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A CONCISE OVERVIEW OF BISOPROLOL FUMARATE ANALYTICAL METHODS USED INPHARMACOLOGICAL PREPARATIONS AND BIOLOGICAL MATRICES FROM YEAR 2000 TO 2020

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ABSTRACT

The goal of this review article was to gather information on methods of analysing bisoprolol fumarate in pharmaceutical preparations and biological fluids. Data is gathered by searching for Google Scholar can be used to find information. The keywords used for data collection are "bisoprolol determination," "bisoprolol," "pharmaceutical preparations," and "biologi cal fluids." The results show that bisoprolol fumarate in raw materials or pharmaceutical preparations can be determined using spectrophotometric, voltammetric, and other techniques and HPLC techniques. It is determined using HPLC, spectrophotometry, spectrofluorimetry, HPTLC, voltammetry, and LC-MS in the form of a mixture of bisoprolol fumarate and other substances. This review focuses on the analysis of bisoprolol fumarate using spectrophotometric, voltammetric, HPLC, HPTLC, and spectrofluorimetric methods, whether in raw materials, pharmaceutical preparations, or biological fluids.

KEYWORDS: Voltammetry, HPLC, HPTLC, Bisoprolol, Spectrophotometry, Spectrofluorometry.

INTRODUCTION

Cardiovascular disease (CVD) affects the heart's arteries and veins. Although this term technically refers to any disorder affecting the cardiovascular system, it is most commonly used to refer to atherosclerosis or arterial disease. This condition is similar in terms of its

cause, mechanism, and treatment. Most countries face high and increasing rates of cardiovascular disease. Each year, deaths from heart disease exceed cancer deaths worldwide.

Bisoprolol fumarate belongs to the drug class of selective 1 adrenergic receptor blockers. It is primarily used to treat cardiovascular disease, has a half-life (t1/2) of 9-12 hours, and has a bioavailability of more than 80%.[2] Bisoprolol fumarate is a white crystalline powder that dissolves easily in water and methanol, is very soluble in chloroform and glacial acetic acid, and is difficult to dissolve in acetone and ethyl. Bisoprolol fumarate has a molecular formula of not less than 97.5% and not more than 102.0%. (C18H31NO4). 2C4H4O4 has the formula weight of 766.96 and the chemical name 1-[[-(2- isopropoxyethoxy)-p-tolyl] oxy]. -3-\s(isopropylamino) [104344-23-2] -2-propanol fumarate (2: 1) (salt).[3]

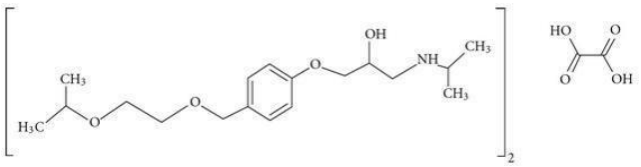

Figure 1: depicts the structure of bisoprolol fumarate.

Bisoprolol fumarate is taken orally and is absorbed through the digestive tract. To achieve good oral bioavailability (approximately 90%), this drug undergoes minimal first-pass metabolism through the liver. It has a long half-life of elimination (10-11 hours). Many factors can be used to change this.[4] Its pharmacokinetics reduce blood flow to the kidneys, blood flow to the liver, and the mass and activity of drug-metabolizing enzymes (cytochrome P450; CYP2D6 and CYP3A4), all of which have an impact on drug metabolism.[5] Diastolic and systolic blood pressure measurements were used to assess the pharmacodynamics response to bisoprolol fumarate, and plasma bisoprolol fumarate levels were measured using a triple quad mass spectrometer (TQ-MS).[6]

Hypertension is a significant public health problem and is known as an independent risk factor for cardiovascular disease. Hypertensive patients frequently develop complications such as hypercholesterolemia. Anti-hypertension beta-blockers are commonly used to treat high blood pressure and an irregular heartbeat. The purpose of this study is to investigate the effect of bisoprolol on systolic and diastolic blood pressure. This study will also look at the effect of bisoprolol on heart rate.

All experimental animals in this study were first made hypertensive. The group with hypercholesterolemia complications was then induced by feeding high fat and propylthiouracil (PTU). A clinic photometer was used to measure blood cholesterol levels. Systolic blood pressure, diastolic blood pressure, and heart rate were calculated using non-invasive blood pressure (NIBP) blood pressure metre. Data from this study were analysed with two-way ANOVA. The results showed that bisoprolol administration at a dose of 2.5 mg, 5 mg, and 10 mg had a significant effect on reducing systolic blood pressure, diastolic blood pressure, and heart rate ($p < 0.05$). The most effective dose of bisoprolol is 10 mg, which lowers systolic blood pressure, diastolic blood pressure, and heart rate.

Several methods for analysing bisoprolol fumarate in pure compounds, pharmaceutical preparations, and biological fluids have been reported. Many analytical methods for quantitatively determining bisoprolol fumarate levels have been developed to date.

Data collection

The technique used in compiling this article is a literature study, which involves locating sources or literature in official books and international journals from the last 20 years (2000-2020). "bisoprolol fumarate analysis," "pharmaceutical preparations," and "biological matrix" were the keywords used in the data search. The primary reference searches for this review article were conducted on trusted websites such as Science Direct, NCBI, Research gate, Google Scholar, and other published and trustworthy journals.

BISOPROLOL ANALYSIS METHODSVOLTAMMETRIC METHOD

Differential pulse voltammetry was used to investigate bisoprolol fumarate on a single-wall carbon nanotube (SWNT) modified with a glass carbon electrode (GCE). The prepared electrodes demonstrated excellent electro-catalytic activity against the oxidation of bisoprolol fumarate, resulting in a significant increase in sensitivity when compared to plain glass carbon electrodes, which lacked electrochemical activity for the analyte. For the oxidation of bisoprolol fumarate, SWNT modified GCE showed a sharp anodic peak at potential 950 mV. With a correlation coefficient of 0.9789 and a detection limit of 8.27 10- 7 M, the linear calibration curve was achieved under ideal conditions in the range of bisoprolol fumarate concentrations from 0.01 to 0.1 mM in a 0.5 M phosphate buffer solution (pH 7.2). As a result, this study demonstrates a straightforward, precise, sensitive, and practical technique for measuring bisoprolol fumarate on glass carbon electrodes modified with SWNT in both pharmaceutical formulations and biological fluids like human urine.

SPECTROPHOTOMETRIC METHOD

For the purpose of determining bisoprolol fumarate in its pure and pharmaceutical form, a quick and precise approach is described. The suggested procedure is the first known spectrophotometric approach for determining bisoprolol fumarate (BF) with stated simplicity, speed, and sensitivity. Blue bromothymol (BTB). This procedure is based on the formation of an ion pair complex (1: 1 drug/dye) by the interaction of medicines with bromothymol blue (BTB) dye in a solution containing KCl-HCl buffer pH 2.2, which maythen be extracted with chloroform and quantified spectrophotometrically at a wavelength of 412 nm.

At room temperature, the reaction happens relatively quickly, and for up to 24 hours, the absorbance value doesn't change. For BF-BTB, Beer's Law is adhered to in the range 0.50–40.88 g/mL. A 100.00– 104.00% recovery has occurred. There was no evidence of interference with other components or excipients.

The second easy, accurate and exact spectrophotometric analysis method is employed for the analysis of bisoprolol fumarate in bulk and tablet dosage forms. The basis for this method is the determination of a solution of bisoprolol fumarate's absorbance at 271 nm. A validation was done. According to ICH recommendations, was carried out. The linear calibration curve is in the concentration range of 5-25 µg/mL with a correlation coefficient of not less than 0.9986. The limits of quantification and detection were 0.66 g/mL and 0.22 g/mL, respectively. The low% RSD figures demonstrate the intraday and intraday precision of the presented approach (1.19 and 0.854, respectively). The recovery rate is 105.0 1.3% with a sample size of 3.

Based on the development of the reaction complex between bisoprolol fumarate and methyl orange at various pH levels, the spectrophotometric approach for the quantitative detection of bisoprolol fumarate was developed. The ion pair between methyl orange and bisoprolol fumarate, in acidic With a maximal absorbance at 427 nm, medium can be extracted in dichloroethane. Limits of quantification (LoQ) and detection (LoD) were 0.66 g/mL and 0.20 g/mL, respectively. The described procedure has been verified. At pH = 7.4, the complex forms with the greatest stability.

A straightforward, quick, and accurate research technique has been created for the spectrophotometric measurement of bisoprolol fumarate. The charge transfer reaction between bisoprolol fumarate, an n- electron donor, and 7,7,8,8, is the foundation of the

suggested procedure. Tetracyanoqumodimethane (TCNQ) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) are used as acceptors to create a complexthat is extremely colourful.

According to ICH criteria, the purpose method's linearity, limit of detection, limit of quantification, accuracy, precision, recovery, and specificity were all validated. Beer's rule was followed with bisoprolol fumarate concentrations of 10-60 and 10-80 g/mL with TCNQ and DDQ, respectively. When testing the presence of bisoprolol fumarate in pharmaceutical preparations, the suggested procedure was successful.

High performance liquid chromatography method The HPLC method with liquid phase extraction and fluorescence detection has been validated to determine the concentration of bisoprolol fumarate in human plasma. This assay involves alkaline pH liquid-liquid extraction with diethyl ether, followed by back extraction with phosphoric acid and liquid chromatography analysis with fluorescence detection at 232 nm and 320 nm excitation and emission wavelengths. Chromatography was carried out on a Chromolith RP-18e octadecyl silica-gel column that had been chemically modified (250x4 mm).Phosphate buffer (pH 3.5), acetonitrile = 77.5: 22.5 (v/v), and a flow rate of 0.6 mL/minute are the components of the mobile phase. Using an injection volume of 50 L, the limit of quantitation was 3 ng/mL. The straight calibration curve, Has a correlation value of 0.9998 between 3 and 200 ng/mL. The evaluation of precision and accuracy, which have a coefficient of variation that was found to not be greater than 8%, is another step in the validation of a method. The typical recovery rate is 72%. By acting at low quantities in human plasma, the detection of bisoprolol fumarate by high-performance liquid chromatography of the derivatization reaction is intended to boost sensitivity. The suggested technique is based on a derivative of bisoprolol fumarate with 4-Nitro-2,1,3- benzoxadiazole in a buffer of borate at a pH of 9.5 to yield a luminous substance. Bisoprolol fumarate was separated chromatographically using isocratic elution at 1.2 mL/min on a C18 reverse-phase column (Inertsil, 4 mm, 150 4.6 mm) at 40°C.

Methanol-water was the mobile phase used for the study (70:30% v/v). The excitation and emission wavelengths of the fluorescence detector were 458 nm and 525 nm, respectively. The method's linearity, detection limit, and quantification limit are validated. Precision, accuracy, system compatibility, and recovery For a concentration range of 10–2000 mg/mL, the test is linear.

The current review is written with the intention of focusing on the use of HPLC. However, only a few analytical methods for simultaneous analysis of this drug in combined dose formulations with HPLC havebeen reported. Furthermore, the development analysis HPLC is the most suitable method for the analysisof bisoprolol fumarate in pure substances, drugs, and biological fluids to carry out routine drug analysis, pharmacokinetics (in vivo bioequivalence), test dissolution for the final dosage form (in vitro bioequivalence, biowaiver procedure).

The purpose of this study was to Investigate a method for developing and validating an analytical method for bisoprolol fumarate in pharmaceutical preparations and biological fluids. The HPLC system is run isocratically at a controlled ambient temperature with a reverse phase C18 column (150 mm 4.6 mm id, particle size 5 m) and a methanol, phosphate buffer (pH 3.5; 0.01 M) (55: 45, v/v) mobile phase at a flowrate of 1.0 mL/min. A photodiode array detector (PDA) at 225 nm was used for detection. Range, linearity (r2 = 0.9999), precision, accuracy, and robustness are all investigated in method validation.

The dissolution test conditions and medium were chosen to be 0.1 M HCl with a stirring speed of 50 rpm, and the methodology was applied to bisoprolol fumarate tablets that produced a similar dissolution profile when compared to the difference and similarity factors (f1, f2), with respective values less than 7.22 and greater than 72.28.

The mobile phase mixture of methanol, acetonitrile, potassium dihydrogen phosphate buffer 45mM (30:25:45) at pH 3.0 and 0.3 mL/minute was developed for the determination of bisoprolol fumarate in tablets. The Nucleosil SB-C18 column (125 4 mm) was used as the stationary phase. UV detection was performed at 225 nm. The method's linearity, detection limit, quantification limit, precision, accuracy, recovery, and system suitability are all validated. Bisoprolol fumarate had a retention time of 2.32 minutes. Linear calibration graph over a concentration range of 0.3 to 10 g/mL.

For the determination of bisoprolol fumarate in pharmaceutical dosage forms, isocratic RP-HPLC was developed. Prontosil, chromium bond, C18, (250 X 4.6) mm, 5 column and buffer (pH 5.6) and acetonitrile were used for chromatographic separation. At a flow rate of 1 mL/minute, a mobile phase of 750:250 was used, with PDA detection at 226 nm. Bisoprolol fumarate had a retention time of 9.15 minutes. The sensitivity, selectivity, linearity, accuracy and precision, roughness, and durability of the developed HPLC method are all determined.

From 25 to 100 g/mL, the test method was found to be linear. The method's accuracy was determined by examining the percentage recovery at six different levels at working concentrations of 50%, 80%, 100%, 150%, 200%, and 300%. The developed method's drug recovery rate was found to be in the range of 97 to 103%, indicating good method accuracy. This method was developed for routine analysis of large quantities of bisoprolol fumarate and pharmaceutical formulations.

LIQUID-CHROMATOGRAPHY-ELECTROSPRAY-IONIZATION-MASS-SPECTROMETRY (LC-ESI-MS) METHOD

A mass-ionization-sensitive electrospray liquid chromatography (LC-ESI-MS) method for determining bisoprolol fumarate in human plasma was developed and validated using metoprolol as the internal standard (I.S.). After alkalinization with sodium hydroxide, the samples were extracted with ethyl acetate and separated by HPLC on a ZORBAX SB-C18 column with a mobile phase containing 10 mM ammonium acetate buffer and 0.1% formic acid-methanol (32:68, v/v) at a flow rate of 1 mL/min. Chromatographic separation takes less than 5 minutes. Linearity was established across a concentration range of 0.05-120 ng/mL. The standard deviation is less than 3.8 and greater than 7.5%. This method is sensitive and specific for determining bisoprolol fumarate in human plasma. Endogenous compounds did not cause any significant disruption or matrix effect. This method is appropriate for pharmacokinetic studies and bioavailability evaluation.

LIQUID CHROMATOGRAPHY-TANDEM MASS SPECTROMETRY (LC-MS) METHOD

One of the most powerful analytical tools for the analysis of organic compounds is liquid chromatography combined with mass spectrometry detection. The LC-MS method has several advantages over the HPLC method, including selectivity, chromatographic integrity, peak determination, structural information, and rapid method development. In this context, a liquid chromatography tandem mass spectrometry method for determining bisoprolol fumarate in human plasma samples has been developed and validated, with metoprolol serving as the internal standard.After a single oral administration of 10 mg bisoprolol tablets to 22 healthy volunteers, the assay was shown to be sensitive, specific, and reproducible, making it suitable for determining bisoprolol concentrations. A bioequivalence study of Bisoprolol 10 mg was conducted. Coated tablet produced by Antibiotice SA versus Merck's Concor® 10 mg.

Based on liquid chromatography-tandem mass spectrometry, an analytical method for determining bisoprolol fumarate in human plasma has been developed (LC-MS).Internal standard analyte and diphenhydramine (IS) were cleaned with acetonitrile before being dissolved in the mobile phase and separated by reverse phase high performance liquid chromatography (HPLC) with methanol, 10 mM ammonium acetate, and acetonitrile.The mobile phase is formic acid (70:30:0.1 v/v/v).The detection was completed in 2.5 minutes by monitoring multiple reactions (MRM) on the LC / MS system. The test has a linear range of 0.5-100 ng/mL and a limit of quantitation (LOQ) of 0.5 ng/mL. Precision ranges between 5.54 and 9.95%, while accuracy ranges between 89.4 and 113%. This method has been used in pharmacokinetic studies in which healthy volunteers were given an oral dose of 5 mg bisoprolol.

ANALYSIS OF A MIXTURE OF BISOPROLOL AND PERINDOPRIL

Two rapid, accurate, and selective stability indication methods for bisoprolol fumarate, perindopril, and its three possible degradations were developed and validated. The gradient reverse phase high performance liquid chromatography (HPLC) method is proposed first, followed by the capillary electrophoresis method. Infrared and mass spectrometry are used to describe the structure of the obtained degradation products. The British Pharmacopoeia has also confirmed that they are drug impurities or precursors to such impurities. Linearity for bisoprolol fumarate and perindopril was achieved in the 1-20 g/mL and 5-30 g/mL ranges for HPLC and capillary electrophoresis methods, respectively. The proposed method has been validated in accordance with the International Conference on Harmonization guidelines. The HPLC method proved to be more sensitive and effective in quantifying the degradation products obtained. Furthermore, it was able to count perindopril impurities that were three times lowerthan the British Pharmacopoeia's desired limit. They have been used successfully to determine the concentrations of bisoprolol fumarate and perindopril in combined pharmaceutical formulations.

ANALYSIS OF BISOPROLOL IN ENANTIOMERIC MIXTURES

To determine S-(-)- and R-(+)- bisoprolol fumarate in human plasma, a sensitive, enantioselective high- performance liquid chromatography (HPLC) method was developed and validated. The stationary phase of the macrocyclic antibiotic teicoplanin (CSP) known as Chirobiotic T was combined with a polar ionic mobile phase (PIM) composed of methanol-acetic acid glacial-triethylamine (100: 0.02: 0.025, v/v/v) at a flow rate of 1.5 mL/min and

fluorescence detection set at 275 nm for excitation and 305 nm for emission. All analyses were performed at room temperature using S – (-) – atenolol as the internal standard. Prior to HPLC analysis, human plasma samples are extracted using a solid phase extraction procedure. Without interruption, the C18 cartridge provides good recovery rates for both enantiomers. For each enantiomeric concentration, this method has been validated in the range of 20-200 ng/mL. The recovery rates for the enantiomers S – (-) – and R – (+) – bisoprolol fumarate are in the 95-102% range. This method was found to be precise (in-run precision expressed as percentage RSD ranged from 1.0—6.2% and inter-run precision ranged from (0.9—6.7%)) and accurate (in-run accuracy expressed as percentage error ranged from 0.2-4.8%) and intermediate-run accuracy ranged from 0.3-1.7%). In human plasma, the quantization and detection limits for each enantiomer are 20 and 5 ng/mL, respectively.

ANALYSIS OF A MIXTURE OF BISOPROLOL AND METOPROLOL

High performance liquid chromatography was used to determine the levels of bisoprolol fumarate and metoprolol in human plasma. The analytical method included two different liquid-liquid extractions of human plasma, one with diethyl ether for bisoprolol fumarate and one with dichloromethane for metoprolol, both of which were combined with a similar Nucleosil C18 reverse phase HPLC column. Both inhibitors were identified using fluorimetric detection. Bisoprolol fumarate and metoprolol fumarate had retention times of 8.7 and 3.2 minutes, respectively. Linear regression for the concentration range 6.25- 200 ng/mL linear calibration curve. For both drugs, intra- and inter-day precision coefficients of variation and accuracy bias were acceptable (within 15%) across ranges. The average recovery for metoprolol was 89% and for bisoprolol fumarate was 98%. After the method was validated, the analytic error function was assigned as SD (ng/mL) = 2.216 + 3.608 10-4 C2 (C = theoretical concentration value) for bisoprolol fumarate and SD (ng/mL) = 0.408 + 0.378 10-1 C for metoprolol. If posological individualization of the drug is required, the developed method and its associated analytic error function would be suitable for pharmacokinetic studies and the determination of plasma concentrations.

ANALYSIS OF A MIXTURE OF BISOPROLOL AND ROSUVASTATIN

In methanol, the fluorescence intensities of bisoprolol fumarate and rosuvastatin were measured at emission wavelengths of 297 and 485 nm and excitation wavelengths of 227 and 242 nm, respectively. Each drug's emission spectrum has a zero value at the emission wavelength of the other drug, allowing simultaneous determination without interruption or

the use of time-consuming derivatization steps. Bisoprolol fumarate and rosuvastatin have excellent linearity in the 10-500 and 20-1000 ng/mL ranges. The high sensitivity of this method motivates its use in the analysis of drugs quoted in human plasma. Analytical and bioanalytic method validation was performed following the International Conference on Harmonization guidelines, as well as statistical analysis with the reported methods, and no significant differences were discovered. The developed method is a spectrofluorimetric method that was originally developed for the simultaneous determination of a newly formulated drug.

ANALYSIS OF A MIXTURE OF BISOPROLOL AND AMLODIPINE

For the simultaneous determination of bisoprolol fumarate and amlodipine besylate in tablets, the fast and robust RP-HPLC method was developed. The mobile phase is a 1 mL/min mixture of Methanol, Acetonitrile, and 50 mM potassium dihydrogen phosphate buffer KH2PO4 (25; 30; 45 v/v). C18 Intersil 150 x 4.6 mm is the stationary phase (id). UV detection was performed at 267 nm.

Chromatographic separation was achieved on a precoated silica gel HPTLC 60 F254 aluminium plate with a mobile phase of chloroform, ethanol, and glacial acetic acid 2: 8: 0.1 (v/v/v). Densitometric scanning at 231 nm revealed the quantitative detection.Amlodipine besylate and bisoprolol fumarate had Rfs of 0.53 and 0.72, respectively. The method is validated in terms of specificity, linearity, accuracy, precision, and robustness, according to ICH guidelines. Linearity was observed for amlodipine besylate and bisoprolol fumarate in the 200-1200 ng/spot concentration ranges, respectively. The detection and quantitation limits for amlodipine besylate were found to be 40 ng/spot and 120 ng/spot, respectively, and 50 ng/spot and 100 ng/spot for bisoprolol fumarate. Amlodipine besylate had a mean recovery percentage of 99.20 0.41% and bisoprolol fumarate had a mean recovery percentage of 99.11 0.13%. The developed method can be used on a regular basis to analyse bisoprolol fumarate and amlodipine besylate from their combined dosage forms.

ANALYSIS OF A MIXTURE OF BISOPROLOL AND HYDROCHLOROTHIAZIDE

A simple and precise high-performance liquid chromatography method for the simultaneous determination of bisoprolol fumarate and hydrochlorothiazide in tablet formulations has been developed and validated. Chromatography was carried out at 25 oC on a 4.6 mm 250 mm 5 m cyano column with 0.1 M isocratic mobile phase of dilute phosphate buffer, acetonitrile, and tetrahydrofuran (85: 10: 5, v/v/v) at a flow rate of 1.0 mL/minute. UV detection was

performed at 225 nm. Without excipient disturbance, hydrochlorothiazide and bisoprolol fumarate were separated in less than 10 minutes with good resolution and minimal tailings. The method was validated in accordance with ICH guidelines, and all acceptance criteria for accuracy, precision, linearity, specificity, and system suitability were met. This method is linearfor bisoprolol fumarate at 50-150 g/mL and hydrochlorothiazide at 125-375 g/mL.

For the simultaneous determination of bisoprolol and hydrochlorothiazide in human plasma, sensitive, specific, and selective methods have been developed. This method employs advanced LC-MS with positive and negative ionisation switching. The analyte and internal standard oxyphloxacin were separated on a Purosphere® STAR C8 column (125 mm 4 mm, 5 m) after a simple sample preparation step involving protein precipitation with acetonitrile. The mobile phase is a solution of ammonium acetate (1 mM) in formic acid (0.2%), methanol, and acetonitrile (65: 17.5: 17.5, v/v/v (%)), with a flow rate of 0.65 mL/minute. Bisoprolol fumarate and hydrochlorothiazide were ionised using an ESI source before detection by Multiple Reaction Monitoring (MRM) mode, with the following transitions monitored: positive m/z 326 116 for bisoprolol fumarate, negative m/z 296 269, and m/z 296 205 for hydrochlorothiazide. The concentration range for bisoprolol fumarate is 0.10-30.0 (ng/mL) and forhydrochlorothiazide is 1.00-80.00 ng/mL. The detection limits for bisoprolol fumarate are 0.100 (ng/mL) and 1.00 (ng/mL) for hydrochlorothiazide. In healthy volunteers, the validated method was successfully applied to the pharmacokinetic study of 5 mg bisoprolol fumarate with 12.5 mg hydrochlorothiazide tablets.

The HPLC method was developd to determine bisoprolol fumarate and hydrochlorothiazide in pharmaceutical dosage forms concurrently. His method makes use of readily available, low-cost laboratory reagents. Separation was accomplished using an isocratic flow on a 3V (25 cm 4.6 mm) 5 m ODS Inertsile column. The mobile phase was a buffer of 0.1 M potassium dihydrogen phosphate and acetonitrile (70:30, v/v) with a flow rate of 1.0 mL/min. UV detection was performed at 228 nm. A linear response was observed for bisoprolol fumarate concentrations ranging from 2.5 to 50 g/mL and hydrochlorothiazide concentrations ranging from 6.25 to 125 g/mL. The detection and quantitation limits for bisoprolol fumarate were 0.01 and 0.03 g/mL, respectively, and for hydrochlorothiazide were 0.01 and 0.05 g/mL. The method was validated successfully using the ICH acceptance criteria for specificity, linearity, accuracy, precision, robustness, ruggedness, and system suitability. Individual drugs (bisoprolol fumarate and hydrochlorothiazide), as well as their combinations and tablets, are

subjected to thermal, photolytic, hydrolytic, and oxidative stress conditions. The proposed method was used to analyse the resulting stress samples. This method provides a high degree of separation between the degradation product and the analyte. The photodiode array detector confirms the purity of the analyte peaks in the stressed sample. This method is used to study acceleration stability in marketed formulations as well as at home. The results of the study showed that this method was selective for simultaneous estimation of bisoprolol fumarate and hydrochlorothiazide and stable.

Voltammetry, chromatography, and spectrophotometric methods were developed to determine bisoprolol fumarate and hydrochlorothiazide at the same time. By measuring approximately 1400 and 1100 mV, respectively, differential pulse and square wave voltammetry techniques were used to simultaneously analyse bisoprolol fumarate and hydrochlorothiazide. The second method for simultaneous compound analysis is RP-HPLC. As an internal standard, a mixture of bisoprolol fumarate, hydrochlorothiazide, and moxifloxacin was separated on an RP Zorbax Eclipse XDB-C18 column (150 4.6 mm, id, particle size 5 m) with acetonitrile – 15 mM phosphate (25 + 75, v/v) mobile phase at 1.0 mL/min.The third method is based on the first derivative of the ratio-spectrum method, which was obtained from amplitude measurements of bisoprolol fumarate and hydrochlorothiazide at 246 and 257 nm, respectively. Without time-consuming extraction, sample preparation, or derivatization procedures, all of the proposed methods are effective for the simultaneous determination of bisoprolol fumarate andhydrochlorothiazide in tablet dosage form.

An ultra-sensitive, selective, and accurate performance liquid chromatography method for the simultaneous determination of bisoprolol fumarate and hydrochlorothiazide in both dosage forms and human urine samples has been developed and validated. Separation was accomplished on a UPLC BEH C18 1.7 m (2.1 50 mm) column at 40 °C using an acetonitrile:phosphate buffer (20 mM) at pH 3.0 with gradient elution at 225 nm. Bisoprolol fumarate and hydrochlorothiazide separated well in 1.5 minutes with good resolution and no tailings resolution or excipient interference. The method has been fully validated in terms of accuracy, precision, linearity, and specificity in accordance with ICH guidelines. Linear response was observed for hydrochlorothiazide over a concentration range of 0.5-150 g/mL and 0.5-250 g/mL for bisoprolol fumarate. The detection and quantitation limits for hydrochlorothiazide were calculated to be 0.01 and 0.03 g/mL, respectively, and for bisoprolol fumarate to be 0.07 and 0.21 g/mL. Furthermore, bisoprolol fumarate and

hydrochlorothiazide were subjected to degradation conditions such as hydrolysis, oxidation, and thermal stress to assess the ability of the proposed method for separating bisoprolol fumarate and hydrochlorothiazide from their degradation compounds.

In this study, 12 impurities of bisoprolol fumarate and hydrochlorothiazide were separated simultaneously using a single HPLC method. Five of the 12 impurities are potential decomposers that have been validated according to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines. Because the two active pharmaceutical ingredients, bisoprolol fumarate and hydrochlorothiazide, have different solubility and polarity, the most important parameters in separating the components are pH, temperature, and solvent. The method is precise (RSD 1.0%), accurate, linear (r2 > 0.999), robust, and stable in the quantification limits (LOQ) to 150% range. The HPLC method was then upgraded to ultra-performance liquid chromatography (UPLC) to reduce operating time and solvent consumption while increasing sample throughput.

Spectrophotometric analysis of a binary mixture UV containing bisoprolol fumarate and hydrochlorothiazide using multivariate calibration methods like principal component regression (PCR) and partial least squares regression (PLS-1) as well as graphical spectrophotometric methods like the second derivative of the 2DD ratio spectrum. The PCR and PLS-1 models were developed using a calibration set of 22 reference samples. The calibration model is optimised by selecting an appropriate wavelength range and does not include any information about the offending excipient.

In addition, to analyse the same mixture, High Performance Liquid Chromatography (HPLC) was developed. The reverse phase of the RP 18 column was used to achieve chromatographic separation with a mobile phase of acetonitrile-0.01 M KH2PO4 (40:60, v/v, pH 3.5). The area of the peaks was used to calculate the quantity using UV detection at 232 nm. The proposed method has been validated and successfully applied to the analysis of laboratory and pharmaceutical formulation mixtures.

CONCLUSION

All analytical methods for determining bisoprolol fumarate in raw materials, pharmaceutical preparations, and biological fluids have been developed. Similarly, an analysis method for bisoprolol fumarate mixtures with other substances has been developed. Spectrophotometric

analysis methods are straightforward, whereas voltammetry and LCMS are more difficult but more sensitive. The HPLC analysis method, on the other hand, is used to determine the bisoprolol fumarate content in the biological matrix. HPLC and voltammetry methods are used to determine the levels of bisoprolol fumarate in a mixture with other substances in pharmaceutical preparations and biological fluids.

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