Determination of doxazosin in different matrices: a review

Alankar Shrivastava 1*, Manali Jain 2, Rakhee Varshneya 2

1 Associate Professor, Department of Pharmacy, Institute of Biomedical Education and Research Mangalayatan University Beswan, Aligarh, 202146 U.P, INDIA
2 Department of Biotechnology, Institute of Biomedical Education and Research Mangalayatan University Beswan, Aligarh, 202146 U.P, INDIA
*Corresponding author E-mail: alankar.shrivastava@mangalayatan.edu.in

Abstract

Doxazosin mesylate is used in the management of hypertension and benign prostatic hyperplasia. It is one of the important alpha one adrenoceptor blocker. Alpha one adrenoceptor blockers are most preferred therapy for symptomatic relief of benign prostatic hyperplasia. In this review analytical methods for the determination of doxazosin in different matrices are discussed. Analytical methods are classified in to spectrophotometry, chromatography and electroanalytical methods. This literature is also focused on advantages, disadvantages of different analytical methods. This review article is an attempt to provide information to the scientists engaged in research related to doxazosin.

Keywords: Benign Prostatic Hyperplasia, Doxazosin Mesylate, Analytical Methods, Spectrophotometry, Chromatography, Electro analytical Methods.

1. Introduction

The prostate is a walnut-sized gland that forms part of the male reproductive system. The gland is made of two lobes, or regions, enclosed by an outer layer of tissue. The prostate is located in front of the rectum and just below the bladder, where urine is stored. The prostate also surrounds the urethra, the canal through which urine passes out of the body (U.S. Department of Health and Human Services, 2006).

The prostate’s job is to make some of the fluid that protects and nourishes sperm cells in semen, making the semen more liquid. Just behind the prostate are glands called seminal vesicles that make most of the fluid for semen. The urethra, which is the tube that carries urine and semen out of the body through the penis, goes through the center of the prostate. The prostate starts to develop before birth. It grows rapidly during puberty, fueled by male hormones (called androgens) in the body. The main androgen, testosterone, is made in the testicles (American Cancer Society, 2014).

The prostate gland is an exocrine gland found in all mammals. It secretes enzymes, amines, lipids and metal ions, essential for the normal function of the spermatozoa. Accumulation and secretion of extraordinarily high levels of citrate is one of the principal functions of the prostate gland of humans and other animals (Kindblom 2013).

The human prostate gland is one of the only internal organs that continue to enlarge throughout adulthood. The specific mechanisms that regulate this growth, as well as the pathological changes leading to the phenotype observed in the disease benign prostatic hyperplasia (BPH), are essentially unknown (Schauer & Solomon, 2011).

The human prostate is subject to a variety of pathologic conditions and syndromes that are not well understood. The prevalence of benign prostatic hyperplasia (BPH) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) greatly exceeds that of prostate cancer, which is the most common non-cutaneous malignancy among males in the United States. Patients suffering from benign prostatic symptoms report a substantially reduced quality of life, and the relationship between benign prostate conditions and prostate cancer is uncertain (Freeman & Solomon, 2011).

Benign Prostatic Hyperplasia (BPH) is a progressive disease that is commonly associated with bothersome lower urinary tract symptoms (LUTS) such as frequent urination, urgency, nocturia, decreased and intermittent force of stream, and the sensation of incomplete bladder emptying. The term BPH actually refers to a histologic condition, namely the presence of stromal glandular hyperplasia within the prostate gland (Shrivastava & Gupta, 2012).

Benign prostatic hyperplasia (BPH) affects over 50 percent of men by age 60 and is the cause of millions of dollars of healthcare expenditure for treatment of lower urinary tract symptoms (LUTS) and urinary obstruction (Bechis et al., 2014).

The condition known as benign prostatic hyperplasia may be defined as a benign enlargement of the prostate gland resulting from a proliferation of both benign epithelial and stromal elements. It might also be defined clinically as a constellation of lower urinary tract symptoms (LUTS) in aging men (McLaren et al., 2011).

α1-Adrenoceptors are present in the prostate, urethra, bladder, ureter, vas deferens, peripheral ganglia, nerve terminals, vascular tissues, and central nervous system (CNS), and could potentially influence overall urinary function and contribute to both the therapeutic and adverse effects of α1-adrenoceptor antagonists (Yamada and Ito, 2011). The α1-blockers reduce smooth muscle tone in the prostate and result in rapid improvements in urinary symptoms and flow (Irani 2006, Shrivastava 2013).

Alpha-1 blockers are the first option for the medical treatment of LUTS caused by BPH (Takahashi 2011). Alpha 1-adrenoceptor antagonists (α-blockers) remain the most widely used pharmacologic agents for treating bladder outflow resistance caused by BPH (Perabo 2012, Shrivastava 2013). The amount of prescriptions for α-blockers has been increasing steadily in the last 10 years (Ding...
osulosin, terazosin. Metabolism of doxazosin in
max
inazoline compounds Doxazosin also
-e-
rlgesic
H
t-
N
intervention (Homma et al., 2009). Another report is of medical
cantly decrease in the risk of acute urinary retention and surgical
Japanese Society of Neurogenic Bladder
produces hydroxylated benzodioxan metabolites and less than 15%
piperazine and diaminoqu
man is similar to prazosin; although have altered pharmacokinetics,
tetrahydrofuran group in tera
the benzodioxan moiety may not be as water

Doxazosine 4
Shrivastava & Gupta 2014). Other names are
mesylate is white or almost white crystalline powder slightly sol
weight of 547.6 and a CAS number of 77883
Cardura, Doxasin, Doxazosin Mesilate and UK
(Thiyagarajan 2002, Shrivastava & Gupta 2011). Other names are

Recent pilot study suggests the potential efficacy of doxazosin
when rapidly titrated in reducing cocaine use (Shorter et al., 2013).
Another recent study recommended use of doxazosin to render
children stone free within a shorter period, which would inevitably
diminish the number of colic attacks and the need for analgesic
usage (Erthuran et al., 2013).

Combined doxazosin and finasteride therapy improved LUTS and
reduced the risk of overall clinical progression of BPH compared
to each drug separately in men followed over 4 years (Wilt &
MacDonald 2006).

Doxazosine [4-(4-amino-6, 7-dimethoxyquinazolin-2-yl)piperazin-1-yl]-2, 3-dihydro-1,4-benzodioxin-2-yl)methanone
(Eu Ph 2007) is a quinazoline compound of the
methanesulphonate family; peak plasma concentration is achieved
within 2 to 3 hours of ingestion, with a bioavailability of 65%
(Thiyagarajan 2002, Shrivastava & Gupta 2011). Other names are
Cardura, Doxasin, Doxazosin Mesilate and UK-33274-27. Its
molecular formula is C23H22N2O2CH2SO3H, with a molecular
weight of 547.6 and a CAS number of 77883-43-3. Doxazosin
mesylate is white or almost white crystalline powder slightly solu-
ble in water and methanol and soluble in a mixture of 15 parts of
water and 35 parts of tetrahydrofuran. It is practically insoluble in
aceton (Xu & Madden 2011).

Terazosin and doxazosin have a very similar plasma clearance (1-
1.2 ml/min/kg) and volume of distribution (0.88-0.97 l/kg). Al-
though doxazosin is found to have a longer half-life than prazosin,
the benzodioxan moiety may not be as water-soluble as the
tetrahydrofuran group in terazosin. Metabolism of doxazosin in
man is similar to prazosin; although have altered pharmacokinetics,
primarily handled by the liver and the metabolites are, as prazosin,
6- or 7- demethyllations or, to a small extent, production of
piperazine and diaminoquiazoline compounds Doxazosin also
produces hydroxylated benzodioxan metabolites and less than 15%
of doxazosin survives unaltered (Humphreys & Waite 1989).

Guideline for male lower urinary tract symptoms published by
Japanese Society of Neurogenic Bladder describes effectiveness of
doxazosin therapy in combination with finasteride causing signifi-
cantly decrease in the risk of acute urinary retention and surgical
intervention (Homma et al., 2009). Another report is of medical
treatment of distal ureteral calculi with doxazosin resulted in a
significantly increased stone-expulsion rate and decreased expul-
sion time (Gurbuz et al., 2011).

On the basis of above explanations it can be stated that doxazosin
is important alpha one adrenoreceptor blocker. Thus there is clear
need for discussion on different analytical methods for the deter-
mination of doxazosin in different matrices. This review will help
scientists and researchers engaged in developing different analyti-
cal method or formulation of doxazosin. This review is divided
into three different parts; spectrophotometry, chromatography and
electroanalytical methods.

2. Analytical methods

All of the analytical methods found in literature survey are catego-
rized into three different parts and are presented here in Table 1, 2
and 3, includes summary of all of the spectrophotometry, chroma-
tography and electroanalytical methods respectively.
Analytical method development and validation procedures are
vital in the discovery and development of drugs and pharmaceuti-
cals (Chandran & Singh 2007, Shrivastava & Gupta 2011). The
word validation originates from the Latin validus meaning strong,
and suggests that something has been proved to be true, useful and
of an acceptable standard (Araujo 2009, Kumar et al., 2012,
Shrivastava & Saxena, 2014). Thus we have included discussion
of important validation parameters such as Linearity range, LOD
and LLOQ in this review.

2.1. Spectrophotometry method

Spectrophotometry methods are among the oldest methods of
analytical chemistry. Spectrophotometry as a measuring technique
has developed enormously as a consequence of the progress in the
technology, and in the development of the new materials and of
methods of data processing. Spectrophotometric methods of iden-
tification and determination of substances are based on the exist-
ence of relationship between the position and the intensity of ab-
sorption bands of electromagnetic radiations, on the one hand, and
the molecular structure on the other (Munzenko & Balcerzak
2000).

In our literature survey fourteen different spectrophotometry
methods for the determination of doxazosin were found. Two
fluorimetry methods (Ayad et al., 2012, Ammar et al., 2014) are
also available. Spectrofluorimetry as an analytical tool provides a
well-defined identity of the compounds present in the sample on
the basis of their unique fluorescent nature. The compounds can
be analysed upto the levels of nanograms (Nahata 2011). Fluorimetry
method developed by Ayad MM et al confirms this
theory and found to be most sensitive method in 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 (Shrivastava et al., 2011). There are eight
different methods based on acid-dye method (Aydoğmuş 2009, El

The differentiation of atomic spectra has considerable advantages
for spectrophotometry in the UV and VIS regions. It is the key for
the potential enhancement of resolution of overlapping bands, it
facilitates the detection poorly absorbed peaks arising from admix-
tures or impurities in solution or for structural reasons and it ena-
tbles the exact determination of lamax of the particular analyte spe-
cies and increases the sensitivity of spectrophotometric procedures.
In addition, it is an excellent background elimination technique
(Sommer, 1989). Only one first derivative spectrophotometry
method for the determination of doxazosin was found (Bebawy et
al., 2002). One negative method of simultaneous determination
of doxazosin with prazosin, terazosin, tamsulosin and alfuzosin
(Shrivastava & Gupta 2011) is also available. The summary of all
of the spectrophotometry methods are provided under Table 1.
2.2. Chromatographic methods

High-performance liquid chromatography (HPLC) was introduced to pharmaceutical analysis not long after its discovery in the late 1960s. By now it has developed into a generally applicable analytical method providing rapid and versatile separation possibilities that meet the increasing requirements for purity testing of bulk pharmaceuticals and pharmaceutical products (Shrivastava & Gupta 2012). Ten different HPLC determinations with UV detectors (Eu Ph 2007, Dhanya et al., 2011, Kulsum et al., 2011, Shrivastava & Gupta 2012, Naidu et al., 2012, Rao et al., 2012, Rao et al., 2012, Sreekavats et al., 2013, Shrivastava & Gupta 2014.) were found in available literature out of which three are based on gradient elution (Eu Ph 2007, Shrivastava & Gupta, 2012, Shrivastava & Gupta 2012). Detectors that measure absorption of light in the ultraviolet (UV) or visible (VIS) regions were used for at least 75% of the applications during the first decade of high performance liquid chromatography (Vickery 1983). The UV-Vis absorbance detector monitors the absorption of UV or visible light in the HPLC client. They are the most common detectors since most analytes of interest (e.g. Pharmaceuticals) have UV absorbance (Papadoyannis 1990). The main disadvantage of these detectors – either fixed wavelength detectors or variable wavelength- is that they do not detect aliphatic components in the samples of clinical interest (Dong 2006).

Gradient elution gave a shorter overall analysis with similar resolution of the critical pair compared to isocratic elution without sacrificing repeatability in retention time, peak area and peak height or linearity of the calibration curve (Karch 2008). In this review three gradient elution methods (Eu Ph 2007, Shrivastava & Gupta, 2012, Shrivastava & Gupta 2012) are also included. Fluorescence detectors, with variable excitation and emission wavelengths, provide high sensitivity and specificity for the detection and quantification of fluorescence compounds, but they are more useful for quantification rather than identification (Schellinger & Carr 2006). There are some reported disadvantages such as decrease in the yield of fluorescence by quenching and reabsorption of reemitted light. Also fluorescence intensity may also be affected by the column temperature in gradient chromatography, since chromatography efficiency is strongly dependent on solvent composition. Despite all of these disadvantages, fluorescence detection is still one of the most valuable techniques for the trace analysis by HPLC (Swadesh 2001). During the preparation of this review seven (Bhavesh et al., 2002, Srilapalakit et al., 2005, Srilapalakit et al., 2006, Wongsinsup et al., 2007, Kwon et al., 2007, Kaewwichit et al., 2007) different HPLC methods with fluorescence detection were found.

Hydrophilic interaction liquid chromatography (HILIC), although not a new technique, has enjoyed a recent renaissance with the introduction of robust and reproducible stationary phases (Cubbon 2010). HILIC can provide better chromatographic retention of highly polar or ionizable analytes, can separate analytes of widely differing polarity in a reasonable time, can enhance sensitivity with electrospray LC-MS, and can resolve an analyte and its counter-ion in the same analysis (Zhang 2012). HILIC-MS/MS method for the quantitation of doxazosin is developed and validated by Ji et al. 2008. This method was claimed to be free from matrix effects assessed by post extraction analyte spiking. The combination of chromatography and mass spectrometry is a subject that has attracted much of interest over the large forty years or so. But the complexity of mass spectrometer has meant that the majority of chromatographers has not had direct access to the instrumentation and has had to rely on service providers. Therefore they are unable to react rapidly to the result of analysis and consequently particularly inconvenient detector to contemplate using. However the combination of HPLC with mass spectrometry allows more definitive identification and the quantitative determination of compounds that are not fully resolved chromatographically (Ardrey 2003). Two LC-MS methods (Chytil et al., 2008, Aydoğmuş 2009, El Sheikh et al., 2012, Aydogmus et al., 2009) were also found for the determination of doxazosin. Both the methods have appreciable sensitivity and may be used in biological matrices.

UPLC has been gradually adopted in industrial labs, especially the pharmaceutical industry due to its high resolution, high speed, and solvent saving since its introduction in early 2004. A UPLC method using a sub-2 μm column could reduce the analysis time by up to 80% compared with the HPLC method using conventional 3.5 μm column without sacrificing separation performance. In addition, much shorter run time significantly reduces UHPLC method development scouting time (Chen & Kord 2013). In this review only one such method (Al-Dirbashi et al., 2011) was found.
The modern HPTLC technique, combined with automated sample application and densitometric scanning, is sensitive and completely reliable, suitable for use in qualitative and quantitative analysis. HPTLC is a valuable tool for reliable identification because it can provide chromatographic fingerprints that can be visualized and stored as electronic images (Srivastava 2011). Advantages of HPTLC over TLC include more rapid separation, better resolution and more sensitive detection (5 - 10 fold), without the need for prior extraction (Andol & Purohit, 2010). HPTLC produces visible chromatograms complex information about the entire sample is available at a glance. Multiple samples are seen simultaneously, so that reference and test samples can be compared for identification (Shepherd et al., 1978). Three HPTLC methods (Shepherd et al., 1978, Altioekka 2001, Sreevatsav 2013) for the determination of doxazosin were found. One of these methods is stability indicating method (Bebawy 2002). The summary of all of the chromatographic methods are presented under Table 2. HPLC-UV method (Kuslum et al., 2011) is the most sensitive method developed by using UV detector. With LOD of 0.1 ng/ml method (Bhavesh et al., 2002) is the most sensitive method in the category of fluorescence detectors. Inspite of many advantages of LC-MS/MS equipments, methods available in literature does not seem to produce any significant advantage in terms of sensitivity. Overall HPLC methods developed by using fluorescence detectors have good sensitivity. UPLC-MS/MS method (Al-Dirbashi et al., 2006) is the most sensitive method in all of the methods developed for the determination of doxazosin in different matrices. Advantages of such methods are already discussed in above texts.

### Table 2: Chromatographic methods for the determination of doxazosin in different matrices

<table>
<thead>
<tr>
<th>Method</th>
<th>Chromatographic Conditions</th>
<th>Mobile Phase</th>
<th>Linear Range</th>
<th>Detection</th>
<th>LOD</th>
<th>LOQ</th>
<th>Application</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPLC-UV</td>
<td>Column 3.9 mm in inside diameter and 15 cm in length, packed with octadeysilized silica gel for liquid chromatography (4 μm in particle diameter), Temperature 25°C</td>
<td>A mixture of 0.05 mol/L potassium dihydrogen phosphate TS, pH 3.0, methanol and acetonitrile (12:8:3).</td>
<td>NM</td>
<td>246 nm</td>
<td>NM</td>
<td>NM</td>
<td>Pure</td>
<td>JP 2007</td>
</tr>
<tr>
<td>Gradient HPLC-UV</td>
<td>Base activated octylsil gel column 250×4.0 mm, 5 μm</td>
<td>10 g/L HEPES and 10 g/L solution of phosphoric acid in ACN. Temp 35°C</td>
<td>NM</td>
<td>210 nm</td>
<td>-</td>
<td>Assay and related substance</td>
<td>Assay and related substance</td>
<td>Eu Ph 2007</td>
</tr>
<tr>
<td>RP-HPLC-UV</td>
<td>Chromolith RP-C18 column</td>
<td>Mixture of potassium phosphate buffer and methanol (40:60 v/v). Mixture of Methanol and Potassium Dihydrogen Orthophosphate in the proportion 60:40. And adjust the pH to 5.0±0.05 with sodium hydroxide solution.</td>
<td>1-5 μg/ml</td>
<td>251 nm</td>
<td>0.1 μg/ml</td>
<td>0.5 μg/ml</td>
<td>Tablets</td>
<td>Dhanya 2011</td>
</tr>
<tr>
<td>HPLC-UV</td>
<td>Chromolith RP-C18, 100 mm x 10 μ</td>
<td>Ortho phosphoric acid: Acetonic acid (60:40:v/v) and adjust the pH to 3.2 by using 0.03M potassium hydrogen phosphate buffer.</td>
<td>48-144 μg/ml</td>
<td>245 nm</td>
<td>0.06 μg/ml</td>
<td>0.08 μg/ml</td>
<td>Tablets</td>
<td>Khosla et al., 2011</td>
</tr>
<tr>
<td>HPLC-UV</td>
<td>Chromolith RP-C18 column, 50 mm x 4 mm</td>
<td>Methanol-water (60/40 % v/v)</td>
<td>1-300 μg/ml</td>
<td>247 nm</td>
<td>0.3 μg/ml</td>
<td>1.2 μg/ml</td>
<td>Pharmaceutical formulations</td>
<td>Rao et al., 2012</td>
</tr>
<tr>
<td>HPLC-UV</td>
<td>Chromolith RP-C18 column, 50 mm x 4 mm</td>
<td>Methanol-water:acetonitrile (25:25:50 v/v)</td>
<td>0.5-2.5 mg/ml</td>
<td>280 nm</td>
<td>40 μg/ml</td>
<td>110 μg/ml</td>
<td>Human plasma and pharmaceutical formulations</td>
<td>Rao et al., 2012</td>
</tr>
<tr>
<td>HPLC-UV Gradient</td>
<td>Kromasil C18 column (250 × 4.6 mm, 5.0 μ)</td>
<td>Phosphate buffer: Methanol (40:60) ratio</td>
<td>50-150 μg/ml</td>
<td>251 nm</td>
<td>NM</td>
<td>NM</td>
<td>Tablet</td>
<td>Sreevatsav et al., 2013</td>
</tr>
<tr>
<td>HPLC-UV Gradient</td>
<td>Kromasil C18 column (250 × 4.6 mm, 5.0 μ)</td>
<td>The gradient condition of the mobile phase (A:B:C:D) was: 60:40:0:0 for 8 min, 60:20:20 for 1 min, 30:0:40 for 6 min, 50:50:0:0 for 1 min, and further 60:0:40:0 for 1 min for system equilibration. A: ACN-diethylamine (0.05 ml), B: methanol, and C: 10 mM Ammonium acetate, (A:B:C) was: 60:40:0:0 for 8 min, 60:20:20 for 1 min, 30:0:40 for 6 min, 50:50:0:0 for 1 min, and further 60:0:40:0 for 1 min for system equilibration. The mobile phase was methanol-acetonitrile-0.04M disodium hydrogen orthophosphate (22:22:56 v/v) adjusted to pH 5 with 0.9M phosphoric acid. All separations were performed isocratically at a flow rate of 1.2 mL/min, and the column temperature was maintained at room temperature.</td>
<td>4-16 μg/ml</td>
<td>230 nm</td>
<td>0.14 μg/ml</td>
<td>0.462 μg/ml</td>
<td>Tablets</td>
<td>Shrivastava &amp; Gupta, 2012</td>
</tr>
<tr>
<td>HPLC-UV Gradient</td>
<td>Kromasil C18 column (250 × 4.6 mm, 5.0 μ)</td>
<td>2-500 μg/ml</td>
<td>254 nm</td>
<td>0.109 μg/ml</td>
<td>0.332 μg/ml</td>
<td>Tablets</td>
<td>Shrivastava &amp; Gupta, 2012</td>
<td></td>
</tr>
<tr>
<td>HPLC-F</td>
<td>Apollo C18 column (250 × 4.6 mm i.d., 5 μm, 250A) (Alltech, Deerfield, IL) fitted with a refillable guard cartridge (Alltech) packed with Apollo C18 (7.5 × 4.6 mm i.d., 5 μm).</td>
<td>The column was maintained at ambient temperature, and the mobile phase was methanol-acetonitrile-D2O (80:20:0.1 v/v).</td>
<td>0.5-20 ng/ml</td>
<td>246 nm</td>
<td>λemin=246 nm</td>
<td>λemax=389 nm</td>
<td>0.125 ng/ml</td>
<td>0.5 ng/ml</td>
</tr>
</tbody>
</table>
Electroanalytical techniques can easily be adopted to compound analysis (Shrivastava 2012, Shrivastava et al., 2013). Modern electrochemical methods are now sensitive, selective, and reproducible way by employing this approach (Zuman 2006).

The MS parameters for the analysis were as follows: ion source temperature 550 °C; ion-spray voltage 5000 V; nebulizer gas 45 psig; auxiliary gas 50 psi; curtain gas 10 psi and medium collision gas.

| RP-HPLC-F | Hypersep C8 5 μm, 250×4.6 mm with 300×4.6 mm guard column | Methanol: heptane sulphonic acid buffer (pH 3.4, 0.02 M) in the ratio 55:45. Flow rate 1.2 ml/min. | 0.5-30 ng/ml | Fluorescence λ<sub>ex</sub> = 246 nm λ<sub>em</sub> = 370 nm | 0.1 ng/ml | 0.5 ng/ml | Human plasma | Bhavesh et al., 2002 |
| HPLC-F | Apollo C18 column (250 × 4.6 mm, 5 μm) | Methanol–acetonitrile–0.04 M disodium hydrogen orthophosphate (pH 4.9 with 0.9 M phosphoric acid) | 1—25 ng/mL | Fluorescence λ<sub>ex</sub> = 246 nm λ<sub>em</sub> = 389 nm | NM | 1 ng/mL | Plasma sample analysis for pharmacokinetic study | Seipalak et al., 2006 |
| HPLC-F | ODS hypersil (5 μm, 125×4.0 mm) column | Acetonitrile : 10 mM ammonium acetate (40:60) at a flow rate of 1.0 ml/min. | 1.0—50.0 ng/mL | λ<sub>ex</sub> = 246 nm, λ<sub>em</sub> = 376 nm | - | 1 ng/mL | Pharmacokinetic and bioequivalence study | Wongsinsap et al., 2007 |
| HPLC-F | C18 column was used for the separation of doxazosin and prazosin (internal standard) | Water/acetonitrile/trimethylamine (68:32:0.2 v/v, pH 5.0) at a flow rate of 1.2 mL/min | - | 246 (excitation) and 389 nm (emission) | NM | 1 ng/mL | Pharmacokinetic study | Kwon et al., 2007 |
| HPLC-F | C<sub>18</sub> column (HyperSpher 250×4, 5 μm) | Acetonitrile:10 mM ammonium acetate (40:60) with a flow rate 1.0 ml/min. | 1.50 ng/ml | Fluorescence λ<sub>ex</sub> = 246 nm λ<sub>em</sub> = 376 nm | NM | 1 ng/mL | Bioequivalence Studies | Kaewvichith et al., 2007 |
| HPLC-F | C<sub>18</sub> column (HyperSpher 125×4, 5 μm) | Acetonitrile:10 mM ammonium acetate (40:60) with a flow rate 1.0 ml/min. | 1.50 ng/ml | Fluorescence λ<sub>ex</sub> = 246 nm λ<sub>em</sub> = 376 nm | NM | 1 ng/mL | Bioequivalence Studies | Kaewvichith et al., 2007 |
| HILIC-MS/MS | Atlantis HILIC Silica column (250×4 mm, 5 μm). | Mobile phase ACN/ammonium formate (100 mM, pH 4.5) (93:7 v/v) | 0.2—50 ng/mL | ESI MS/MS | - | 0.2 ng/mL | Pharmacokinetic study | Zhang et al., 2012 |
| LC-MS/MS | Agilent Zorbax Eclipse XBD-C18 column (1.8 μm, 50x4.6mm I.D.), protected by a C18 security guard cartridge (4x2 mm I.D.) | 5mM ammonium formate with 0.02% formic acid and (B) 0.02% formic acid in acetonitrile (55:45, v/v) | 1 and 500 ng/mL | - | 1 ng/mL | human serum | Ji et al., 2008 |
| LC-MS/MS | XTerra MS C18 column (150 mm×2.1 mm, 3.5 μm particle size) equipped with an XTerra MS C18 guard column (20 mm×2.1 mm, 3.5 μm particle size) | Gradient mobile phase was composed of acetonitrile–2 mM ammonium acetate (10:90, v/v) as mobile phase A and acetonitrile–2 mM ammonium acetate (90:10, v/v) asmobile phase B. Mobile phase A at times 0, 1, 8, 10, and 15 min was 90%, 90%, 30%, 90%, and 90%, respectively. The flow rate was 400 μL/min, and the injection volume was 100 μL. Mobile phases A and B consisted of 0.05 (w/v) pentadecfluorooctanoic acid in acetonitrile and 0.05 (w/v) pentadecfluoroocanonic acid in water, respectively. The gradient program was as follows: 0—1.45 min from 10% to 99% mobile phase A at 0.4 ml min<sup>−1</sup>, 1.45—1.55 min from 99% to 10% mobile phase A at 1 ml min<sup>−1</sup>, and 1.55—2 min 10% mobile phase A at 1 ml min<sup>−1</sup>. | 0.2—100 ng/ml | Reaction monitoring of the transitions: m/z 452→344 | 0.02 ng/ml | 0.07 ng/ml | Human Plasma | Erceg et al., 2010 |
| UPLC-MS/MS | 2.1x50 mm column packed with 1.7 μm particles (ACQUITY UPLC BEH C18, Waters) designed to withstand 15,000 psi. | Mobile phases were composed of acetonitrile–2 mM ammonium acetate (90:10, v/v) as mobile phase A and acetonitrile–2 mM ammonium acetate (10:90, v/v) asmobile phase B. Mobile phase A at times 0, 1, 8, 10, and 15 min | 1—20 ng/mL | MS | 0.4 ng/mL | 1.2 ng/mL | Pharmacokinetic profiles in dogs | Chytli et al., 2010 |
| HPTLC stability indicating | Silica Gel F<sub>254</sub> | Gradient mobile phase was composed of acetonitrile–2 mM ammonium acetate (95:5, v/v) as mobile phase A and acetonitrile–2 mM ammonium acetate (5:95, v/v) asmobile phase B. Mobile phase A at times 0, 1, 8, 10, and 15 min was 90%, 90%, 30%, 90%, and 90%, respectively. The flow rate was 400 μL/min, and the injection volume was 100 μL. Mobile phases A and B consisted of 0.05 (w/v) pentadecfluoroocanonic acid in acetonitrile and 0.05 (w/v) pentadecfluoroocanonic acid in water, respectively. The gradient program was as follows: 0—1.45 min from 10% to 99% mobile phase A at 0.4 ml min<sup>−1</sup>, 1.45—1.55 min from 99% to 10% mobile phase A at 1 ml min<sup>−1</sup>, and 1.55—2 min 10% mobile phase A at 1 ml min<sup>−1</sup>. | 0.2—100 ng/ml |反应 monitoring of the transitions: m/z 452→344 | 0.02 ng/ml | 0.07 ng/ml | Human Plasma | Erceg et al., 2010 |
| HPTLC | Silica gel 60 F<sub>254</sub> | Mobile phases were composed of acetonitrile–2 mM ammonium acetate (95:5, v/v) as mobile phase A and acetonitrile–2 mM ammonium acetate (5:95, v/v) asmobile phase B. Mobile phase A at times 0, 1, 8, 10, and 15 min was 90%, 90%, 30%, 90%, and 90%, respectively. The flow rate was 400 μL/min, and the injection volume was 100 μL. Mobile phases A and B consisted of 0.05 (w/v) pentadecfluoroocanonic acid in acetonitrile and 0.05 (w/v) pentadecfluoroocanonic acid in water, respectively. The gradient program was as follows: 0—1.45 min from 10% to 99% mobile phase A at 0.4 ml min<sup>−1</sup>, 1.45—1.55 min from 99% to 10% mobile phase A at 1 ml min<sup>−1</sup>, and 1.55—2 min 10% mobile phase A at 1 ml min<sup>−1</sup>. | 0.2—100 ng/ml | Reaction monitoring of the transitions: m/z 452→344 | 0.02 ng/ml | 0.07 ng/ml | Human Plasma | Erceg et al., 2010 |
| HPTLC | Silica gel precoated aluminium plate 60F<sub>254</sub>, 254 plates, (20 x 10 cm with 250 μm thickness) | Silica gel precoated aluminium plate 60F<sub>254</sub>, 254 plates, (20 x 10 cm with 250 μm thickness) | Chloroform: methanol (9.5: 0.5) | 254 nm | 0.03 mg/ml | 0.09 mg/ml | Tablets | Shrivastava & Gupta 2012 |

**2.3. Electroanalytical methods**

Modern electrochemical methods are now sensitive, selective, rapid and easy techniques applicable to analysis in the pharmaceutical fields, and indeed in most areas of analytical chemistry. They are probably the most versatile of all trace pharmaceutically active compound analysis (Shrivastava 2012, Shrivastava et al., 2013). Electroanalytical techniques can easily be adopted to solve many problems of pharmacological interest with a high degree of accuracy, precision, sensitivity and selectivity, often in a spectacularly reproducible way by employing this approach (Zuman 2006).

Two methods based on the mechanism of oxidation of amine group of the drug is described by Arranz et al. Both the methods based on adsorptive stripping (AdS) of doxazosin at the C8 modified carbon paste electrode (C8-MCPE), before its voltammetric determination by using Differential pulse voltammetry (DPV) and Square wave voltammetry (SWV). Limit of detection described were 7.4×10<sup>−10</sup> mol/L and 7.7×10<sup>−10</sup> mol/L for DPV and SWV.
methods respectively. Both the methods were utilized for the determination of doxazosin in urine and formulations.

Another voltammetric determination method found was described by Altiookka et al. This method is based on the oxidation on the surface of platinum electrode in the stationary and rotating conditions for determining and determine doxazosin in the tablets by differential pulse technique at only rotating condition. Detection limits were calculated to be 2×10⁻⁶ M and 1.5×10⁻⁷ M DOX accepting signal-to-noise is equal to 3, for limiting current and peak current, respectively.

DC polarography and the determination of doxazosin employing superimposed increasing amplitude pulse (SIAP) and superimposed constant amplitude pulse (SCAP) polarographic techniques are described by Altiookka and Tuncel 1998. This method is based on the fact that doxazosin molecule has a quinazoline group this group can be reduced by two electrons on the mercury electrode. Another voltammetric technique for the determination of doxazosin is also available (Arranze et al., 1997). They evaluated cathodic adsorptive stripping (Ads) response with respect to pH, accumulation variables and instrumental parameters, using differential-pulse (DPV) and square-wave voltammetry (SWV) as redissolution techniques. When the Tenax-modified carbon paste electrode was used, the limits of detection were 4.35×10⁻⁷ M and 5.18×10⁻⁸ M for Ads–DPV and Ads–SWV, respectively.

2.4. Cerimetric method

Quadrivalent cerium is a powerful oxidizing agent in acidic solutions. The normal oxidation potential with reference to hydrogen is 1.96 volts (Rani 2014). The available cerimetric method (Walb 1940) is based on the oxidation of Doxazosin drug by a known excess amount of cerium IV sulphate in acid medium. Unreacted cerium IV sulphate was treated with Iron II sulphate and the remaining Iron III sulphate was treated with (1M) Ammonium thiocyanate to forms blood red colour of Iron III sulphate thiocyanate drug complex solution. This resultant solution was then measured at 505 nm against reagent blank.

3. Conclusion

It is essential to ensure that these analytical methods are fit for their purpose. Method validation is aimed at providing this guarantee (Rozet et al., 2012). This review includes discussion on sensitivity of methods and also highlights on advantages or disadvantages of different types of method. In this way all of the analytical methods for the determination of doxazosin mesylate in different matrices are discussed here. The summary of all of the spectrophotometry methods are presented in Table 1, whereas all chromatographic and adsorptive methods are presented under Table 2. This review is helpful for researchers and scientists engaged in the development of new analytical method or formulation for doxazosin.

References


