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Overview of Determination of Doxazosin Levels in Pharmaceutical Preparations and Biological Matrix

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Abstract

Doxazosin is an alpha-adrenergic antagonist that selectively inhibits the alpha-1 subtype commonly used to treat hypertension and benign prostatic hyperplasia. Determination of doxazosin levels in pharmaceutical preparations and biological matrices needs to be known more deeply. This review gathered information on analytical methods for the determination of doxazosin in pharmaceutical preparations and biological matrices. Information gathering was conducted with Google Scholar from 2000-2020. The results showed that the analysis method of doxazosin could be classified into spectrophotometric methods and chromatographic methods. These two groups of methods are described in more detail in this article. This article is useful for researchers and scientists involved in developing new analytical methods or formulations for doxazosin.
Keywords: Doxazosin, Analysis, Spectrophotometry, Chromatography

1. Introduction

Doxazosin is a quinazoline derivative with antihypertensive and antineoplastic properties. Doxazosin is an alpha-adrenergic antagonist that selectively blocks alpha-1 adrenergic receptors. Inhibition of alpha-1 adrenergic action on vascular smooth muscle leads to decreased vascular resistance and antihypertensive activity. This agent also shows a high affinity for the alpha-1c adrenoceptor, the primary functional type in the prostate, which can be partly attributed to its effect in treating benign prostatic hyperplasia. Furthermore, doxazosin induces apoptosis in prostate cancer cells, mediated by inhibition of the protein kinase B (PKB)/Akt signaling death receptor regulatory pathway [1]. The chemical structure of doxazosin can be seen in Figure 1 [42].

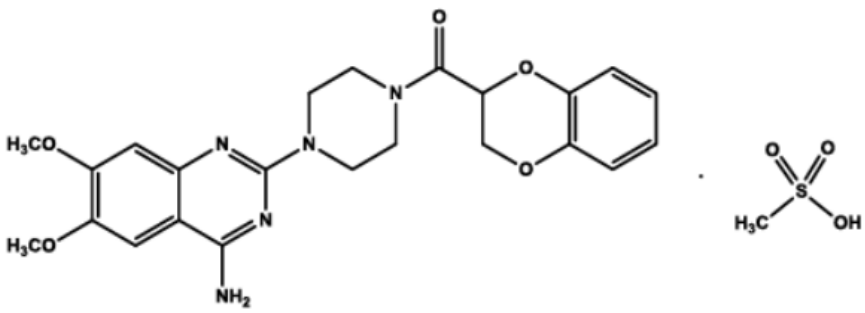

Figure 1: Chemical structure of doxazosin [42]

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Doxazosin is given orally as doxazosin mesylate, but the dosage is usually expressed on a basis. 1.2 mg of doxazosin mesylate is equivalent to about 1 mg of doxazosin. After an oral dose, the maximum blood pressure drop can occur within 2 to 6 hours, and the effect is maintained for 24 hours, allowing once-daily dosing. Because of the risk of collapse in some patients after the first dose, the initial amount is 1 mg, preferably at bedtime. We can increase the quantity after 1 or 2 weeks according to the response. The usual maintenance dose for hypertension is up to 4 mg daily; the amount of 16 mg daily should not be skipped. For benign prostatic hyperplasia, the usual maintenance dose is 2 to 4 mg daily; a quantity of 8 mg daily should not be ignored [2].

Many methods exist in the literature for the determination of doxazosin in various pharmaceutical preparations and biological matrices. These methods can be classified as spectrophotometric methods and chromatographic methods. The following will discuss strategies for determining doxazosin levels in pharmaceutical preparations and biological matrices.

2. Data Collection

In compiling this review article, the technique used to collect data is to use literature studies by finding sources or literature in primary data or the form of international journals in the last 20 years (2000-2020). In making this review article, the search for data used online media with doxazosin, assay, pharmaceutical preparations, and biological matrices. Search for the primary references used in this review article through trusted websites such as Mendeley, Science Direct, NCBI, ResearchGate, Google Scholar, and other published and reliable journals.

3. Spectrophotometric Methods

The spectrophotometric method is one of the oldest forms of chemical analysis. Spectrophotometry is a measurement technique that has developed rapidly due to technological advances, new materials, and data processing methods. Identification with spectrophotometric process and determination of compound content is based on the existence of a relationship between the position and the absorption intensity of the electromagnetic radiation band, on the one hand, and the molecular structure on the other [3].

In data collection, we found eight different spectrophotometric methods for the determination of doxazosin. Two fluorimetric ways are also available [4, 5]. As an analytical tool, Spectrofluorimetry provides a clear identity of the compounds present in the sample based on their unique fluorescent properties. These compounds can be analyzed up to the nanogram level [6]. The fluorimetric method developed by Ayat et al. [4] confirms this theory and is the most sensitive method on this list. The acid dye method can provide a more sensitive technique for certain amines and quaternary ammonium compounds that absorb weakly in the ultraviolet region [7]. There are eight different methods based on the acid dye method [8, 9].

Atomic spectrum differentiation has considerable advantages for spectrophotometry in the ultraviolet and visible regions. Atomic spectrum differentiation is the key to the potential increase in the resolution of the overlapping bands. It facilitates the detection of poorly absorbed peaks arising from mixing or impurities in the solution. For structural reasons, it allows the precise determination of the maximum wavelength of a particular analyte species and increases the spectrophotometric procedure's sensitivity [10]. Only one first-derived spectrophotometric method for the determination of doxazosin was found [11], and three simple spectrophotometric techniques were found for the determination of doxazosin [12, 13, 14]. A summary of all spectrophotometric methods is presented in Table 1 (Appendix).

4. Chromatographic Methods

High-performance liquid chromatography (HPLC) was introduced to the pharmaceutical analysis not long after its discovery in the late 1960s. It has now developed into generally applicable analytical methods providing fast and versatile separation possibilities that meet the increasing requirements for purity testing of bulk drugs and pharmaceutical products [15]. Seven different HPLC determinations in the use of U.V. detectors [15-21] were found in the available literature, two of which were based on gradient elution [16, 17].

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Detectors that measure light absorption in the ultraviolet (U.V.) or visible (VIS) region are used for at least 75% of applications during the first decade of high-performance liquid chromatography [22]. The UV-Vis absorbance detector monitors the absorption of U.V. or visible light in the HPLC eluent. They are the most common detectors because most of the analytes of interest have U.V. absorbance [23]. These detectors' main disadvantage is that they are fixed wavelength or variable wavelength detectors, and they do not detect aliphatic components in clinically attractive samples [24]. Gradient elution provides a shorter overall analysis with a similar resolution of the critical pair than isocratic elution without sacrificing repeatability in retention time, peak area, and peak height or the linearity of the calibration curve [25]. In this review, two gradient elution methods [16, 17] are also included.

Fluorescence detectors with variable excitation and emission wavelengths provide high sensitivity and specificity for detecting and measuring fluorescence compounds but are more useful for quantification than identification [26]. There are some disadvantages reported, such as decreased fluorescence yield by quenching and reabsorption of re-emitted light. The fluorescence intensity can also be affected by the column temperature in gradient chromatography because the chromatographic efficiency is very dependent on the composition of the solvent. Despite all these shortcomings, fluorescence detection is still one of the most valuable techniques for trace analysis by HPLC [27]. During the preparation of this review, six different HPLC methods with fluorescence detection were discovered [28–33].

Hydrophilic interaction liquid chromatography (HILIC), although not a new technique, has recently enjoyed a revival with the introduction of a robust and reproducible stationary phase [34]. HILIC can provide better chromatographic retention for highly polar or ionizable analytes, separate analytes of very different polarity in a reasonable time, increase sensitivity with LC-MS electric spray, and complete analytes and their counterions in the analysis same [35]. The HILIC – MS / MS method for calculating doxazosin was developed and validated by Ji et al. [36]. This method is claimed to be free of matrix effects as assessed by spiking the analytes after extraction. The combination of chromatography and mass spectrometry is a subject that has attracted a great deal of attention for forty years or so. But the mass spectrometer's complexity means that the majority of chromatography does not have direct access to instrumentation and has to rely on service providers. Therefore they cannot react quickly to the results of the analysis, and as a result, the detectors are very inconvenient to use. However, the combination of HPLC with mass spectrometry allows more definite identification and quantitative determination of compounds that are not entirely resolved by chromatography [37].

Two LC-MS methods [38–39] were also found for the determination of doxazosin. Both approaches have considerable sensitivity and can be used in biological matrices. UPLC has been gradually adopted in industrial laboratories, especially the pharmaceutical industry, due to its high resolution, high speed, and solvent savings since its introduction in early 2004. The UPLC method using sub-2 µm columns can reduce analysis time by up to 80% compared to HPLC methods using conventional 3.5 µm column without sacrificing separation performance. Moreover, the much shorter timeframe significantly reduces the development time of the UPLC method [40]. In this review, only one such practice [41] was found.

A summary of all chromatographic methods is presented in Table 2. The HPLC-UV method [19] is the most sensitive method developed using a U.V. detector. With a LOD (Limit of Detection) of 0.1 ng / mL [28], this method is the most sensitive in the fluorescence detector category. Despite the many advantages of LC-MS / MS equipment, the methods available in the literature do not appear to produce significant gains in insensitivity. The entire HPLC method developed using a fluorescence detector has good sensitivity. The UPLC-MS / MS method [41] is the most sensitive method among all the techniques developed to determine doxazosin in different matrices. The advantages of such a technique have already been discussed in the text above. A summary of all chromatographic methods is presented in Table 2 (see appendix).

5. Conclusion

It is essential to ensure that these analytical methods serve their purpose. This article includes a discussion of method sensitivity and focuses on the advantages or disadvantages of different procedures. In this way, all the analytical methods for determining doxazosin in various pharmaceutical preparations and biological matrices

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are discussed here. A summary of all spectrophotometric techniques is presented in Table 1, whereas all chromatographic methods are shown in Table 2. This article is useful for researchers and scientists involved in developing new analytical methods or formulations for doxazosin.

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A Brief Author Biography

Prof. Dr. Harrizul Rivai, M.S., was born in Payakumbuh, West Sumatra, on 4 September 1953. His father is Rivai Said, and his mother is Saridahanum Syofyan. The Author obtained a Bachelor of Pharmacy from the Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Padjajaran University, Bandung (1976), a Master of Science degree from the Bandung Institute of Technology (1984), and a Doctorate from the Department of Chemistry, Faculty of Mathematics and Natural Sciences, Andalas University, Padang (2011). Now the Author is a Professor and Researcher at the Faculty of Pharmacy, Andalas University, Padang. The Author also serves as Deputy Chair of Academic Affairs at the YPTIK Padang College of Pharmacy (STIFARM). The Author wrote the book "Principles of Chemical Examination" (Publisher UI-Press, 1995), translated the book "Pharmaceutical Statistics" (EGC Medical Book Publishers, 2010), and wrote "Chapter 4" in the book "Recent Research Advances in Biology Vol. 4 "(International Book Publisher, India, and United Kingdom, 2020). The Author has also written articles in various international journals in various science fields, such as chemistry, biology, and pharmacy.

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Appendix

Table 1: Spectrophotometric methods for the determination of doxazosin levels

No.	Principles	Wavelength	Linear Range	Detection Limit	Quantitation Limits	Application	Ref.
1.	Simple spectrophotometric test by dissolving drugs in water	330 nm	1.0 x 10^{-5} M and 5.0 x 10^{-5} M	-	1.0 x 10^{-5} M	Raw material	[12]
2.	Shows the spectrophotometric stability of the first derivative	256 nm	8-120 µg/mL	-	0.8 g/mL	Bulk and Tablets	[11]
3.	Ion pair complexes with sulfophthalein acid bromocresol purple dye (BCP) and bromophenol blue (BPB) in phosphate buffer pH 3,3 and 4,5	BCP: 403 nm	BCP: 3-18 µg/mL	BCP: 0,314 µg/mL	BCP: 1,045 µg/mL	Tablet	[8]
		BPB: 411 nm	BPB: 3-20 µg/mL	BPB: 0,408 µg/mL	BPB: 1,360 µg/mL		
	Charge transfer reaction of the drug as an n-electron donor with either 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or 7,7,8,8-tetracyanoquinodimethane (TCNQ) as pi-acceptors, to give colored radical anions	Q: 457 nm	Q: 15-95 µg/mL	Q: 1,935 µg/mL	Q: 6,449 µg/mL		
		TCNQ: 838 nm	TCNQ: 10-100 µg/mL	TCNQ: 1,610 µg/mL	TCNQ: 5,367 µg/mL		
4.	Acetylacetone with formaldehyde reacts with primary amines by the Hantzsch reaction to form a yellow product (dihydrolutidine derivatives) measured spectrophotometry and Spectrofluorimetry	336 nm,	8-36 µg/mL,	0,693 µg/mL,	2,289 µg/mL,	Pure Doxazosin and Tablets	[4]
		λ_{ex} : 400 nm	0,02-0,22	0,01 µg/mL	0,02 µg/mL		

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		λ_{em} : 475 nm	µg/mL				
5.	U.V. spectrophotometric test of drug solution in 0.01 N HCl solvent	245 nm	2-10 µg/mL			Tablet	[13]
6.	Ion pair complexes with bromocresol green, bromothymol blue, methyl orange, and alizarin red dyes in acid buffer pH 3.0-5.0.	418 nm	1,0-12 $\mu g/mL^{-1}$	0,275 $\mu g/mL^{-1}$	0,915 $\mu g/mL^{-1}$		
		414 nm	1,0-16 $\mu g/mL^{-1}$	0,296 $\mu g/mL^{-1}$	0,988 $\mu g/mL^{-1}$		
		425 nm	1,0-12 $\mu g/mL^{-1}$	0,164 $\mu g/mL^{-1}$	0,547 $\mu g/mL^{-1}$		
		426 nm	4,0-50 $\mu g/mL^{-1}$	0,672 $\mu g/mL^{-1}$	2,24 $\mu g/mL^{-1}$		
7.	A simple spectrophotometric test based on the formation of a complex reaction with 1,10 – Phenanthrroline / $FeCl_3$	510 nm	10-60 µg/mL	0,60916 µg/mL	1,845 µg/mL	Tablet	[14]
8.	Ion pair complexes with Eosin Y reagent in acetate buffer at pH 3 were measured spectrophotometrically and Spectrofluorimetry.	547 nm,	2-14 µg/mL,	0,393 µg/mL,	1,191 µg/mL,	Tablet	[5]
		λex : 340 nm Λem: 570 nm	1-10 µg/mL	0,0784 µg/mL	0,241 µg/mL		

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Table 2: Chromatographic methods for determining doxazosin levels

No.	Method	Chromatographic conditions	Mobile phase	Linearity range	Detection	Detection limit	Quantitation limit	Application	Ref.
1	HPLC– U.V.	Columns with an inner diameter of 3.9 mm and a length of 15 cm were packed with octadecylsilane for liquid chromatography (4 µm particle diameter). Temperature 25 ° C	A mixture of 0.05 mol/L Potassium Dihydrogen Phosphate T.S. pH 3.0, Methanol and Acetonitrile (12: 8: 3)	-	246 nm	-	-	Pure Doxazosin	[18]
2	HPLC-UV gradient	250 × 4.0 mm octylsilane silica gel base active column	10 g /L H_3PO_4 and 10 g/L phosphoric acid solution in ACN. Temperature 35 °C	-	210 nm	-	-	Test and related compounds	[16]
3	RP-HPLC-UV	RP-C18 Chromolith Column	The mixture of buffered potassium phosphate and methanol (40:60 v / v)	1-5 µg/ml	251 nm	0,1 µg/mL	0,5 µg/mL	Tablet	[18]
4	HPLC-UV	RP-C18 Chromolith Column, Column 100 mm x 10 µm	The mixture of Methanol and Potassium Dihydrogen Orthophosphate with a ratio of 60:40. And adjust the pH to 5.0 ± 0.05 with sodium hydroxide solution.	50-150 µg/mL	251 nm.	-	-	Pharmaceutical preparations	[20]
5	HPLC-UV	LiChroCART Lichrosphere 100, C18, R.P. column (250 mm × 4 mm × 5 µm) maintained at ambient	Methanol-water (60:40% v/v)	1-300 µg/mL-1	247 nm	0,3 µg/mL	1,2 µg/mL	Pharmaceutical preparations	[21]

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		temperature, eluted with the mobile phase at a flow rate of 1 mL/min for 10 minutes							
6.	HPLC-UV gradient	Kromasil C18 column (250 × 4.6 mm, 5.0 µm)	Ammonium acetate, (A: B: C) is: 60:40: 0: 0 for 8 minutes, 60: 20: 20: 0 for 1 minute, 60: 0: 40: 0 for 5 minutes, and 60:40: 0: 0 gradient for 1 minute for system equilibrium	2-500 µg/mL	254 nm	0,109 µg/mL	0,332 µg/mL	Tablet	[17]
7.	HPLC-UV	Chromolith RP-C18 column [100 mm x 4.6 mm x 10 µm]	Phosphate Buffer: Methanol ratio (40:60)	50-150 µg/mL	251 nm	-	-	Tablet	[15]
8.	RP-HPLC-F	Hypersil, 5µ, ODS, C18, 5 µm, 250 × 4.6 mm with guard column A 30 × 4.6 mm	Methanol: Heptane Sulfonic Acid Buffer (pH 3.4, 0.02 M) with a ratio of 55:45 (v/v). Flow rate 1.2 mL/min.	0,5–30 ng/mL	Fluorescence λ_{ex} = 246 nm λ_{em} = 370 nm	0,1 ng/mL	0,5 ng/mL	Blood plasma	[28]
9.	HPLC-F	The Apollo C18 column (250 × 4.6 mm, id, 5 µm, 250A) (Alltech, Deerfield, IL, USA) is equipped with a protective cartridge that can be refilled in the Apollo C18 package (7.5 × 4.6 mm id, 5 µm)	Methanol – Acetonitrile – 0.04M Disodium Hydrogen Orthophosphate (22:22:56 v/v) adjusted to pH 5 with phosphoric acid 0.9. All separations were performed isocratically with a flow rate of 1.2 mL, and the column temperature was maintained at room temperature	0,5–20 ng/mL	Fluorescence λ_{ex} = 246 nm λ_{em}= 389 nm	0,125 ng/mL	0,5 ng/mL	Analysis of blood plasma samples	[29]

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10.	HPLC-F	The Apollo C18 column (250 × 4.6 mm, id, 5 µm, 250A) (Alltech, Deerfield, IL, USA) is equipped with a protective cartridge that can be refilled in the Apollo C18 package (7.5 × 4.6 mm id, 5 µm).	Methanol – Acetonitrile – 0.04M Disodium Hydrogen Orthophosphate (22:22:56 v/v) adjusted to pH 5 with phosphoric acid 0.9. All separations were performed isocratically with a flow rate of 1.2 mL, and the column temperature was maintained at room temperature	1–25 ng/mL	λ_{ex} = 246 nm λ_{em}= 389 nm	0,5 ng/mL	1 ng/mL	Blood plasma	[30]
11	HPLC-F	C18 column (Hypersil, 250 × 4 mm, 5 µm), column temperature 25 ^{o}C	Acetonitrile: 10 mM Ammonium Acetate (40:60) with a flow rate of 1.0 mL/min.	1-50 ng/mL	λ_{ex} = 246 nm λ_{em}= 376 nm	-	1 ng/mL	Bioequivalence studies	[31]
12.	HPLC-F	Column C18 (4.6 x 250 mm, 5 µm)	Water: Acetonitrile: Triethylamine (68: 32: 0.2 v/v, pH 5.0) with a flow rate of 1.2 mL/min.	-	λ_{ex} = 246 nm λ_{em}= 389 nm	0,2 ng/mL	1 ng/mL	Pharmacokinetic studies	[32]
13.	HPLC-F	Hypersil ODS Column (5 µm, 125 x 4.0 mm)	Acetonitrile: 10 mM Ammonium Acetate (40:60) with a flow rate of 1.0 mL/min	1,0–50 ng/ml.	λ_{ex} = 246 nm λ_{em} = 376 nm	-	-	Pharmacokinetic and bioequivalence studies	[33]
14.	HILIC-MS/MS	Atlantis HILIC Silica column (5 µm, 3 mm x 50 mm).	ACN / Ammonium Format (100 mM, pH 4.5) (93: 7 v/v)	0,2–50 ng/mL	ESI MS/MS	-	0,2 ng/mL	Blood plasma	[36]
15.	LC-MS/MS	Agilent Zorbax Eclipse XDB-C18 column (1.8 µm, 50 x 4.6 mm) is protected by security	5 mM ammonium formate with 0.02% formic acid and (B) 0.02% formic acid in acetonitrile (55:45 v/v) at a	1-500 ng/mL	MS	-	1 ng/mL	Plasma serum	[38]

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		guard cartridge C18 (4 x 2 mm)	flow rate of 1.1 mL/min. Thermostat mobile phase at 40 ± 0.5 °C						
16.	LC-MS-MS	XTerra MS C18 column (150 mm × 2.1 mm, 3.5 µm particle size) is equipped with Xterra MS C18 column (particle size 20 mm × 2.1 mm, particle size 3.5 µm)	The gradient mobile phase consisted of acetonitrile-2 mM ammonium acetate (10:90 v / v) as mobile phase A and acetonitrile-2 mM ammonium acetate (90:10 v / v) as mobile phase B, phase A at time 0.1 , 8, 10, and 15 minutes are 90%, 90%, 30%, 90%, and 90%, respectively. The flow rate is 400 µL / min, and the injection volume is 100 µL.	1–20 ng/mL	MS	0,4 ng/mL	1,2 ng/mL	Pharmacokinetic profile in dogs	[39]
17.	UPLC-MS/MS	The 2.1 × 50 mm column is packed with 1.7 µm particles (ACQUITY UPLC BEH C18 column, Waters) is designed to withstand 15,000 psi.	The mobile phases A and B consist of 0.05 (w/v) pentadecafluoroctanoic acid in acetonitrile and 0.05 pentadecafluoroctanoic acid in water, respectively. The gradient program is as follows: 0–1.45 minutes from 10% to 99% mobile phase A at 0.4 mL minute-1, 1.45–1.55 minutes from 99% to 10% mobile phase A at 1 mL min^{-1}, and 1.55–2 minutes 10% mobile phase A at 1 mL min^{-1}	0,2 - 100 ng/mL	Monitoring reaction of the transition: m / z 452 → 344	0,02 ng/mL	0,07 ng/ mL	Blood plasma	[41]

