm. Using a mobile phase buffered ammonium acetate (pH adjusted to 4.5 ± 0.05 with glacial acetic acid), acetonitrile, and methanol (35:30:35 v/v). The buffers used in the mobile phase contain ammonium acetate in double-distilled water. The chromatographic conditions were a flow rate of 1.5 mL/min, a column temperature of 40 ˚C, and a detector wavelength of 237 nm. Both drugs resolved well in the stationary, and retention times were about 1.5 minutes for atenolol and 3.4 minutes for amlodipine. The method is validated and proven to be linear for atenolol and amlodipine. The correlation coefficients for atenolol and amlodipine were 0.999963 and 0.999979, respectively. The relative standard deviation for the six repeat measurements in two sets of each drug in tablets is always less than 2 %, and the mean % error for active recovery is not more than ± 1.5 %. The method is validated for accuracy and accuracy. The proposed method is successfully applied to pharmaceutical dosage forms containing the drug above combinations without any interference by excipients.[19]

This study describes second-derived spectrophotometry for atenolol and amlodipine simultaneous determination in pure form and commercial formulations. The method is simple, accurate, precise, and economical. The zero-cross point technique is used for the analysis of drugs in combined formulations. The methods were linear in the concentration ranges of 5.0-50.0 µg/mL atenolol at 251 nm and 5.0–45.0 µg/mL amlodipine at 264 nm. The proposed method has been successfully applied to determine atenolol and

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amlodipine in combined doses and separate doses. The results were obtained according to standard methods.[20]

4.2 A mixture of atenolol and bisoprolol

A method based on gas chromatography-mass spectrometry (GC-MS) is described to determine bisoprolol and atenolol in human bone. After adding lobivolol as an internal standard, the powder samples were incubated in acetonitrile for 1 hour under ultrasound. After adjusting the samples' pH to 6, they were centrifuged, and the supernatant was subjected to solid-phase extraction. Elution is achieved using 3 mL 2 % ammonium hydroxide in an 80:20 solution of dichloromethane: isopropanol. The eluted sample was evaporated and derivatized. Chromatography was performed on the capillary column of fused silica, and the analyte was determined in the ion monitoring mode (SIM) selected. The test is validated in the range of 0.1-0.3 ng/mg (depending on the drug) to 150 ng/mg. The mean absolute recovery is 60 % for bisoprolol and 106 % for atenolol, 69 % matrix effect for bisoprolol, and 70 % for atenolol, and the process efficiency was 41 % for bisoprolol and 80 % for atenolol. Intra and inter-assay accuracy values are always better than 12 %. The validated method was then applied to bone samples from two real forensic cases. The blood toxicological analysis was complimentary for atenolol in the first case (0.65 µg/mL) and bisoprolol in the second (0.06 µg/mL). Atenolol was found in bone samples from points corresponding to an estimated 148 ng/mg concentration, and bisoprolol was found at 8 ng/mg.[21]

4.3 A mixture of atenolol and carvedilol

This study aimed to study the effect of different parameters on the fluorescence intensity of atenolol (ATE) and carvedilol (CAR) and optimization by response surface methodology (RSM) to provide a simple analytical method for quantification of ATE and CAR in pharmaceutical formulations. Various parameters that affect the fluorescence intensity, namely the concentration of sodium dodecyl sulfate (SDS), pH, and volume fraction of the solvent, were optimized using RSM. Then, the optimized parameters were applied to validate the fluorimetric determination method of β-blockers in their pharmaceutical preparations. It was found that under optimum conditions for the determination of ATE, this method provides a linear range between 130 and 750 ng/mL with a correlation coefficient (r) of 0.9996. The limits of detection and limits of quantification (LOD and LOQ) were 40 ng/mL and 130 ng/mL, respectively. Also, it was observed that the method linearity for the determination of CAR was between 0.37 to 4.0 ng/mL, and the LOD and LOQ methods were 0.11 ng/mL and 0.37 ng/mL, respectively. An accurate, sensitive, and reliable spectrofluorimetric method was developed and used successfully to determine (ATE) and carvedilol (CAR) in their pharmaceutical preparations.[22]

4.4 A mixture of atenolol and chlorthalidone

The resolution of a binary combination of atenolol (ATE) and chlorthalidone (CTD) with minimum sample pretreatment and without analyte separation has been achieved, using a new and rapid method based on partial least squares (PLS1) analysis of UV spectral data. Simultaneous determination of both analytes is possible by processing PLS1 of absorbance samples between 255 and 300 nm for ATE and evaluation of absorbance in the 253-268 nm region for CTD. The mean recoveries for synthetic samples were 100.3 ± 1.0 % and 100.7 ± 0.7 % for ATE and CTD. The application of the proposed method for the two commercial tablet preparations in the content uniformity test showed that they both contained 103.5 ± 0.8 % and 104.9 ± 1.8 % ATE, respectively, as well as 103.4 ± 1.2 % and 104.5 ± 2.2 % CTD. This method also elaborates the drug dissolution profile in two commercially combined formulation products by simultaneously determining the two drugs during the dissolution test. At the 45 min dissolution time specified by USP XXIV, both pharmaceutical formulations met the test.[23]

The high-performance liquid chromatography method has been optimized and validated to determine atenolol and chlorthalidone (CT) in breast milk. Milk samples were extracted and purified using ACN and phosphoric acid for protein deposition, followed by removing ACN and milk fat by extraction with methylene chloride. After the extraction procedure, the model was applied to the cyanide column using a mobile phase consisting of ACN/water (35:65 v/v) and built at a pH of 4.0 with a flow rate of 1.0 mL/min. The quantity was achieved by UV detection at 225 nm using guaifenesin as the internal standard. The effectiveness of protein precipitation and cleaning procedures was investigated. This method is validated in the range of 0.3-20 µg/mL for atenolol and 0.25–5 µg/mL for CT.[24]

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A simple, sensitive, selective, and fast liquid chromatography method - tandem mass spectrometry developed and validated for the simultaneous separation and quantification of atenolol and chlorthalidone in human plasma using metoprolol and hydrochlorothiazide as internal standards. After solid-phase extraction, the analytes were separated by the isocratic mobile phase in the reverse phase C column and analyzed by MS in the dual reaction monitoring mode (atenolol in positive and chlorthalidone in negative ion mode). The calculation limits for this method are 10 and 15 ng/mL, and the linear dynamic ranges are generally 10–2,050 ng/mL and 15–3,035 ng/mL for atenolol and chlorthalidone, respectively.[25]

The capillary zone electrophoresis (CZE) method for the simultaneous determination of the b-blocking drugs atenolol and chlorthalidone in pharmaceutical formulations has been developed. The CZE separation was carried out under the following conditions: capillary temperature, 25 ^{o}C; applied voltage, 25 kV; 20 mM H_3PO_4 - NaOH running buffer (pH 9.0) detection wavelength, 198 nm. Phenobarbital is used as an internal standard. This method is validated and shows not only good precision and accuracy but also good robustness. This method has been applied successfully for the simultaneous determination of atenolol and chlorthalidone in pharmaceutical tablets.[26]

A simple, sensitive, and rapid chromatography method was developed and validated for the simultaneous quantification of atenolol and chlorthalidone in human plasma using hydrochlorothiazide as the internal standard (IS). This method uses protein precipitation with acetonitrile as the only sample preparation involved before the HPLC-reverse phase. The analyte was chromatographed on a Shim-pack cyanopropyl column with isocratic elution with 10 mM KH_2PO_4 (pH 6.0) - methanol (70:30, v/v) at room temperature with a flow rate of 1 mL/min and UV detection at 225 nm. The chromatography processing time is less than 10 minutes for the mixture. The calibration curve is linear in the range of 0.1-10 µg/mL. This method is validated in accuracy, precision, complete recovery, freeze-thaw stability, bench-top stability, and re-injection reproducibility. Accuracy and precision within and between days were found to be within acceptable limits of < 15 %. The analyte is stable after three freeze-thaw cycles (deviation < 15 %). The method explicitly proposed for atenolol and chlorthalidone's simultaneous determination in human plasma where there is no interference from endogenous biological substances.[27]

4.5 A mixture of atenolol and nifedipine

A new method, simple, fast reverse-phase high-performance chromatography (RP-HPLC), has been developed and validated to determine Atenolol and Nifedipine in tablet dosage forms. Isocratic chromatography was set on a Hyperthermosil column (250 x 4.6 mm, 5 µ) with a mobile phase consisting of a buffer and acetonitrile (30:70) with a flow rate 1 mL/minute with a PDA detector at 284 nm. The total running time is 10 minutes. The retention times for Atenolol and Nifedipine were found to be 2.11 and 4.58 minutes, respectively. Chromatographic parameters are validated according to ICH guidelines and can be applied for routine quantitative analysis of drugs in combined tablet dosage forms.[28]

4.6 A mixture of atenolol and propanolol

A simple, fast, sensitive, inexpensive, and accurate oxidative method for two beta-blockers in pharmaceutical dosage form was developed and evaluated. The method used was the atenolol and propanolol oxidimetric treatment with 2 x 10^{-3} mol/L $KMnO_4$ in an alkaline medium (pH ≥ 9). The oxidized complexes' scanning spectrum showed typical absorption at 460, 520, 540, and 570 nm. An array of observed color changes - from purple to blue; blue becomes bluish-green and yellow. The colors are exhibited due to the metal-ligand charge transfer. Indirect spectrophotometric determination of atenolol and propranolol was carried out after 12-15 minutes at 520 nm. The optimum test conditions showed linearity ranging from 0 - 15.0 µg/mL for both beta-blockers (R = 0.9997 - 0.9999). The molar absorptivity values were 4.79 x 10^3 and 4.88 x 10^3 L/mol/cm for atenolol and propranolol, respectively, with Sandell's corresponding sensitivity values of 0.056 and 0.053 µg/cm^2. The limits of detection and quantification were 0.50 and 1.65 µg / mL for atenolol and 0.58 and 1.91 µg/mL for propranolol, respectively, whereas the relative standard deviation for intra- and inter-day precision was < 2.0 %. The applicability, accuracy, and reliability of this method are demonstrated by the determination of atenolol and propranolol in the tablet formulation. Recovery studies ranged from 93.33 - 103.00 % for beta-blockers, and the number in brands was from 97.53 ± 2.68 to 100.84 ± 1.82 %.[29]

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4.7 A mixture of atenolol and trimetazidine

A simple RP-HPLC-PDA method for determining atenolol (ATN) and trimetazidine (TMZ) in tablets and human urine has been developed. The analyte was separated on a Caltrex BI column (125 × 4.0 mm, 5 μm) with a mobile phase of 25 mM potassium dihydrogen phosphate pH 3,3, methanol, and acetonitrile. The PDA detector was operated at 210 nm for TMZ and 225 nm for ATN and a flow rate of 1.0 mL/min. Linearity was obtained in the concentration range (1.0-100 μg/mL) for both analytes in standard solutions. The method was successfully applied for the determination of target analytes in their pharmaceutical tablets. Excellent linearity was also obtained over the concentration range (0.25-25 -25 g/mL) and (0.5-25 μg/mL) in human urine for TMZ and ATN. Simple liquid-liquid extraction is applied to clean urine samples, and the gradient method is used for chromatographic separation. The lower limits of quantitation (LOQ) were 0.99 and 0.60 g/mL for ATN and TMZ, respectively. The limitations of detection (LOD) were 0.30 and 0.18 μg/mL for ATN and TMZ, respectively. Inter- and intraday precision and accuracy for ATN were within ± 1.89 % in the pure form and within ± 2.85 % in the urine sample. Inter-and-day precision and accuracy for TMZ are within ± 3.99% in a refined way and within ± 3.19% in urine samples.[30]

4.8 A mixture of atenolol, amiloride hydrochloride, and chlorthalidone

Three methods are presented for the simultaneous determination of atenolol (AT), amiloride hydrochloride (AM), and chlorthalidone (CD). The high-performance liquid chromatography (HPLC) method depends on separating each drug in the reverse phase, RP 18 column. Elution is carried out with a mobile phase consisting of acetonitrile - 5 mM heptane sulfonic acid sodium salt (20:80, v/v, pH 4.4). The quantity was achieved by UV detection at 274 nm based on peak area. Other two-chemometric-assisted spectrophotometric methods applied were principal component regression (PCR) and partial least squares (PLS-1). This approach is successfully applied to measure each drug in a mixture using information included in the appropriate solution's absorption spectrum in the range 240-290 nm with an interval of Dk = 0.2 nm. The three methods were successfully applied to pharmaceutical formulations (tablets), and the results were compared with each other.[31]

4.9 A mixture of atenolol, hydrochlorothiazide, and chlorthalidone

Atenolol is a selective beta inhibitor that can be used alone or in combination with hydrochlorothiazide or chlorthalidone to treat hypertension and prevent heart attacks. This work aims to improve the modern, easy, accurate, and selective liquid chromatography (RP-HPLC) method for the determination of these drugs in the presence of degradation products. This method can be used as an analytical gadget in quality control laboratories for routine checks. In this method, the separation is carried out through an Inertsil® ODS-3V C18 column (250 mm x 4.6 mm, 5 µm). The mobile phase used is a 25 mM aqueous potassium dihydrogen orthophosphate solution adjusted to pH 6.8 using sodium hydroxide. 0.1 M. and acetonitrile (77: 23, v/v), the flow rate used was 1 mL/min, and detection was achieved at 235 nm using UV. All peaks were sharp and well separated, retention times were atenolol degradation (ATN Deg.) 2,311 minutes, atenolol (ATN) 2,580 minutes, hydrochlorothiazide degradation (HCT Deg.) 5,890 minutes, hydrochlorothiazide (HCT) 7.016 minutes, chlorthalidone CTD Deg. 8,018 minutes and chlorthalidone (CTD) 14,972 minutes. Linearity was obtained, and the concentration ranges were 20-160 µg/mL for atenolol, 10-80 µg/mL for hydrochlorothiazide, and 10-80 µg/mL for chlorthalidone. Based on ICH guidelines, method validation has been carried out. This method includes linearity, accuracy, selectivity, precision, and durability. The optimized method is specific, robust, and accurate for quality control of drugs cited in pharmaceutical dosage forms.[32]

5. Conclusion

Methods for analyzing atenolol as a drug raw material can be carried out using titrimetric, spectrophotometric, high-performance liquid chromatography, gas chromatography, and electrometry methods. Atenolol in pharmaceutical dosage forms can be determined by spectrophotometric methods, high-performance liquid chromatography, gas chromatography, and electrometry. Atenolol in biological fluids can be determined by the high-performance liquid chromatography method. In contrast, atenolol in mixtures with other substances can be determined using the high-performance liquid chromatography method.

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A Brief Author Biography

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