Iranian Journal of Analytical Chemistry
Volume 2, Issue 2, September 2015 (77-99)

مجله ایرانی شیمی تجزیه
دوره ۲، شماره ۲، مهرماه ۱۳۹۴ (۹۹-۷۷)

تعیین آلفوزوسین، سیلودوسین و نفتوپیدیل در ماتریس های مختلف – یک مقاله مروری

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بخش دارویی، دانشگاه منگالایاتان، بسوان، آلیگار، هند
تاریخ دریافت: ۱۶ خرداد ۱۳۹۴ تاریخ پذیرش: ۸ شهریور ۱۳۹۴

Determination of Alfuzosin, Silodosin and Naftopidil in Different Matrices - A Review

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Received: 6 June 2015 **Accepted:** 30 August 2015

چکیده
غده خوش خیم غده پروستات عموما" مردان بالای ۴۰ سال را تحت تاثیر قرار می دهد و اثرات معنی داری روی کیفیت زندگی خواهد داشت. این بیماری یکی از علت های هزینه های میلیون دلاری در بخش سلامت می باشد. مسدود کننده های آلفا به طور معمول در وضعیت بزرگ شدن غده پروستات مورد استفاده قرار می گیرند که علت آن اثر این داروها در اثرات معنی دارشان در بهبود ذخیره سازی، دفع، وضعیت عمومی و حجم و سرعت جاری شدن ادرار باقیمانده بیمار می باشد. مطالعه حاضر عبارتست از مروری به روش های اندازه گیری سه مسدود کننده آلفا شامل آلفوزوسین، سیلودوسین و نفتوپیدیل در بافت ها و ترکیبات مختلف. این نوع از مطالعه برای محققینی که بر روی اندازه گیری این داروها مطالعه می کنند، کمک کننده خواهد بود تا بتوانند شرایط اولیه تحقیق خود را راحت تر به دست آورند. همچنین این مقاله مروری به محققین در توسعه فرمولاسیون این داروها کمک می کند.

واژه‌های کلیدی
آلفوزوسین؛ سیلودوسین؛ نفتوپیدیل؛ روش اسپکترومتری؛ روش کروماتوگرافی؛ روش الکتروشیمیایی.

Abstract
Benign Prostatic Hyperplasia generally affects males above fourty years of age and has significant effect in overall quality of life (QOL). This is one of the cause of millions of dollors in healthcare expenditure. Alpha one adrenoreceptor blockers are frequently used for the benign prostatic enlargement because of their significant effect on storage and voiding symptoms, QOL, flow rate and post void residual urine volume. The present study is review on the determination of three alpha one adrenoreceptor blockers Alfuzosin, Silodosin and Naftopidil in various matrices and combinations. This kind of literature is helpful for those scientists engaged in the determination of these drugs by supporting them in terms of current available literature is one platform so that they can decide the initial conditions of their research such as decisions of mobile phase, dilutions etc. This review article also helps scientists engaged in developing formulations of these drugs.

Keywords
Alfuzosin; Silodosin; Naftopidil; Spectrophotometry Method; Chromatographic Method; Electroanalytical Methods.

1. INTRODUCTION

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 [1]. BPH can be defined as "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 (LUTSs) in aging men [2]. BPH affects over 50 percent of men by age 60 [3]. This is one of the cause of the expenditure of millions of dollors in healthcare sector.

More serious complications of BPH include acute urinary retention, renal insufficiency, urinary tract infection, gross hematuria, bladder stones and renal failure. Lack of or inadequate management of

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BPH may precipitate or worsen these conditions [4]. Alpha blockers are the most effective drug for improving lower urinary tract symptoms and short term quality of life [5]. The predominance of α_1-adrenergic receptors in the bladder neck or prostate (40 times the bladder concentration) helped focus interest on α_1-adrenergic blocking agents in the treatment of symptomatic BPH [6]. The α_1-blockers reduce smooth muscle tone in the prostate and result in rapid improvements in urinary symptoms and flow [7].

α_1-Adrenergic receptors (AR) mediate many of the physiological functions of the endogenous catecholamines noradrenaline and adrenaline such as smooth muscle contraction or cellular hypertrophy. Moreover, they are the molecular target for clinically used drugs for the treatment of e.g. arterial hypertension or benign prostatic hyperplasia [8]. α-Adrenoreceptor antagonists are frequently used to treat patients with LUTS and benign prostatic enlargement because of their significant effect on storage and voiding symptoms, QOL, flow rate, and post void residual urine volume [9-10]. The amount of prescriptions for α-blockers has been increasing steadily in the last 10 years [11-12].

Starting from the initial drug discovery phase, analytical chemistry applications are found throughout the drug development process. These applications can be categorized into two major subdivisions: pharmaceutical analysis and bioanalysis. Pharmaceutical analysis involves the measurement of an analyte in a neat sample or formulation, whereas bioanalysis is the quantification of an analyte in a biological matrix [13].

Analytical method development and validation procedures are vital in the discovery and development of drugs and pharmaceuticals [14-16]. 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 [17-18]. This is the reason for inclusion of important validation parameters such as Linearity range, LOD and LOQ in this review.

1.1 Alfuzosin

Alfuzosin, an alpha-adrenergic antagonist has been in clinical use for more than three decades. The drug has a better adverse event profile as compared to other alpha-adrenergic antagonists of its class. In terms of efficacy, there is little difference among the alpha-adrenergic antagonists. Alfuzosin is metabolized extensively in the liver to form inactive metabolites which are mostly excreted in the faeces. CYP3A4 has been identified to be the major metabolizing enzyme. It has a plasma half-life of 7 h (immediate release formulation) and a clearance of 0.36 L/h/kg. The pharmacokinetics is unchanged in cardiac insufficiency, though the prolonged release formulation is contra-indicated in patients with hepatic insufficiency [19].

Alfuzosin, a quinazoline derivative, is a selective and competitive alpha(1)-adrenoceptor antagonist. It distributes preferentially in the prostate, compared with plasma, and decreases the sympathetically controlled tone of prostatic smooth muscle. As a result lower urinary tract symptoms suggestive of benign prostatic hyperplasia (BPH) are improved. Prolonged-release alfuzosin 10 mg once daily controls symptoms associated with BPH throughout a 24-hour dosage interval as effectively as immediate-release alfuzosin 2.5mg three times daily but with fewer vasodilatory adverse events. For the medical management of men with BPH, prolonged-release alfuzosin 10mg is an effective, well tolerated and convenient treatment option [20].

Sustained release alfuzosin *N*-[3-[(4- amino-6, 7-dimethoxy – quinazolin-2- yl)-methyl-amino] propyl] oxolane-2-carboxamide hydrochloride is the fourth α_1-selective blocker approved by the FDA for the treatment of symptomatic BPH [21].

Prolonged-release alfuzosin effectively improved LUTS, quality of life, erectile function, and sexual satisfaction in men with BPH and mild to severe erectile dysfunction. Alfuzosin is an effective treatment option for the management of patients with BPH/LUTS and concomitant sexual dysfunction [22].

In a randomized control study performed by Dellis *et al* [23], to evaluate the effect of 2 different α-blockers in improving symptoms and quality of life in patients with indwelling ureteral stents. Patients were randomly assigned to receive tamsulosin 0.4 mg, alfuzosin 10 mg, or placebo. These α-blockers reduce stent-related symptoms and the negative impact on quality of life [23].

Alfuzosin hydrochloride contains not less than 98.5 percent and not more than the equivalent of 101.0 per cent of (*RS*)-*N*-[3-[(4-amino-6,7-dimethoxyquinazolin-2-yl)(methyl)amino]propyl] tetrahydrofuran-2-carboxamide hydrochloride, calculated with reference to the anhydrous substance. A white or almost white, crystalline powder, slightly hygroscopic, freely soluble in water, sparingly soluble in alcohol, practically insoluble in methylene chloride [24]. Its melts at approximately 240° C [25].

1.2 Silodosin

Silodosin is a new α_1-adrenergic receptor antagonist that is selective for the α_{1A}-adrenergic receptor. It was approved by the US Food and Drug Administration (FDA) in 2008 for the treatment of

lower urinary tract symptoms (LUTS) associated with BPH [26].

By antagonizing α_{1A}-adrenergic receptors in the prostate and urethra, silodosin causes smooth muscle relaxation in the lower urinary tract. Since silodosin has greater affinity for the α_{1A}-adrenergic receptor than for the α_{1B}-adrenergic receptor, it minimizes the propensity for blood pressure-related adverse effects caused by α_{1B}-adrenergic receptor blockade. In the clinical studies, patients receiving silodosin at a total daily dose of 8 mg exhibited significant improvements in the International Prostate Symptom Score and maximum urinary flow rate compared with those receiving placebo [27].

Research of Masciovecchio S *et al* [28] found therapy silodosin therapy may have a real role in the treatment of the premature ejaculation.

Two researchers (Rossi and Roumeguère, 2010) [29] highlighted mechanism of action of silidosin. The α_1-ARs belong to the family of G protein-coupled receptors and blockage of α_{1A}-AR induces prostatic and urethral smooth muscle relaxation, and may improve voiding symptoms. However, silodosin also seems to target afferent nerves in the bladder, and thereby acts on bladder overactivity and storage symptoms.

Silodosin is an α_1-adrenoceptor antagonist with unequalled selectivity for the a_{1A}-adrenoceptor subtype (α_{1A}-to-α_{1B} binding ratio: 162:1). Silodosin is approved for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) in Europe, the United States, and Japan. As with many other medicinal products, the recommended dose is different in Europe and the United States as compared to Japan: one 8-mg capsule daily (with a starting dose of one 4-mg capsule daily in patients with moderate renal function impairment) in both Europe and the United States versus either one 2-mg or 4-mg capsule twice daily in Japan [30].

A recent study by Buono R *et al* supports the clinical application of a combination of an α_{1A}-adrenoceptor antagonist and a phosphodiesterase 5 inhibitor for symptomatic BPH and suggests that the drug combination requires endogenous nerve-activity for optimal effect [31].

Some less common side effects are chills, cold sweats, confusion, dizziness, dizziness, faintness, or lightheadedness when getting up suddenly from a lying or sitting position [32].

1.3 Naftopidil

Naftopidil, firstly approved only in Japan, is an α_1-adrenergic receptor antagonist (α_1-blocker) used to treat lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH). Different from tamsulosin hydrochloride and silodosin, in that it has higher and extremely higher affinity respectively, for the α_{1A}-adrenergic receptor subtype than for the α_{1D} type, naftopidil has distinct characteristics because it has a three times greater affinity for the α_{1D}-adrenergic receptor subtype than for the α1A subtype [33].

In a recent study concluded naftopidil might act on the bladder and spinal cord to improve detrusor hyperreflexia in the storage state in SCI female rats. Naftopidil also suppressed bladder wall fibrosis, suggesting that it may be effective for the treatment of neurogenic lower urinary tract dysfunction after spinal cord injury [34].

Another study [35] describes the effects of intrathecal injection of tamsulosin (an alpha-1A adrenergic receptor antagonist) and naftopidil (an alpha-$_{1D}$ adrenergic receptor antagonist) on isovolumetric bladder contraction were investigated in rats. Authors of this study found decrease in amplitude of bladder contraction by intrathecal injection of naftopidil (3–30 μg), but not by tamsulosin. This study suggested that naftopidil may also act on lumbosacral cord and thus may improve collecting disorders in patients with benign prostatic hyperplasia. however tamsulosin also shows similar effect but intensity of beneficiary effects are more pronounced in the case of naftopidil.

The clinical usefulness of Naftopidil was also proved by Oh-oka H [36] in 122 patients with benign prostatic hyperplasia for urinary tract symptoms and signs, focused in particular on nocturia who did not respond tamsulosin. Naftopidil has novel effects in patients with BPH whose main complaints are storage and voiding symptoms, especially that of nocturia of >or=3 times, as well as in patients with a low compliance bladder and detrusor overactivity.

Another study reported by Satoru T *et al* [37] that α_{1D} -selective blockers may possess superior property of preserving sexual function, compared with α_{1A} -selective blockers. Since Naftopidil has more affinity for α_{1D} receptors than α_{1A} receptors thus likelihood of such incidences may be less in case of naftopidil as compared to other selective alpha one adrenoreceptor blockers for BPH.

Structures of Alfuzosin, Silodosin and Naftopidil are presented under Fig. 1.

Gotoh M *et al*. [38] compared the efficacy and safety of two α_{1A}/α_{1D} adrenoceptor (AR) antagonists with different affinity for the α1AR subtypes, tamsulosin and naftopidil, in the treatment of benign prostatic hyperplasia (BPH). There was no significant intergroup difference in the improvement of any efficacy variable between the groups. The adverse effects were comparable, with no significant differences in systolic and diastolic blood pressure after treatment in both

groups. There was no difference in clinical efficacy or adverse effects between the α_1 AR antagonists with different affinity to α1 subtypes, α_{1A} and α_{1D}.

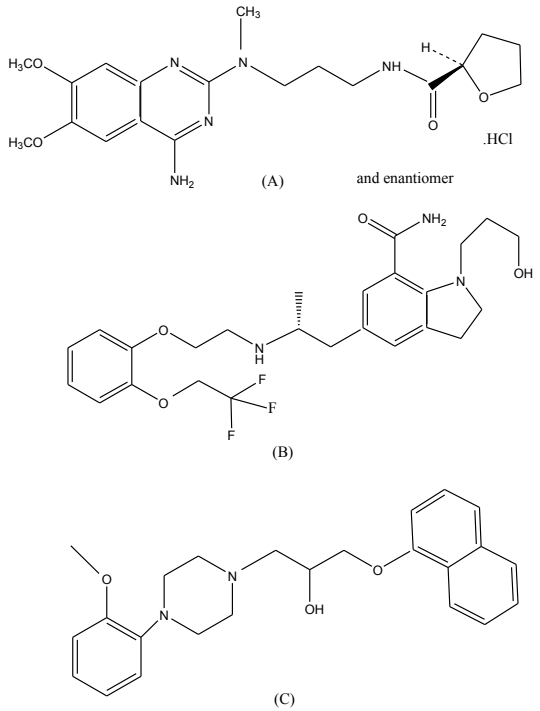

Fig. 1. Structure of Alfuzosin (A), Silodosin (B) and Naftopidil (C).

Adverse effects of naftopidil were few, most commonly dizziness and hypotension [39].

Thus this is out of any doubt that these alpha one adrenoreceptor blockers are clinically useful and have important place in control of BPH symptoms. This forms the background of this study to search about the determination methods in different matrices.

In search for analytical methods for the determination of these drugs database like Sciencedirect, Pubmed, Medknow, NCBI, Taylor and Francis and Google scholar were explored by using keywords "Analytical methods for ……..", "Determination of ……", "Spectrophotometric method for …….. determination, "Chromatographic method for …….. determination", "Electroanalytical methods for determination of ……". A gap represents the name of drugs under the presented study.

Total 65 different analytical methods were found including 31 spectrophotometry, 32 chromatography, 2 electroanalytical methods for the determination of Alfuzosin either alone or in combination in different matrices. For Silodosin 23 different analytical methods were found including 9 spectrophotometry, 11 chromatography, 2 electroanalytical methods for the determination alone or in combination in different matrices. For Naftopidil total 14 different analytical methods were found including 3 spectrophotometry, 11 chromatography, 2 Phosphorimetric, 1 Luminescence and Chemiluminescence methods for determination in different matrices.

2. ANALYTICAL METHODS

2.1 UV Spectrophotometry

Ultraviolet and visible spectrophotometer has become a popular analytical instrument in the modern day laboratories. However, the low concentrations of many analytes in samples make it difficult to directly measure them by UV–Vis spectrophotometry. With recent advances in sensitive array detectors, fiber optic wave guides, high speed electronics and powerful software, many new generations of spectrometers have been developed. UV–Vis spectrophotometry is known for its availability, simplicity, versatility, speed, accuracy, precision, and cost-effectiveness [40].

Derivative spectrophotometry (DS) is one of the advanced modern spectrophotometric techniques. It is based on so called derivative spectra which are generated from parent zero order ones. The derivatisation of zero-order spectrum can lead to separation of overlapped signals, elimination of background caused by presence of other compounds in a sample. The mentioned properties can allow quantification of one or few analytes without initial separation or purification. Nowadays, this technique becomes very useful, additional tool which helps to resolve various analytical problems. It has found application in many fields of analysis, especially in pharmaceutical, clinical and biochemical as well as in inorganic or organic analysis [41].

The summary of different spectrophotometry methods are given under Table 1, 2 and 3 for Alfuzosin, Silodosin and Naftopidil, respectively.

2.2 Chromatography

High-performance liquid chromatography (HPLC) was introduced to pharmaceutical analysis not long after its discovery in the late 1960s [65]. The phenomenal growth in chromatography is largely due to the introduction of the versatile technique called high-pressure liquid chromatography, which is frequently called high-performance liquid chromatography. The number of HPLC applications has increased enormously because a variety of complex samples have to be analyzed to solve numerous problems of scientific interest. Additionally, this demand is being continuously driven by the perpetual need to improve the speed of analysis [66].

No technique over the last decade, however, has seen such widespread growth in so many areas of quantitative pharmaceutical analysis as high

performance liquid chromatography (HPLC). This remarkable progress may be attributed to two major factors:

(i) the ability of reversed phase HPLC to analyse a wide variety of pharmaceutical samples and

(ii) to the dramatic improvement in HPLC technology, which has involved major advances in column technology, pumping systems. detectors, data handling and automation [67].

Spectrophotometric detectors in the ultraviolet (UV)-visible range for HPLC are used more frequently than any other by analysts in general, so they are relatively inexpensive and tend to be one of the first to which lipid analysts have access. Mass spectrometry (MS) is a powerful analytical tool that can supply both structural information about compounds and quantitative data relating to mass. Under optimum conditions, it can provide the molecular weight, the empirical formula and often the complete structure of an unknown compound in addition to giving a measure of the amount present [68]. Compared with conventional UV absorbance detection used in HPLC, fluorescence detection can greatly enhance the sensitivity leading to limits of detection similar to those obtained with mass spectrometry, offering researchers a sensitive, robust and relatively inexpensive instrumental method [69].

HPTLC allows fast and inexpensive method of analysis in the laboratory and in the field. 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 chromate-graphic fingerprints that can be visualized and stored as electronic images [68].

The summary of chromatographic methods are presented under Table 4, 5 and 6 for Alfuzosin, Silodosin and Naftopidil respectively.

Table 1. Summary of spectrophotometry methods for Alfuzosin.

Principle	Wavelength	Linear Range	LOD	LOQ	Application	Ref.
Ion-pair complex from sample solution containing KCl-HCl buffer pH 2.2, 2.4 and 2.6 into $CHCl_3$ Method A: bromocresol purple (BCP) Method B: bromophenol blue (BPB) Method C: bromothymol blue (BTB)	407, 413 and 412 nm respectively for Method A, B and C.	1.20-38.3, 0.85-46.0 and 0.63-34.0 µg/ml respectively for Method A, B and C.	0.28, 0.24 and 0.18 µg/ml respectively for Method A, B and C.	-	Tablets	[42]
Reaction with nitrite in acid medium to form diazonium ion, which is coupled with ethoxyethylenemaleic ester (Method A), or ethylcyanoacetate (Method B) or acetyl acetone (Method C) in basic medium to form azo dyes.	440, 465 and 490 nm [for Method A, B and C resp.]	4-20 µg/mL of AFZ for methods A, B and 3-15 µg/mL of AFZ for method C	0.127, 0.096, and 0.127 µg/mL [for Method A, B and C resp.]	-	Tablets	[43]
Reaction of alfuzosin with ninhydrin reagent in *N, N*'-dimethylformamide medium (DMF) [Method A], the second method is based on the reaction of drug with ascorbic acid in DMF medium [Method B], The third method is based on the reaction of alfuzosin with *p*-benzoquinone (PBQ) [Method C]	575, 530, 400 nm [Method A, B and C resp.]	12.5-62.5, 10-50, 15.0 – 75.0 µg/mL [Method A, B and C resp.]	0.682 0.216 0.313 µg/mL [Method A, B and C resp.]	-	Tablets	[44]
Method A: zero order Method B: first order Method C: third order	Method A: 330.8 nm Method B: 354.0 nm Method C: 241.2 nm	Method A: 1.0–40.0 µg/ml Method B: 1.0–40.0 µg/ml Method C: 1.0–10.0 µg/ml	Method A: 0.07 µg/ml Method B: 0.09 µg/ml Method C: 0.03 µg/ml	Method A: 0.22 µg/ml Method B: 0.30 µg/ml Method C: 0.08 µg /ml	Bulk powder and pharmaceutical formulations.	[45]

Two spectrofluorimetric methods; Method A: Measurement of fluorescence of ALF in deionized water Method B: reaction of fluorescamine with the primary aliphatic amine group produced on the degradation product moiety.	Method A: λ_{ex} = 325.0 nm, λ_{em} = 390.0 nm Method B: λ_{ex} = 380.0 nm, λ_{em} = 465.0 nm	Method A: 50.0–750.0 ng/ml Method B: 100.0–900.0 ng/ml	Method A: 1.60 ng/ml Method B: 9.04 ng/ml	Method A: 4.86 ng/ml Method B: 27.39 ng/ml		
Formation of purple color and red- violet colored chromogens obtained when the drug was diazotized with nitrous acid followed by coupling with Phloroglucinol [Method A] and Resorcinol [Method B].	520 and 600 nm	4-20 and 2-10 µg/mL	-	-	Tablets	[46]
Method 1: oxidation followed by complex formation with potassium ferricyanide in presence of ferric chloride to give a green colored chromogen. Method 2: oxidation followed by complex formation with 1, 10-phenanthroline in presence of ferric chloride.	783 and 510 nm	2-8 and 10-50 µg/ml.	-	-	Tablets	[47]
Ion-pair complex of the drug with acidic dye bromocresol green (BCG) in acidic condition, followed by its extraction in organic solvent (chloroform).	416 nm	2-10 µg/ml	0.1807µg/ml	0.547 µg/ml	Tablets	[48]
Oxidation reaction of the drug with iron (III) and a subsequent chelation of the produced iron (II) with ferricyanide to form turnbull's blue colored product.	790 nm	0.4 − 4.0 µg mL^{-1}	-	-	Tablets	[49]
Colorimetry: Reaction with gold (III) chloride in the pH range 1.0 – 5.0 forming red color complex solution	510 nm.	10 – 110 µg/ml	4.4352 µg/ml	14.7841 µg/ml	Formulations	[50]
Measurement in methanol [Method A], Integrating area under the curve between wavelengths nm [Method B], first order derivative [Method C]	244.99, 243.34-246.63 nm, [Method A, B and C resp.]	2.5-20 µg/mL for each method	0.158, 0.167, 0.217 µg/mL [Method A, B and C resp.]	0.481, 0.509, 0.658 µg/mL [Method A, B and C resp.]	Tablets	[51]
Hydrotropic solubilization using 5.0M Urea aqueous solutions, as a hydrotropic agent	266.3 nm	10-60 µg/mL	-	-	Tablets	[52]
Extraction of ALF into chloroform as ion pairs with bromocresol green (BCG) or into dichloromethane with phenol red (PR).	417 nm and 422 nm resp.	1-17 and 2-17 µg mL^{-1}	0.18 and 0.25 µg/ml	0.54 and 0.76 µg/ml	Pure and pharmaceutical dosage forms	[53]
First and second derivative spectrophotometric methods.	237 nm and 245 nm. resp.	1-5 µg/ml	0.8 and 0.7 µg/ml	2.5 and 2.0 µg/ml	Formulations	[54]

Table 2. Summary of Spectrophotometry for Silodosin.

Principle	Wavelength	Linear range	LOD	LOQ	Application	Reference
Absorbance measurement in acetonitrile	270 nm	10-50 µg/ml	0.77 µg/ml	2.34 µg/ml	Formulations	[55]
Absorbance measurement in methanol	269 nm	5-50 µg/ml	0.5 µg/ml	1.55 µg/ml	Bulk and pharmaceutical dosage formulations.	[56]
Colorimetry: Orange red colour with MBTH (3-methyl 2-benzthiazolinone hydrazone hydrochloride reagent	508 nm	10-50 µg/ml	0.1016 µg/mL	0.307 µg/mL	Raw material and dosage form	[57]
Oxidation with iron (III) and chelation of iron (II) with 1,10 Phenanthroline [red complex]	479 nm	10-50 µg/ml	-	-	Bulk and capsules	[58]
Oxidation or reduction with folin ciocalteu (FC) reagent [blue complex]	732 nm	300-500 µg/ml	-	-		
Method I: Drug dissolved in 0.1 N HCl Method II: First order derivative spectra Method III: Area under Curve (AUC)	273, 265 and 268-278 nm for Method I, II and III resp.	2-120, 2-120 and 10-120 µg/mL	0.46, 0.47 and 0.47 µg/mL	1.435, 1.432 and 1.436 µg/mL	Formulations	[59]
Spectrofluorimetric	λ_{ex} = 272 nm, λ_{em} = 450 nm	0.01 to 1µg/ml	0.003 µg/ml	0.0091 µg/ml	Bulk and formulations	[60]
First derivative UV in methanol solution	260.40 nm	18.2-182.0 µM	6.51×10^{-6} M	2.15×10^{-5} M	Formulations	[61]

Table 3. Summary of spectrophotometry method for Naftopidil**.**

Principle	Wavelength	Linear range	LOD	LOQ	Application	Ref.
Simple UV method, ACN: Water ratio 50:50 used as solvent.	285 nm	5-25 µg/ml	0.03387 µg/ml	0.10264 µg/ml	In bulk and formulations	[62]
Simple UV method, Methanol used as solvent.	232 nm	2-10 µg/ml	0.089 µg/ml	0.27197 µg/ml	In bulk and formulations	[63]
ACN-HCl acid (pH 1.2, 100 mM) (25:75, v/v)	280 nm	5-45 µg/ml	0.68 µg/ml	2.08 µg/ml	Tablet	[64]

Table 4. Summary of chromatography methods for Alfuzosin.

Method	Chromatography conditions	Linear range	LOD	LOQ	Applications	Ref.
HPLC-UV	Xterra RP_{18} column and acetonitrile/0.02 M KH_2PO_4 (pH = 3) ratio 20:80 as mobile phase. The flow rate was 1 mL/min λ = 247 nm	0.25 to 11 µg/mL	0.05 µg/mL	0.15 µg/mL	Tablets, kinetics of alkaline and acid degradation of the drug.	[70]
	C_{18} column (150 mm x 4.6 mm I.D., particle size 5 µm). mobile phase consists of phosphate buffer (pH 3.8) and acetonitrile in the ratio 650 : 350 (v/v). Column temperature 30° C, λ = 244 nm, flow rate of 1.0 mL/min.	0.02-20 µg/mL	-	-	Bulk drug samples and Pharmaceutical dosage forms	[71]

	Narrow-bore, 5-µm particle size, 250.0 mm × 2.1 mm i.d. C_8 analytical column, Mobile phase 35:65 (v/v) 0.0125 M Ammonium formate–ACN. Flow rate 0.35 mL min^{-1}. λ = 245 nm	200–800 ng mL^{-1}	22.9 ng mL^{-1}	69.5 $ngmL^{-1}$	Tablets	[72]
	Phenomenex C_{18} column (250 mm, 4.6 mm i.d, 5 µm particle size) Mobile phase water-methanol-ACN (60+30+10, v\v\v) flow rate of 1.0 mL/min, λ =245 nm	0.2–8 µg/mL	125.82 ng/mL	192.36 ng/mL	Bulk and in pharmaceutical formulations	[73]
	Intersil ODS-3V (150×4.6 mm, 5µ). Mobile phase ACN:Water:THF:Perchloric acid in ratio 250:740:10:1 flow rate 1 ml/min, λ = 245 nm.	25-150 µg/mL	-	-	Tablet	[74]
	Intersil ODS-3V (150×4.6 mm, 5µ). Mobile phase ACN:Water:THF:Perchloric acid in ratio 250:740:10:1 flow rate 1 ml/min, λ = 245 nm.	25-150 µg/mL	-	-	Tablet	[75]
	Agilent TC-C_{18} (250 mm X 4.6 mm, 5 µm), mobile phase consist of Water: Methanol (55:45 %v/v) pumped at a constant flow rate of 1 mL min^{-1}. λ =245 nm.	20-100 µg ml^{-1}	1.0617 µg/mL	3.2172 µg/mL	Formulations	[76]
	Intersil C_8 (150×4.6 mm, 5µ). Mobile phase Phosphate Buffer (pH 3.5) and water in ratio flow rate 0.8 ml/min, λ = 245 nm.	0.05-5 µg/mL	-	0.05 µg/mL	Rabbit plasma	[77]
	HiQ sil C_8 HS column, Mobile Phase: mixture of ACN: Sodium acetate buffer (0.04M) containing n-hexane sulphonic acid salt (0.005mM) (pH 4.0, adjusted with glacial aceteic acid) (55:45 v/v), flow rate of 1 ml/min λ = 244nm.	25-45ng/ml	-	25ng/ml	Human plasma	[78]
	Sil C_{18} HS column having 250 × 4.6 mm ID and 10 µm particle size, mixture of Tetrahydrofuran, Acetonitrile and buffer (pH 3.5) in the ratio of (1:20:80) v/v as mobile phase, λ = 244 nm.	80-120 µg/mL	0.3212 µg/mL	0.5764 µg/mL	Bulk, fixed dose combination tablets and dissolution studies.	[79]
UPLC	THF, acetonitrile, water and perchloric acid in the ratio of 10:220:770:1 (v/v) on Inertsil ODS-3, 3.0 x 50 mm, 2µ column. 1.0mL/min	10-300 µg ml^{-1}	-	-	Tablets	[80]
HPLC-F	Column (15 cm x 4.6 mm I.D.), Spherisorb ODS, 5 µm. Mobile phase [ACN-0.02 *M* potassium dihydrogen phosphate (pH 2.5), 3:2], flow-rate of 1 ml/min. λ_{ex} = 334 nm and λ_{em} = 378 nm	1-200 ng ml^{-1} in Blood Plasma. 0.05-10 pg ml in Urine	0.5-l ng ml^{-1}	-	Pharmacokinetic studies in man.	[81]
	Chiral-AGP column (100 mm x 4.0 mm I.D.), 5-µm. Mobile phase of 0.025 M phosphate buffer (pH 7.4) containing 0.025 M tetrabutylammonium bromide-acetonitrile (94:6, v/v). flow-rate of 0.9 ml/min, λ_{ex} = 265 nm and λ_{em} = 400 nm.	2-100 ng/ml	-	1 ng/ml.	Pharmacokinetic profile of alfuzosin enantiomers in healthy volunteers after intravenous administration of the racemate.	[82]
	BDS Hypersil-C18 column (50 mm × 4.6 mm i.d., particle size 5µm),	0.1–25 ng/ml	0.025 ng/ml	0.1 ng/ml	Bioequivalence and	[83]

	mobile phase containing 25 % v/v acetonitrile and 75 % v/v water (containing 1ml/L triethylamine as peak modifier, pH adjusted to 2.5 with orthophosphoric acid), flow rate 0.5 mL / min. λ_{ex} = 265 nm and λ_{em} = 380 nm.				pharmacokinetic studies	
	Acetonitrile and 20 mM phosphate buffer (pH 6.3) (60:40, v/v) containing 25 mM Sodium dodecyl sulfate. λ_{ex} = 250 nm and λ_{em} = 389 nm	0.5-20 ng mL^{-1}	0.16-0.71 ng mL^{-1}	0.53-2.14 ng mL^{-1}	in rabbits	[84]
LC-MS-MS	Supelco Discovery C 5 µm, 2.1×150 mm. Mobile Phase ACN, methanol and aqueous formic acid (0.2%), (20:20:60, v/v) at a flow-rate of 0.2 ml/min.	0.298 and 38.1 ng/ ml	-	0.298 ng/ ml	Human plasma	[85]
HPTLC	Aluminium-backed layer of silica gel 60F_{254} using toluene-methanol-triethylamine (3:1:0.2, *v:v:v*) as mobile phase. λ = 245 nm.	50-400 ng/spot	20.55 ng/spot	45.96 ng/spot	Bulk as well as Pharmaceutical formulation.	[73]
	Aluminium plates precoated with silica gel 60 F_{254} using Toluene: Methanol: Triethylamine (7:3:0.2%v/v/v)as mobile phase λ = 244nm	100-180 ng/ml	-	-	Human plasma	[78]
	Alugram Nano-SIL silica gel 60 F254 plates; the optimized mobile phase was methanol/ammonia (100:1.2). λ = 245 nm.	0.5–7 µg/spot	0.01 µg/mL	0.49 µg/mL	Tablets	[70]

Table 5. Summary of chromatography methods for Silodosin.

Method	Chromatographic condition	Linear range	LOD	LOQ	Application	Ref
HPLC-UV	C_{18} column (250 mm× 4.6mm, 5µ). The mobile phase: Methanol, ACN, Water in the ratio 40:40:20 v/v. λ = 269 nm. Flow rate 1 ml/min	10-60 µg/ml	5.46 µg/ml	16.57 µg/ml	In Bulk and formulations	[86]
	Phenomenex C_{18}, 5µ Silica (250×4mm). Mobile phase : Methanol-water -ACN-GAA (60:27:10:3 %. Flow rate 1 ml/min, λ = 270 nm.	10-100 µg/ml	0.0031628µg	0.0105427µg	Capsules	[87]
	Ammonium acetate buffer pH 4.5: acetonitrile 50:50 using Zorbax Eclipse C-8 column (150 × 4.6 mm, 5 µ). λ = 268 nm	40-120µg/ml	-	-	Bulk and dosage forms	[88]
	Column: Phenomenax Luna C_{18} (150 mm×4.6 mm i.d. particle size 5 µm). Mobile Phase: Phosphate buffer: ACN (40:60), adjusted to pH 3.0 with H_3PO_4. λ = 219 nm. Flow rate 0.8 ml/min	50-90 µg/ml	2.93 µg/ml	9.91 µg/ml	Capsule	[89]
	C_{18} column. Mobile phase: ACN: Buffer (1 ml triethylamine in 1000 mL water pH 3 (by orthophosphoric acid) in the ratio of 22:78 v/v. λ = 270 nm	54-104 µg/ml	0.2463 µg/ml	0.7465 µg/ml	Capsule	[90]

NP- chiral HPLC	Polysaccharide-Based Chiral Stationary Phase, Chiral pak AS-H column (250 mm ×4.6 mm i.d.; particle size, 5µ) at a temperature of 28°C using a mobile phase consisting of *n*-Hexane, Ethanol and Diethyl amine (600 : 400 : 0.1 v/v/v), flow rate of 1 $mL.min^{-1}$. λ = 270 nm.	LOQ to 150%	0.04µg.mL^{-1}	0.13µg.mL^{-1}	Determination of *S*-Silodosin	[91]
HPTLC	Aluminium plates precoated with silica gel 60 F_{254}. solvent system consisted of toluene/methanol/diethylamine (8:1:1). Detection by fluorescence mode at 366 nm	140-1400 ng per spot	85 ng/ spot	260 ng/spot	Bulk and capsules	[92]
UPLC-UV	Column: HSS C_{18}, 100 mm x 2.1 mm, column with 1.7µm particles column, using pH 3.2 phosphate buffer and ACN. Mobile phase[Gradient mode] A = 50 mM phosphate buffer with pH adjusted to 3.2 with dilute ortho phosphoric acid, B = ACN. Flow rate 0.5 ml/min. The gradient was set as: T/%B: 0/28, 3/28, 5.5/80, 7.5/80, 7.7/28 and 10/28. λ = 225 nm	-	-	-	Estimation of impurities	[93]
UHPLC	Agilent Poroshell 120 EC-C_{18} column (50×4.6mm i.d.; particle size, 2.7 mm). Mobile phase: Acetonitrile and 10 mM ammonium acetate buffer with 0.1% triethyl amine, with pH adjusted to 6.0, λ = 273 nm.	LOQ to 200% (seven levels)	0.00008 mg/mL	0.00020 and 0.00025 mg/mL	Separation of process impurities	[94]
LC–MS/MS	Agilent C_8 column with the mobile phase of acetonitrile–10 mM ammonium acetate (40:60, v/v) adjusted to pH 4.5 with acetic acid, mass transitions monitored at m/z 496.3→261.4.	0.50–50.0 ng/ml	-	0.50 ng/ml	Pharmacokinetic study in healthy volunteers	[95]

Table 6. Summary of chromatographic methods for the determination of Naftopidil.

Method	Chromatography conditions	Linear range	LOD	LOQ	Applications	Ref.
HPLC-UV	Mobile phase ACN and 0. 05 $molL^{-1}$ phosphate buffer (pH 6.5) (60:40). λ = 230	10-1200 $ngml^{-1}$	-	-	Pharmacokinetics of high dose naftopidil capsules in dogs	[96]
	Chiralpak ADH (250×4.6 mm, 5 µm) column hexane–isopropanol–diethylamine (85:15:0.1, v/v/v) was pumped at a flow rate of 1.0 mL/min. λ = 283	0.78–50 µg/mL	-	-	Enantiomers	[97]
	Phenomenax Luna C_{18} (4.6×150 mm, 5µ), Methanol: Water (90:10). Flow rate 0.8ml/min, λ = 232 nm	1-5 µg/ml	0. 7552 µg/ml	0.2288 µg/ml	Formulations	[98]
	Phenomenax Luna C_8 (4.6×150 mm, 5µ), Methanol: Water	1-5 µg/ml	0.0683 µg/ml	0.207 µg/ml	Formulations	[99]

	(90:10). Flow rate 0.8ml/min, λ = 232 nm					
	C_{18} GRACE column (250 mm × 4.6 mm i.d., 5 µm particle size) Gradient mobile phase (A) 10 mM of ammonium acetate buffer pH adjusted to 4.0 with glacial acetic acid and (B) acetonitrile. The flow rate was 1.0 mL/min with λ = 284 nm	10-150 µg/mL	0.6 µg/mL	2.04 µg/mL	Bulk drug and in formulation	[100]
	Zorabax SBC_{18} (150x4.6 MM, 5µ), Mobile phase: ACN: Ammonium Acetate (75:25 v/v). The flow rate 1.2 mL/min. The detection was carried out at 232 nm.	0.1 – 0.6 mg/ml	-	-	Formulation	[101]
Chiral HPLC of naftopidil (NAF) and its *O*-desmethyl metabolites (DMN) enantiomers	Chiralpak IA column by methanol–acetonitrile–acetate buffer (pH 5.3; 5mM; 45:33:22, v/v/v) flowing at 0.5 mL/min. 290nm (λ_{ex}) and 340nm (λ_{em})	22.5–15,000 ng/mL	-	22.5 ng/mL	Enantiomers in rat after single oral administration of (±)-NAF	[102]
Chiral solid phases (CSPs) HPLC	Chiralpak IA column mobile phase of MeOH–ACN–acetate buffer (pH 5.3; 5 mM) (50:25:25, v/v/v) flowing at 0.5 mL/min. λ_{ex} = 290, λ_{em} = 340 nm	10.6–4000/ 9.6–4000 for (+)-/(−)-NAF ng/mL	0.4/ 0.5 ng/mL for (+)-/(−)-NAF ng/mL	1.1/1.8 ng/mL of (+)-/(−)-naftopidil	Enantiomers in rat plasma	[103]
Pre-column derivatization HPLC	Agilent Hypersil ODS column with a mixture of MeOH–ACN–phosphate buffer (pH 4.1; 20 mM) (40:30:30, *v/v/v*) flowing at 1 mL/min as the mobile phase. (+)-diacetyl-l-tartaric anhydride (DATAN) as derivatization reagent. λ_{ex} = 290, λ_{em} = 340 nm	1.1–4000/ 1.8–4000 for (+)-/(−)-NAF ng/mL	3 ng/mL for both isomers	10.6/9.6 ng/mL (+)-/(−)-naftopidil	Pharmacokinetic study of enantiomers in rats	
RRLC–MS/MS	Daicel Chiral-pak IA-3 column (150 mm × 2.1 mm, 3 µm; Shanghai, China) with a similar 10 mm × 4.6 mm precolumn. 0.3 mL/min. ion transitions from m/z 392.8/189.9 for *R*(+)- and *S*(−)-NAF and m/z 427.0/235.0 for Z10	0.24 to 1000 ng/mL	-	-	NAF enantiomers in rat plasma, tissues, urine and feces.	[104]
LC–MS-MS	C_{18} (5µ×4.6) column methanol:2 mM ammonium formate (90:10) Detection by MS using electrospray ionization in positive mode	0.495–200.577 ng/mL	-	0.495 ng/mL	Pharmacokinetic studies in humans.	[105]

2.3 Electroanalytical Methods

Electroanalytical techniques have undergone many important developments in recent decades [106]. Electroanalytical chemistry is a branch of analytical chemistry that uses electrochemical techniques to study an analyte in solution [107]. Electrochemical techniques are powerful and versatile analytical techniques that offer high sensitivity, accuracy, and precision as well as large linear dynamic range, with relatively low-cost instrumentation [108]. Electroanalytical techniques can easily be adopted to solve many problems of pharmaceutical interest with a high degree of accuracy, precision, sensitivity and selectivity, often in a spectacularly reproducible way by employing this approach [109].

2.3.1 Alfuzosin

Conductometric method for the determination of alfuzosin hydrochloride and fexofenadine

hydrochloride in pure form and pharmaceutical formulations. The method is based on the formation of ion association complex of cations coming from the cited drugs with tetraphenylborate anions and the conductance of the solution is measured as a function of the volume of titrant. Linear range found was 0.085 – 0.426 mg/ml [110].

Based on combination of a new sensor with Coulometric FFT Linear sweep Voltammetry. The electrode was constructed by the pareparation of a matrix of ZrO_2 in graphene oxide and ionic liquid (1-butyl-3-methylimidazolium tetra fluoroborate) on glassy carbon electrode. The linearly concentrations ranges of Alfuzosin was from 2.0 – 150 nM with a detection limit of 0.5×10^{-9} M [111].

2.3.2 Silodosin

Voltametry method developed by Toker B *et al* [61] for determination in silodosin's commercial formulations. The electrochemical oxidation of SLD on glassy carbon electrode (GCE) was thoroughly investigated by cyclic voltammetry and differential pulse voltammetry. A linear range concentration and limit of detection were estimated to be 0.001-1.0 mM and 11.6 µM. Electrochemical sensor based on graphene nanosheets/gold nanoparticles/nafion nanocomposite modified electrode (GRP/AuNPs/NFN) was developed [112] for the electro-oxidation and quantification of silodosin (SLD). The chemical formation of GRP/AuNPs nanocomposite was verified by x-ray diffraction (XRD), fourier transform infrared spectroscopy (FT-IR) and transmission electron spectroscopy (TEM). The electrochemical oxidation of SLD has been investigated at GRP/AuNPs/NFN by the use of adsorptive stripping differential pulse voltammetry (AdSDPV). The developed electrode exhibited excellent electrochemical activity towards the electrochemical oxidation of SLD. Under optimal conditions, GRP/AuNPs/NFN demonstrated a wide linearity ranging from 10-330 nM with a detection limit of 3.8 nM (S/N=3). As author claimed this method is suitable for determination of SLD in pharmaceutical or biological samples.

3. METHODS IN COMBINATION

Summary of analytical methods for determinations in combinations are presented under Table 7 and 8 for Alfuzosin and Naftodipil, respectively.

Table 7. Summary of analytical methods in combinations with Alfuzosin

Drug	Method	Chromatographic conditions	Linear range	LOD	LOQ	Application	Ref.
Dutasteride	HPLC-UV	Column: Symmetry C_{18} (4.6 x 150 mm, 5µm). Mobile phase mixture of Potassium dihydrogen phosphate buffer adjusted to pH 6.5+ 0.1 with 0.1N NaOH, ACN and Water in the ratio of 15:75:10. Flow rate 0.8ml/min, λ = 245 nm.	5-25 µg/ml	2.97 µg/ml	10.1 µg/ml	Dosage form	[113]
	HPLC-UV	Column Nucleosil (4.6 mmx 125mm 5µm). Mobile phase: mixture of phosphate buffer and ACN (20:80). Flow rate 1.5 ml/min Column: (Nucleosil 100-5 (4.6mmx125mm, 5µm) at ambient temperature λ = 220 nm	5-30 µg/ml	-	-	Dosage form	[114]
	UPLC–MS–MS	Hypurity C_{18} (50 × 4.6 mm i.d., 5 µm particle size) column. Flow rate: 0.6 mL min^{-1}. Mobile phase: 10 mM ammonium formate buffer, pH adjusted to 3.00 ± 0.05 with formic acid: ACN, (20:80 v/v). The multiple reaction monitoring (MRM) mode using the following precursor and product ion (m/z) transitions for alfuzosin (390.2 → 156.2)	0.25–20.0 ng mL^{-1}	-	0.25 ng mL^{-1}	Bioequivalence study	[115]

	HPLC-UV	Column: Kromasil C_{18} column (150 mm × 4.6 mm, 5 µm particle size) Mobile phase: Phosphate buffer: ACN (30:70 % v/v). Flow rate: 0.8 ml/min. λ = 242 nm.	5-30 µg/ml	2.394 00 µg/mL	7.472 4 µg/mL	Tablet	[116]
	HPLC-UV	HiQ Sil C_{18} HS column (4.6mm I.D X 250 mm) Mobile phase methanol: water (90:10 v/v). Flow rate of 1 ml/min at an ambient temperature. λ = 244 nm	1-5 µg/ml	0.2 µg/ml	0.6 mg /ml	Dosage form	[117]
	HPLC-UV	Symmetry C_{18} (4.6 x 150 mm, 5 µm). Mobile phase 0.1N Sodium hydroxide, Acetonitrile and Water in the ratio of 15:75:10 flow rate 0.8ml/min, λ = 245nm	5-25 µg/ml	-	-	Dosage form	[118]
	HPLC-UV	Column: Thermoscientific Hypersil BDS C_{18} (150mm×4.6mm, 5µm). Mobile phase Ammonium dihydrogen phosphate buffer(pH 4.9): ACN (30:70 v/v). Flow rate: 0.75 ml/min at ambient temperature. λ = 292 nm.	2.5-15µg/ml	-	-	Dosage Form	[119]
	HPTLC	Silica gel 60 F_{254} with toluene–methanol–dichloromethane–triethylamime 6:1:1:0.6 (v/v) as mobile phase. λ = 247 nm	300–600 ng per band	100 ng/band	200 ng/band	Tablets and bulk	[120]
Terazosin HCl, prazosin hydrochloride and doxazosin mesylate and finasteride	HPTLC	60F_{254} (20 x 15 cm, 200 µm thickness) Methylene chloride:n-hexane:methanol (8.8:0.3:0.9, by volume). λ = 254 nm	30–350 ng/spot	7.85 ng/spot	23.80 ng/spot	Respective pharmaceutical preparations.	[121]
Solifenacin	LC–ESI-MS/MS	Column: Hypurity C_8 (50mm×4.6mm internal diameter, 5 µm particle size). Flow rate: 0.4 mL/min. Mobile phase: 2mM ammonium formate (pH 3.0, adjusted with formic acid) in water: acetonitrile (15:85, v/v). The column oven temperature was maintained at 45 °C. Multiple reaction monitoring (MRM) and positive ionization mode, using mass transition *m*/*z* 390.2→235.2.	0.25–25 ng/mL	-	0.25 ng/mL	Bioavailability study	[122]
	First-order derivative spectrophotometric method (In methanol)	257 nm	6-36 µg/ml	0.95 µg/ml	2.88 µg/ml	Pharmaceutical formulation	[123]
Finasteride	First derivative	258 nm	2-12 µg/ml	-	-	Tablet dosage form.	[124]

	spectrophotometric method	
Tamsulosin, doxazosin, prazosin, and terazosin	Methanol used as diluents, negative result because of spectral overlap	[125]

Table 8. Summary of methods of Silodosin in combination with other drug

Drug	Method	Conditions	Linear range	LOD	LOQ	Application	Ref
Dutasteride	RP-HPLC	Zorbax SB C_8 Column (250 mm×4.6 mm , 5 µm) at 40°C. Mobile phase: Buffer (Dipotassium hydrogen phosphate, pH 3) and Organic mixture (methanol: acetonitrile, 50:50 ratio), 20:80. Flow rate of 1.0 mL/min and UV detection gradient at 270 nm (0 to 5 min.) and 210 nm (5 min to 10 min)	39.56 - 118.68 µg/mL	9.58 µg/ml	95.8 µg/ml	Formulations	[126]

4. OTHER METHODS

4.1 Phosphorimetric method

Pulgarín JMA *et al* [127] reported phosphorimetry method for the determination of Naftopidil in human urine. The method is based on obtaining a phosphorescence signal from this antihypertensive drug using $TlNO_3$ as a heavy atom perturber and Na_2SO_3 as a deoxygenator agent without a protective medium. Phosphorescence intensity was measured at λ_{em} = 526 nm and λ_{em} = 296 nm in the concentration range 0.05–1.00 mg. Detection limit observed was 21.0 ng mL^{-1}.

Another phosphorimetry method for the determination of Naftopidil in human serum an urine [128] is also reported in literature. The maximum phosphorescence signal appeared instantly and the intensity was measured at λ_{ex}=287 nm and λ_{em}=525 nm. The response obtained was linearly dependent on concentration in the range 50 to 600 ng mL^{-1}. Detection limit obtained was 7.93 ng mL^{-1}.

4.2 Luminescence method

Determination of naftopidil, directly in biological fluids by heavy atom induced room temperature phosphorescence (HAI-RTP); this technique enables us to determine analytes in complex matrices, biological fluids, without the need for a tedious prior separation process [129]. The maximum signal of phosphorescence appears instantly once the sample has been prepared and the intensity was measured at λ_{ex}=287 nm and λ_{em}=525 nm. Calibration curve plotted was between 0.05 to 0.6 mgL^{-1} concentrations.

4.3 Chemiluminescence determination

A flow injection method [130] is proposed for the determination of naftopidil based upon the oxidation by potassium permanganate in a sulfuric acid medium and sensitized by formaldehyde and formic acid. The optimum chemical conditions for the chemilumines-cence emission were 0.25 mM potassium permanganate and 4.0 M sulfuric acid. Calibration graph over the concentration range 0.1–40.0 mg L^{-1} with a detection limit calculated of 92.5 ng mL^{-1}. In the presence of 1.15 M formic acid, naftopidil gives a second-order calibration graph over the concentration range 0.05–40.0 mg L^{-1} with a detection limit of 14.2 ng mL^{-1}. The former results in better reproducibility and the latter is more sensitive.

5. COMPARISION OF DIFFERENT ANALYTICAL METHODS

5.1 Alfuzosin

5.1.1 Spectrophotometry method

There are 31 different spectrophotometry methods [42-54] available in the literature available out of these 18 methods [42-50, 52-53] are based on reactions i.e. the coloured product was estimated at higher wavelengths because of addition of chromophore.

Reaction based methods are more tedious and they are not proving any distinct advantage in terms of increase in sensitivity. Moreover with additional step of chemical reaction the time and cost of analysis also increases as compared to direct methods. Although there are number of sectrophotometry methods found but no method is applicable in biological sample determinations. Two spectrofluorometry [45] and one by hydrotrophy solubilizing technique [52] are also available. Latter method employs hydrotropic solutions to extract the drugs from their dosage forms precluding the use of costlier organic

solvents and is eco friendly too. Two first order derivative methods for estimation in combination with Solifenacin [123] and Finasteride [124] are also available. One negative result [125] is also found with an attempt for simultaneous determination with other alpha one adrenoreceptor blockers tamsulosin, doxazosin, prazosin and terazosin.

5.1.2 Chromatography method

There are 19 different types of chromatographic methods [70-85] are available for the determination of alfuzosin in different matrices. Ten different chromatographic methods [113-122] for the determinations in combinations e.g. with Solifenacin [122] and many methods with Dutasteride [113-120] including one HPTLC method [120] is also reported. One HPLC method for simultaneous determination with Terazosin HCl, prazosin hydrochloride and doxazosin mesylate and finasteride [121] is also reported. Many methods are suitable for determinations in biological fluids [77,78,81-85,115,122] and rest can be utilized at formulations level. Two combinations methods are also applied for bioequivalence[115] or bioavailability [122] determinations. With detection limit of 0.025 ng/ml, method developed by Shakya AK *et al* [83] is the most sensitive method available in current literature. HPLC with fluorescence detector [81-84] are again proved themselves in terms of sensitivity because of their applicability in pharmacokinetic profile development or biological matrices determinations.

5.2 Silodosin

5.2.1 Spectrophotometry methods

Nine different spectrophotometry methods [55-61] for the determination of Silodosin in bulk or formulations are available in current literature. One colorimetry [57] and spectrofluorimetry method [60] is also available. Three methods based on chemical reaction [57,58] applicable in bulk and in formulations are also available but does not adding any additional advantage in this segment by increase in sensitivity. They have same linear range as compared to other simple method. On the other hand spectroflurometry method [60] with detection limit 0.01 to 1µg/ml is the most sensitive method available.

5.2.2 Chromatography methods

Eleven different chromatography methods [86-95] were found in literature survey. In these methods only one method was for simultaneous determination with dutasteride [126]. Out of these methods UHPLC[94] and LC-MS/MS [95] methods are the most sensitive methods for the determination of silodosin. NP chiral HPLC [91] method for the determination of enantiomers and HPTLC method [92] for silidosin determination are also available. UHPLC [94] is applied for separation for process related impurities and LC-MS/MS [95] method is developed for pharmacokinetic study in healthy volunteers. Some sensitive methods are HPLC-UV[87], HPTLC[92], UHPLC[94] and LC-MS/MS[95].

5.3 Naftopidil

5.3.1 Spectrophotometry

Only three spectrophotometry methods [62-64] are available in literature. With the detection limit of 0.03387 µg/ml method developed was by Kumar MS *et al* [62] is most sensitive method available for the determination of Naftopidil. These methods included solvents in the analysis and are not suitable for biological level determinations.

5.3.2 Chromatographic methods

Eleven chromatographic methods [96-105] are available in current literature. Six HPLC-UV methods [96-101] for the determination of Naftodipil in formulations are available with variable wavelengths measurements. UV detector are the most commonly used detectors for HPLC equipment with economy as additional advantage as compared to LC-MS or other hyphenated techniques associated with liquid chromatography. Four HPLC methods [102-104] for the separation of enantiomers are also available including three methods with fluorescence detection and one by MS detection [104]. All of these methods were developed for separation of isomers in biological samples of rat. Two bioanalytical HPLC methods developed by Liu *et. al* [103] are the most sensitive methods available.

4. CONCLUSIONS

Spectrophotometry methods are among the oldest methods of analytical chemistry [131]. But they are suitable for the determinations at formulation levels only and cannot be extended for biological sample determinations. Increased sensitivity of LC-MS methods is mostly compromised with complicated instrumentations, procedures, and mobile phases [132].

Alfuzosin, Silodosin and Naftopidil are important alpha one adrenoreceptor blockers currently available for symptomatic relief of BPH. The reasons for their wide acceptance are lower side effects, greater symptom relief and improvement in overall quality of life.

In this way different analytical method for the determination of Alfuzosin, Silodosin and Naftopidil is discussed here. Absence of any

HPTLC method for the determination of Naftopidil explores new opportunity for the researchers. Economy of the method can be easily understood by usage of complicated mobile phases (for HPLC/HPTLC methods) and costlier solvents (for spectrophotometry methods).

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