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A COMPREHENSIVE REVIEW OF ANALYTICAL METHODS FOR THE ESTIMATION OF DOXAZOSIN MESYLATE

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ABSTRACT

Doxazosin Mesylate is a quinazoline derivative and selective α_1 -adrenoceptor antagonist widely used in the management of benign prostatic hyperplasia (BPH) and hypertension. The development of reliable, accurate and sensitive analytical methods is essential for the identification, quantification and quality control of Doxazosin Mesylate in bulk drug substances, pharmaceutical dosage forms and biological matrices. The present review summarizes the physicochemical and pharmacological characteristics of Doxazosin Mesylate and provides a comprehensive overview of the analytical methods reported for its determination. Various analytical techniques, including UV-visible spectrophotometry, reverse-phase high-performance liquid chromatography (RP-HPLC), stability-indicating HPLC, high-performance thin-layer chromatography (HPTLC) and ultra-performance liquid chromatography (UPLC), have been reported for the estimation of Doxazosin Mesylate. The reviewed spectrophotometric methods commonly employ detection around 245nm, while chromatographic methods utilize different stationary phases and mobile-phase compositions depending on the analytical objective. The reported methods have been evaluated for important validation parameters such as linearity, accuracy, precision, specificity, sensitivity, robustness, limit of detection and limit of quantification. Stability-indicating methods have also demonstrated the ability to separate Doxazosin Mesylate from degradation products generated under different stress conditions. Overall, the available analytical approaches provide useful tools for routine quality control and pharmaceutical analysis of Doxazosin Mesylate. The review highlights the evolution of analytical methodologies and provides a useful reference for the selection and further development of simple, rapid, accurate, precise and stability-indicating methods for Doxazosin Mesylate.

KEYWORDS

Doxazosin, UV Spectroscopy, RP-HPLC and ICH Guidelines.

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INTRODUCTION

A common source of troublesome lower urinary tract symptoms in males is benign prostatic hyperplasia (BPH), which is histologically characterized by prostatic stromal and epithelial hyperplasia. About 40% of men over 60 experience lower urinary tract symptoms, such as frequent

urination, nocturia, decreased urine flow and intermittency and a feeling of incomplete bladder emptying. About 35% of men who turn 50 are that to need treatment for BPH at some point in their lives.

Apart from the structural bladder outlet obstruction caused by prostatic enlargement, there seems to be a dynamic component as well, with sympathetic α 1-adrenoceptor activation raising smooth muscle tone in the bladder neck and prostate. Doxazosin is a well-established, safe and effective α 1-adrenoceptor selective antagonist that was first used to treat hypertension. It is administered once daily to relieve clinical symptoms in BPH. However, a multiple-step titration strategy is necessary when using doxazosin in its conventional formulation to reduce the possibility of a first-dose hypotensive impact.

In order to alter the pharmaceutical treatment to prevent heart attack trial, a new formulation called doxazosin gastrointestinal therapeutic system (doxazosin GITS; Cardura® XL, Cardular® PP Uro, Diblocin® PP ALLHAT (Antihypertensive and Lipid-Lowering Uro)1) was created. It did not alter the pharmacokinetic profile of doxazosin and more precisely controlled the drug delivery rate, enabling a higher and more clinically effective initial dose as well as a simpler titration regimen. The pharmacology and clinical characteristics of doxazosin GITS in patients with symptomatic BPH are reviewed in this paper¹.

Physical Properties

Appearance

Odourless, white to off-white crystalline solid.

Melting point

The stable polymorphs melt at elevated temperature, typically between 276°C and 278 °C.

Solubility

The mesylate salt is freely soluble in dimethyl sulfoxide (DMSO) and dimethyl formamide; soluble in methanol and ethanol; very slightly soluble in acetone and methylene chloride and slightly soluble in water (approximately 0.8% at 25°C).

Chemical Name

1-(4- amino – 6, 7- dimethoxy- 2- quinazoline) -4- [(2, 3 – dihydro-1, 4- benzodioxine-2- yl) carbonyl] piperazine methane sulfonate.

Molecular Formula: C₂₃H₂₅N₅O₅CH₄O₃S.

Structural Class: It is a quinazoline derivative.

Polymorphism

Doxazosin Mesylate exhibits several polymorphic modifications (including forms A, D, E, F, G, H, I and an amorphous state). Form A and form F are stable up to their melting point. whereas other forms vary in hygroscopicity and thermal stability.

REVIEW OF LITERATURE

Shilpa P. Chaudhari, M. P. Ratmaparkhil² et al, (2012)

The UV Spectrophotometric method was used to determine doxazosin mesylate in a fixed dosage form. The absorbance values were measured at 245nm for various drug dilutions, and they were utilized to estimate the drug without excipient interference. 0.01 N Methanol. served as the dilution's solvent. In the concentration range of 2-10µg/ml, this method complies with Beer-Lambert's law. The accuracy of this suggested approach has been confirmed by recovery studies and statistical validation of the analysis results.

Priyanka S. Yadav, Ashok A Hajare³ et al, (2022)

One antihypertensive medication that falls under BCS class II is doxazosin mesylate (DX). The invention of a spectrophotometric method for its analysis in pharmaceutical dosage forms and bulk using 0.1N HCl is not documented in any literature. Therefore, an effort was made to create and evaluate a new UV spectrophotometric technique that would be quick, easy, precise and sensitive for quantitative estimation in tablets utilizing 0.1N HCl as the solvent. With a correlation value (R²) of 0.9981 and a maximum absorbance wavelength of 245nm, DX was linear over the concentration range of 2–14µg/mL. The drug content of two commercial brands, brand I and brand II, was ascertained using the current method. In these brands, the estimated DX content was 99.02% and 99.13%, respectively. During its validation investigation, the suggested approach produced data that supported the label

April – June

30

claim and demonstrated accuracy, precision, sensitivity, and robustness. Recovery study was used to assess the technique's accuracy at three different levels: 80%, 100% and 120%. The percent recovery rate was found to be between 98% and 102%, indicating that the suggested approach is accurate. In accordance with ICH standards, precision and robustness were within allowable bounds. DX in API and dose forms could be measured using the suggested technique.

Young Jae Kim, Yoonjin lee⁴ et al, (2006)

For the measurement of doxazosin in human plasma, a highly sensitive high-performance liquid chromatographic quantification method with fluorescence detection was developed and validated. The method involved one-step extraction of doxazosin from plasma matrix with ethyl acetate using propranolol as an internal standard; chromatographic separation was achieved in 8.0 minutes using a reverse-phase Capcell-Pak C18 column (150 × 4.6mm i.d., 1.8 mM sodium heptane sulfonic acid (50:50, v/v) as the mobile phase. The calibration curve was linear in the range of 0.3-50.0ng/mL. Compared to the reported HPLC procedures, the suggested method attained a lower limit of quantification of 0.3 ng/mL. Doxazosin and the internal standard were recovered from human plasma matrix at average rates of 87.0 and 85.9%, respectively. By assessing the precision and accuracy for intraday and inter-day variation in the concentration range of 0.3-50ng/mL, the current approach was verified. In the intraday and inter-day validation, the precision values, represented as relative standard deviations, were 0.84-5.94% and 1.17-6.29, respectively. The bioequivalency study of two doxazosin-controlled release tablets in male human participants in good health was effectively conducted using this technique. Copyright copyright 2006 Wiley and Sons, Ltd.

Monika Bakshi, Tina Ojha, Saranjit Singh⁵ et al, (2004)

The development of stability-indicating high-performance liquid chromatographic (HPLC) assay techniques for three alpha-adrenergic-blocker drug substances-prazosin, terazosin, and doxazosin-in the presence of degradation products produced by

forced decomposition studies is described in this paper. A reversed-phase C-18 column was used to separate drugs from degradation products. For prazosin and terazosin, the mobile phase was water/acetonitrile/methanol/glacial acetic acid/diethylamine (25:35:40:1:0.017), while for doxazosin, it was acetonitrile/water/glacial acetic acid/diethylamine (65:35:1:0.02). At 254nm, the detection was made. The linearity, precision, accuracy, specificity and robustness of the methods were verified.

B. Dhanya, A. Suganthi⁶ et al, (2011)

To determine doxazosin mesylate in pharmaceutical formulations, a straightforward, accurate, and quick HPLC approach was created. Potassium phosphate buffer and methanol (40:60 v/v) were used in the procedure on a Chromolith RP-C18 column, and detection was performed at 251nm. The range of linearity was 1-5µg/ml. The medication was retained for 3.8 minutes. The results showed that the LOD and LOQ were 0.1µg/ml and 0.5µg/ml, respectively.

Maslarska V⁷ et al, (2023)

For the measurement of doxazosin mesylate, a straightforward, precise, repeatable, and sensitive method was created and verified. Using a LiChrospher RP-18 column and isocratic elution at a flow rate of 1.0ml/min, doxazosin mesylate was extracted via HPLC. The mobile phase was a 45:55 solution of buffer solution (pH=3.9) and acetonitrile. A wavelength of 330 nm was used for the detection. The suggested approach's linearity, accuracy, precision, detection limit and quantification limit were all verified. Doxazosin had a linear range of 0.04-0.13 mg/ml. Doxazosin recovery as a percentage ranged from 99.50-101.5%. Regular quality control analysis of a named medication or combination of tablet formulations is appropriate for the developed method

K.S. Rao, K. B. Deb⁸ et al, (2012)

For the quantitative measurement of doxazosin mesylate (DXM) in pharmaceutical dosage form in the presence of its degradation products, a stability-indicating LC assay method was developed. Kinetic determinations were assessed in both acidic and alkaline degradation conditions. A LiChroCART-April – June

Lichrosphere100 RP-18 column (250 x 4.0mm, 5 [micro]m) was used to accomplish chromatographic separation. DXM was more stable under thermal and photolytic conditions, but it deteriorated under acidic, alkaline, and hydrogen peroxide environments. The method for determining DXM was linear over the range of 1.0-300 [micro]g [mL.sup.-1] (r = 0.9992).

Mohamed S. Mahrous Magdi Mabelkhalek⁹ et al (2014)

One of the most prevalent chronic conditions affecting men is benign prostatic hyperplasia (BPH), which rises in incidence and prevalence with age. In this work, a generic high-performance thin layer chromatographic (HPTLC) approach for the simultaneous determination of five medications indicated for the treatment of BPH is presented. It is straightforward, sensitive, and quick. These medications include the 5 α -reductase inhibitor finasteride (FIN) as well as the α 1-adrenergic blockers alfuzosin hydrochloride (ALF), terazosin hydrochloride (TER), prazosin hydrochloride (PRZ), and doxazosin mesylate (DOX). A mobile phase consisting of methylene chloride: n-hexane: methanol (8.8:0.3:0.9, by volume) was used to separate the mentioned medications on TLC-silica plates. The α -blockers were subjected to densitometric analysis at 254nm, whereas FIN was evaluated at 220nm.

Alankar Shrivastava, Vipin B. Gupt¹⁰ et al, (2012)

The goal of the current study was to use liquid chromatography to separate drugs with similar structures. Under these circumstances, spectrophotometric methods were typically inadequate due to the spectral overlap of medications with similar functional groups. Because terazosin, doxazosin, and prazosin all share the same parent quinazoline nucleus, it is particularly challenging to distinguish between the former two medications due to their strikingly similar structures. For the routine identification of these medications in pharmaceutical formulations, an easy-to-use and sensitive method was tried. We discovered that these medications were successfully separated by the mobile phase made up of A: ACN-

dimethylamine (0.05ml), B: methanol and C: 10mM ammonium acetate. A new Kromasil C18 column with a wavelength of 254nm was used for the separations.

L.I Bebawy A.A Moustafa¹¹ et al, (2002)

Two stability-indicating techniques were created to measure celecoxib (II) and doxazosin mesylate (I) in the presence of their breakdown products. First derivative spectrophotometry (D1) at 256 and 269nm for (I) and (II), respectively, is the basis of the first approach. With mean percentage accuracy of 99.21 $\pm$ 0.88 and 99.59 $\pm$ 1.67% for (I) and (II), respectively, this method determines (I) and (II) in concentration ranges of 0.8-12 and 1-20 μ g ml⁻¹. The mobile phases for (I) and (II) were methyl isobutyl ketone-glacial acetic acid-water (20:10:10) and cyclohexane-dichloromethane-diethylamine (50:40:10), respectively. For (I) and (II), the chromatograms were scanned at 248 and 253nm, respectively. With mean percentage accuracy of 100.19 $\pm$ 0.95 and 99.91 $\pm$ 1.95%, respectively, this approach determines (I) and (II) in concentration ranges of 1-4 μ g per spot for both drugs. Doxazosin mesylates and celecoxib in bulk powder, laboratory-prepared mixes and pharmaceutical dosage forms (Cardura tablet and Celebrex capsule) were measured using the recommended techniques. The outcomes of using the suggested techniques were statistically examined and contrasted with the outcomes of the described techniques.

Bulusu Lakshmi Sushma¹² et al, (2017)

For doxazosin mesylate, related compounds, and degradation impurities created in forced degradation, a straightforward, sensitive and stability representative UPLC technique has been devised. The medication was subjected to oxidative, acidic, base hydrolysis, photolysis, and thermal degradation stress conditions. Under both basic and acid hydrolysis, doxazosin mesylate was found to degrade. In the remaining situations, doxazosin mesylate is stable. Using aqueous 2% H₃PO₄ as eluent-A and a combination of methanol as eluent-B, effective separation from process impurities and degradation contaminants in forced degradation was achieved on an Acquity UPLC BEH C18 stationary phase: Water: Gradient mode acetonitrile April – June

(200:100:700). At 210nm, the analysis was performed. The precision, specificity, robustness, accuracy, and linearity of the new UPLC technology were certified. Doxazosin mesylates routine and stability samples can be analysed using this tried-and-true method.

K. S. Nataraj, A. Srinivasa Rao¹³ et al, (2018)

A novel, simple, accurate and reproducible reverse phase high-performance liquid chromatographic (RP-HPLC) method has been developed for the development and validation of Doxazosin Mesylate in Presence of its degradation Products and Related compounds in its tablet dosage form. Chromatography was performed on a 150×4.6mm, Thermo Hypersil BDS C8-column within a runtime of 55.00 min under gradient elution by a mixture of buffer and Acetonitrile and water at a flow rate of 0.8ml/min. A photodiode array (PDA) detector set at 210nm was used for detection. The method was validated according to the ICH guidelines with respect to specificity, precision, accuracy linearity and robustness. All the validation parameters have come under the limits.

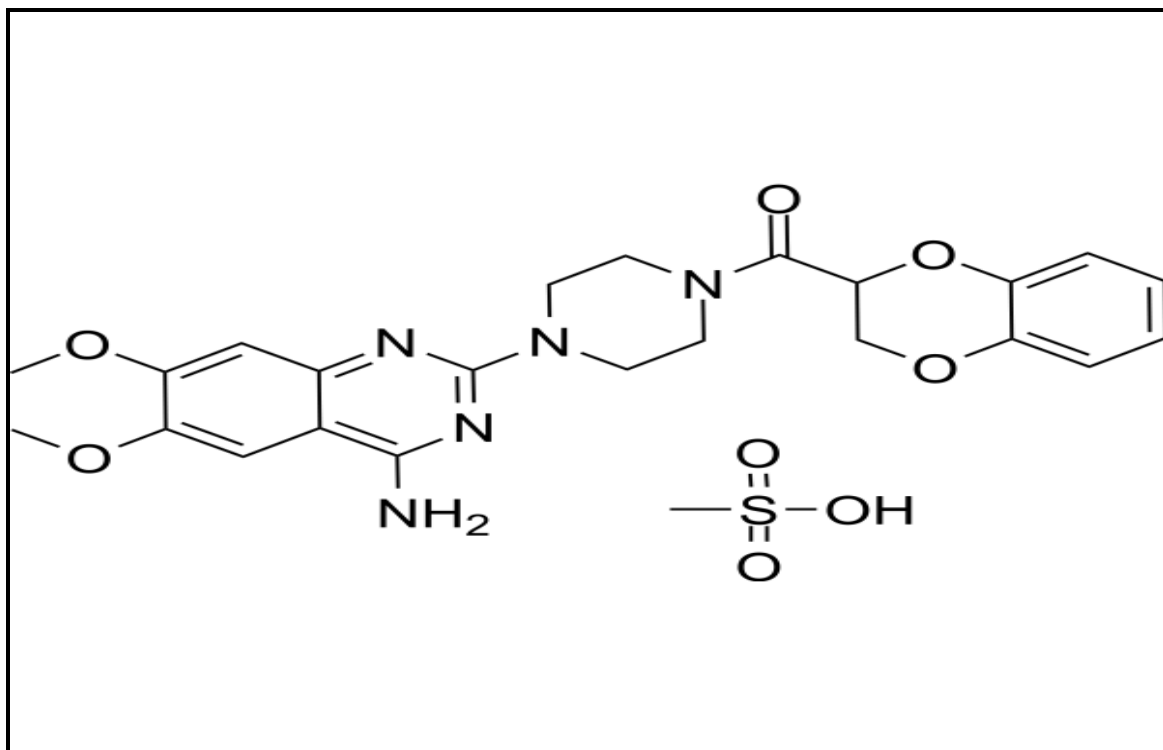


Figure No.1: Structure of Doxazosin mesylate

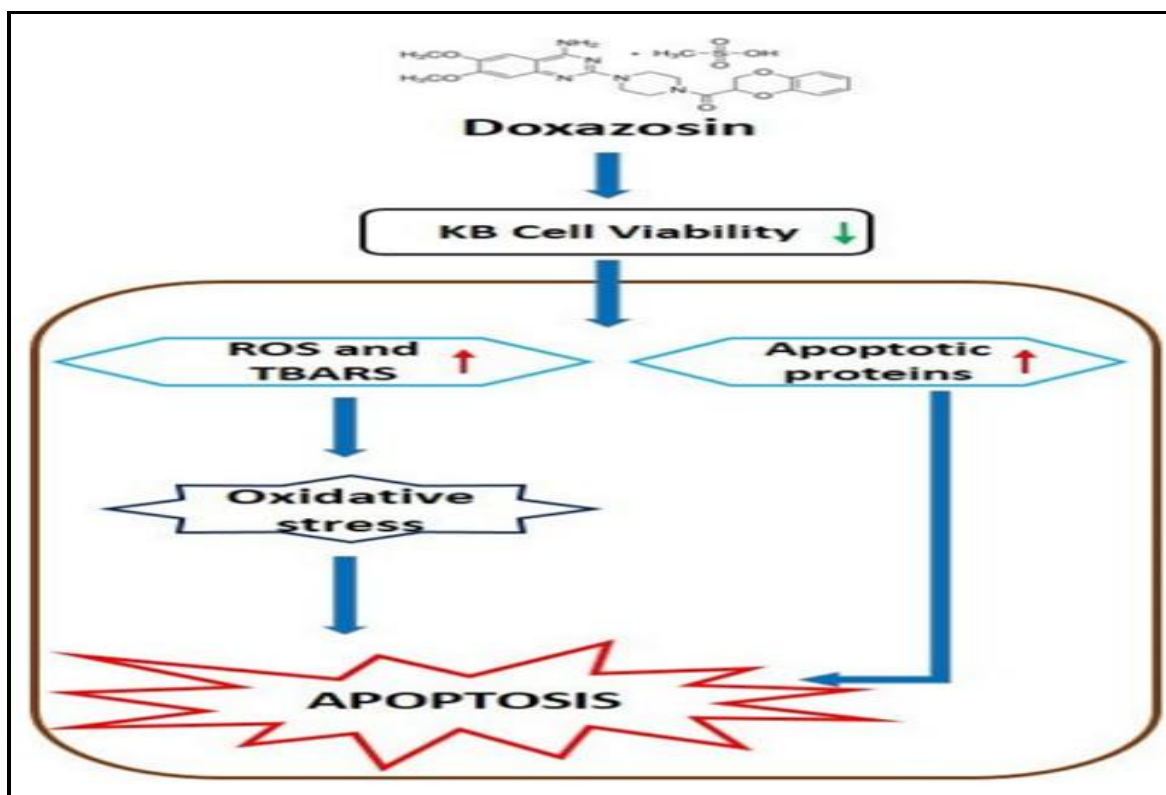


Figure No.2: Mechanism of action of doxazosin mesylate

CONCLUSION

Doxazosin Mesylate is an important quinazoline derivative used primarily in the management of benign prostatic hyperplasia and hypertension. The literature reviewed demonstrates that several analytical methods have been developed for its identification, quantification, and quality control in bulk drug substances, pharmaceutical dosage forms, and biological matrices. UV-visible spectrophotometric methods offer simple, rapid, economical and convenient approaches for routine estimation, with several reported methods showing good linearity, accuracy, precision, sensitivity and robustness. Chromatographic techniques such as RP-HPLC, stability-indicating HPLC, HPTLC, and UPLC provide higher selectivity and are particularly useful for the separation of Doxazosin Mesylate from degradation products, related substances and other structurally similar drugs. The reviewed stability-indicating methods also demonstrate the applicability of chromatographic techniques for studying drug degradation under

different stress conditions. Overall, the available analytical methods provide reliable options for pharmaceutical quality control. The review further indicates that there is scope for developing newer analytical methods that are simple, rapid, sensitive, accurate, precise, economical and environmentally friendly, while complying with current ICH guidelines. Such methods can support routine analysis, formulation development, stability studies and quality assurance of Doxazosin Mesylate.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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