(REVIEW ARTICLE)

Aliskiren: analytical review for estimation in pharmaceutical formulations

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Abstract

Aliskiren (AL) is classified as angiotensin converting enzyme inhibitors (ACEIs) used as antihypertensive drug it acts by dilating blood vessel. These dilation of blood vessel caused due to the renin inhibition. There have been numerous methods developed so far for quantitative estimation of AL in bulk and pharmaceutical dosage form. Pharmaceutical analytical methods include UV Visible Spectrophotometry, Reversed Phase High Performance Liquid Chromatography and hyphenated techniques like Liquid chromatography- Mass Spectrometry. This review paper includes various publications focuses on advanced analytical methods. The chromatographic methods primarily RP-HPLC and LC-MS found more promising and sensitive compared to other pharmaceutical methods.

Keywords: Aliskiren; High performance liquid Chromatography (HPLC) and Hyphenated techniques

1. Introduction

Aliskiren (AL) is chemically (2S,4S,5S,7S)-5-amino-N-(2-carbamoyl-2,2-dimethylethyl)-4-hydroxy-7-{[4-methoxy-3-(3-methoxypropoxy)phenyl]methyl}-8-methyl-2-(propan-2-yl) nonanamide. It was approved by the U.S. Food and Drug Administration in 2007 for the treatment of hypertension [https://www.drugbank.ca/drugs/DB09026/Last accessed on28/01/2020].
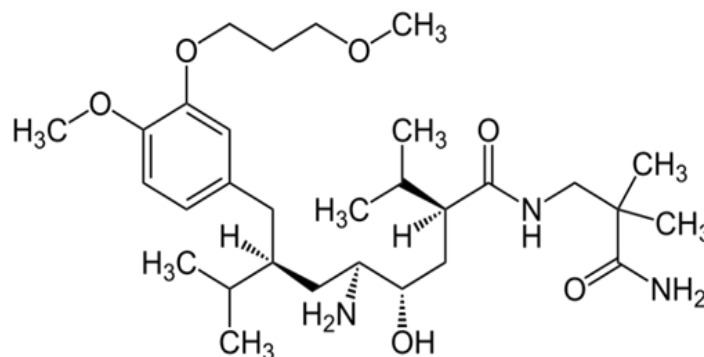

Figure 1 Structure of Aliskiren

Aliskiren is a direct renin inhibitor, decreasing plasma renin activity (PRA) and inhibiting the conversion of angiotensinogen to angiotensin I (Ang I) [https://www.drugbank.ca/drugs/DB09026/ Last accessed on28/01/2020, 1]. It is used for the treatment of mild to moderate hypertension. It may be used alone or in combination with other antihypertensive agents.

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Methods for pharmaceutical analysis are significantly much simpler comparatively with metabolites in biological samples as in urine, blood and plasma. The estimation of a drug is to a great extent important in complex matrices because the pharmaceutical product quality is directly associated to patient wellbeing. Analytical methods play a key role in the drug development and pharmaceutical control, to ensure a high efficacy and safety for patients [2].

2. Analytical methods for estimation of Aliskiren

2.1. UV-visible methods

However, UV–Visible Spectrophotometry method is not able to give broad spectra for estimation of certain drugs, it has accuracy, speed, gives sensitive and precise results. It consists of calculating and plotting first order and second order derivative of the mathematical expression of a spectral curve and area under curve.

Nita Yadav and Anju Goyal [3] have developed three spectrophotometric methods as method I: zero order derivative, Method II: first order derivative and method III: area under curve.

Table 1 Results of above mentioned methods of UV

Parameters	Method I	Method II	Method III
Wavelength	279	289	269-289
Linearity Range (µg/ml)	25-150	25-150	25-150
Regression equation (Y = mx+c)	y = 0.006x + 0.002	y = 0.0006x - 0.001	y = 0.034x - 0.104
Correlation coefficient (r2)	0.999	0.999	0.999
% Label claim	98.54±0.50	100.32±1.35	100.38±0.53
%RSD	0.50	1.35	0.53

Micheli Wrasse-Sangoi [4] et al. has developed UV method was linear in the range between 40 and 100 µg mL-1 ($r2$ = 0.9997, n = 7) and exhibited suitable specificity, accuracy, precision, and robustness. It is simple, it has low cost, and it has low use polluting reagents. Therefore, the proposed method was successfully applied for the assay and dissolution studies of aliskiren in tablet dosage forms, and the results were compared to a validated RP-LC method, showing non-significant difference ($P > 0.05$).

Mai A. Ramadan [5,6] et al has developed two method based on the reaction of ALS with o-phthalaldehyde (OPA) and n-acetylcysteine (NAC) in a basic buffer (method I) and with ninhydrin in the presence of ascorbic acid (0.1%) as a reducing agent, in slightly acidic media (phosphate buffer 0.2 M, pH 6.0) at 90°C for 20 min (method II). These are summarized in table no. 2.

Table 2 A summary of above mentioned methods

Parameters	λmax (nm)	Conc. Range (µg/ml)	r2	% recovery	reference
Method I	335	10-200	0.9996	99.45 ± 0.76	5
Method II	569	10-170	0.9982	100.15± 1.29	6

2.2. Chromatographic methods and Hyphenated Techniques

This method encompasses a device and important group of methods that permit the scientist to separate closely related components of complex mixtures, many of these separations are impossible by other means.

2.1.1 HPLC methods

Nita Yadav [7] et al has been reported a reverse phase high performance liquid chromatographic method for the estimation of Aliskiren in tablet dosage form with LC system used consists of pump (Model Shimadzu; LC-10 AT VP) with universal loop injector (Rheodyne 7725) of injection capacity 20 μl.

K. Satish Babu [8] et al. has developed a reverse phase high performance liquid chromatographic method for the estimation of Aliskiren in tablet dosage form with HPLC from Shimadzu (version LC-2010C), equipped with a quaternary pump and a thermostat column jacket for maintaining ambient temperature during chromatographic separation was used for analysis.

Shalini Pachauri [9] et al have been reported gradient high performance chromatographic method with Waters Alliance HPLC system (waters 2695 separation module), equipped with a photo diode array detector (Waters 2996 photo diode array detector).

G. Kumara Swamy [10] et al reported RP-HPLC method for estimation of Aliskiren in bulk and tablet with Shimadzu HPLC system containing SPD-10 ATVP pump and SPD-10AVP UV-Visible detector.

Table 3 Reverse phase HPLC methods

Column	Dimension (mm×mm×μ)	Mob phase	λmax (nm)	Linearity μg/ml	% Recovery	Detector	r²	Reference
C8 Chromasil	150 × 4.6 , 5	phosphate buffer, methanol and CAN (55:10:35)	220	30-150	100.06-100.43	PDA	0.9999	[7]
Water Xbridge C18 column	150×4.6, 5	0.03% trifluro acetic acid in water and 0.03% trifluroaceticacid in ACN and water (95:5)	230/254	1-100	98.36-99.12	Duel Wavelength Detector	0.999	[8]
PUROSPHERE STAR RP 18e	150×4.6, 5	0.2 %v/v TEA buffer (pH: 3.0): ACN	215	20-120	-	PDA	0.9993	[9]
Phenomenax LunaC18 column	150 X 4.6 , 5	phosphate buffer pH 3.0: Acetonitrile (60:40, v/v)	293	5-30	101.10	UV	0.9999	[10]

Sigala Ashok [11] et al have been reported a LC method for determination of enantiomeric impurity (enantiomeric separation of (R)-aliskiren from (S)-aliskiren) in Aliskiren in bulk drug sample.

The method was developed by using a mixture of acetonitrile–n-butylamine 100:0.1(v/v) as a mobile phase with a flow rate maintained at 1.0 mL/min with column used was a Chiralpak-IC (250 × 4.6 mm) with 5-μ particles. Ultraviolet detection was carried out at 228 nm. Resolution between the two enantiomers was greater than 3.0. The LC system used for method development and method validation was a Waters 2695 binary pump plus auto sampler and a 2996 photodiode array detector. The details of study with different columns and mobile Phase is summarized in Table No.4.

Table 4 Chiral selectivity results

Column	Mobile Phase	Retention time (min)	Resolution
Chiralpak AD-H	80:20 n-hexane–isopropyl alcohol;	3.9 and 3.9	No resolution
Chiralpak OD-H	80:20 n-hexane–isopropyl alcohol; 1 mL/min	3.4 and 3.2	No resolution
Chiralpak -OJ	80:20 n-hexane–isopropyl alcohol; 1 mL/min	3.2 and 3.2	No resolution
Chiralpak -IA	80:20:0.1 n-hexane–isopropyl alcohol–diethyl amine; 1 mL/min	17.09 and 18.45	Less than 1.0
Chiralpak -IB	80:20:0.1 n-hexane–isopropyl alcohol–diethyl amine; 1 mL/min	4.32 and 4.32	No resolution
Chiralpak –IC	80:20:0.1 n-hexane–isopropyl alcohol–diethyl amine; 1 mL/min	4.75 and 4.75	No resolution
Cyclobond	90:10 0.1% acetic acid–acetonitrile, pH 4.0 with ammonia solution.	2.25 and 2.25	No resolution
Chiral AGP	95:5 0.01M ammonium acetate–methanol, pH 4.5 with acetic acid	5.7 and 6.06	Less than 1.0
Chiralpak -IA	95:5:0.1 n-hexane–Ethanol -n-butylamine	16.32 and 17.77	1.54
Chiralpak –IC (RP mode)	100:0.1 acetonitrile–n-butylamine	14.53 and 11.81	3.23

Belal F. [12] et al have been reported HPLC method for the determination of aliskiren in human plasma through derivatization with 1-naphthyl isocyanate. The separation was achieved on a C18 column using a mobile phase consisting of acetonitrile/water/phosphoric acid (45:55:0.01, v/v/v, pH 3.2) in a flow rate of 1 ml/min with UV detection at 230 nm. Caffeine was used as an internal standard. The method was linear over the concentration range of 5–400 ng/ml. The percentage recovery was in the range 97.1–98.6%.

Lefevrea and Gauronb [13] proposed HPLC method with fluorometric detection for aliskiren determination in blood serum and urine. The samples were extracted in an automated way from 400 μl of serum or urine with methyl alcohol–acetic acid mixture (99:1, v/v) on 100-mg Bond-ElutCN cartridges using the Gilson ASPEC system. Chromatographic separation was conducted on LiChrospher 100 RP8 5-μm particle size packed analytical column (25 × 0.4 cm I.D.). The mobile phase was acetonitrile-0.01 M potassium dihydrogen phosphate (65:35, v/v) mixture with a flow rate of 0.8 ml·min-1, fluorometric detection with excitation and emission wavelength of 280 and 330 nm, respectively, was used, an internal standard was (2S,4S,5S,7S)-N-butyl-5-amino-4-hydroxy-2,7-diisopropyl-8-[3-(3-methoxypropoxy)-4-methoxyphenyl] octanamide hydrochloride (CGP-56962A). Linearity range for the proposed method was 4.5-450 ng·mL-1 in serum, and 9.0–900 ng·mL-1 in urine, quantification limits were 4.5 ng·mL-1 and 9.0 ng·mL-1, respectively.

2.1.2 Hyphenated Techniques

A couple of decades ago, Hirschfield introduced the term "hyphenation" to refer to the on-line combination of a separation technique and one or more spectroscopic detection techniques. The hyphenation does not always have to be between two techniques; the coupling of separation or detection techniques, more recently, so called double hybrid e.g. LC-PDA-MS, LC-MS-MS, LC-NMR-MS instruments have become available and have been applied to pharmaceutical problem solving [14].

HPLC MS/MS method was used for aliskiren determination in blood serum, in which benazepril was applied as an internal standard. Samples preparation involved an addition of 500 mL phosphoric acid (2%, v/v) and 10 mL methanol benazepril solution to 100 μL serum. The whole was mixed, and then centrifuged at a temperature of 40°C for 10 min. The extraction was performed using Oasis W MCX solid-phase extraction (SPE) cartridges. SPE system was initially

prepared by rinsing with ammonia solution in methanol (10%, v/v), and then methanol and 2% formic acid. Acidified serum samples were applied on SPE columns, and rinsed with 2 mL of 2% formic acid and 2 mL methanol. An analyte was eluted by three-times system rinsing with 0.5 mL and once with 0.3 mL of ammonia solution in methanol (10%, v/v). Eluent was evaporated to dry form in nitrogen atmosphere, and then dissolved in 100 μL of mobile phase, which was methanol-water-formic acid mixture (75:25:0.005, v/v/v). Such prepared samples were subjected to separation on XselectTM C18 CSH column, with mobile phase flow rate of 0.4 ml·min^{-1}, total time of analysis was about 5 min, and the results obtained were characterized by a high precision and accuracy. The linearity range was 0.146– 1200 ng·ml^{-1}. Due to an application of small volume of the examined sample, the elaborated method may be successfully used in monitoring of aliskiren level in pediatrics [15].

The another method of aliskiren determination in the saliva of healthy volunteers was conducted using LC-ESIMS/ MS. Sample preparation for the study involved mixing of 100 μL of undiluted saliva with 10 μL of internal standard, which was benazepril hydrochloride solution (166 ng/ml) and 490 μL formic acid (2%, v/v). The sample was subject to extraction to solid phase (Oasis R MCX) using SPE columns which were suitably prepared by rinsing with 1 mL of a mixture of ammonia solution–methanol–acetonitrile (10:45:45, v/v/v), and then 1 mL of methanol and finally equilibrated with 2% formic acid. The samples were applied on such prepared SPE system and eluted with 1 mL of formic acid (2%, v/v) followed by 1 mL methanol– acetonitrile (50:50, v/v). Analyte was released by elution using 0.5 mL (three times) and one time 0.4 mL of a mixture of ammonia solution-methanol-acetonitrile (10:45:45, v/v/v). Eluent was evaporated at the temperature of 40°C. The sample was diluted using 100 μL mixture of acidified methanol-water (20:80, v/v). Chromatographic separation was carried out on a Xselect™ CSH C18 column (3.0 × 150 mm, 3.5 μ) protected by a corresponding Xselect™ CSH C18 guard column (3.0 × 20 mm, 3.5 μm). Time of analysis was 7.5 min with a mobile phase gradient of acidified methanol (A) and acidified water (B) (each 0.1% formic acid, v/v) to separate the compounds. Gradient was as follows: starting with 30% of A, after 0.2 min 50% A, at 6 min 80% A, at 6.3 min 100% A, decreased to 50% A at 7 min and staying at 50% for the rest of the run time. The elaborated procedure is characterized by a wide range of linearity, i.e. 0.586-1200 ng·mL-1, low quantification limit, as well as good precision and accuracy. Based on the results obtained the authors concluded that the concentration of aliskiren in human saliva is measurable, but considerably lower than expected [16].

3 Conclusion

In this paper, recent analytical methods employed for quantitative analysis of aliskiren in pharmaceutical formulations were reviewed. Several techniques like UV - Visible spectrophotometry including Area under curve, zero order, first order, colorimetric methods, Chromatographic methods primarily (high performance liquid chromatography) and hyphenated techniques were reviewed. Liquid chromatography is the major techniques that have been used, of which it is observed a development to use quicker techniques with cost savings and lessening in solvent consumption. From this work, it has been observed that High Performance Liquid Chromatography is extensively utilized for estimation of Aliskiren in bulk material and pharmaceutical formulations. Further there has been always greater need to develop more sophisticated method to determine content of aliskiren in bulk and pharmaceutical dosage form.

Compliance with ethical standards

Disclosure of conflict of interest

We declare no conflict of interest.

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