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Review Article

ANALYTICAL METHODS FOR THE DETERMINATION OF AMINOGLYCOSIDES ANTIBIOTICS BY CHROMATROGRAPHIC TECHNIQUE

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ABSTRACT

Aminoglycosides antibiotics are considered to be the antimicrobial agents used frequently in the treatment of human diseases caused by a bacterial infection. Most of the aminoglycosides antibiotics are highly polar in nature and they are lacking the UV absorbing chromophore in the molecules. The present articles accentuate the analytical method associated with the analysis of aminoglycosides molecules. Various chromatographic techniques like liquid chromatography, gas chromatography; mass spectrometry were used for the detection of aminoglycosides antibiotics. However, due to its limitation in the ultraviolet-visible spectrophotometry (UV/Vis) technique, different types of detection techniques like corona-charged aerosol detector (CAD), electrochemical detector (ECD) were used as a most powerful and versatile technique for the demonstration of these molecules in the analytical field. Analytical methods help to ensure the quality of the drug products. This review paper is devoted to providing an overview of the key performance technique used for the application and detection of these aminoglycosides molecules.

Keywords: Aminoglycosides antibiotics, Chromophore, Liquid chromatography

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INTRODUCTION

Aminoglycosides are a group of highly potent antimicrobial agents used frequently in the treatment of human-caused by both gram-positive and gram-negative bacterial infection. This class of antibiotics also has imperative solicitation in veterinary medicine. Streptomycin is the foremost antibiotics isolated from Streptomyces griseus and it is active against gram-negative bacteria, which were used in clinical studies in 1944, followed by neomycin from Streptomyces fradiae, kanamycin from Streptomyces kanamyceticus, gentamicin from Micromonospora purpurea, sisomicin from Micromonospora inyoensis [1, 2]. Semisynthetic aminoglycosides like netilmicin from Sisomicin, tobramycin from Streptomyces tenebrarius and amikacin from kanamycin [3]. Aminoglycosides molecules contain aminocyclitol and an amino sugar joined to a ribose unit. They interfere with bacterial protein synthesis by binding irreversible to ribosomes. Aminoglycosides antibiotics have lots of contribution towards the health of human and animals. Most of the aminoglycoside antibiotics are derived by the fermentation process. To improve the safety and efficacy of these classes of molecules various chromatographic technique was used to monitor the purity of the molecule [4]. Chromatographic technique especially high-performance liquid chromatography considered to be used mostly for the analysis of these aminoglycosides.

Due to lack of volatility, absence of chromophore, and hydrophilicity of aminoglycosides, some of the methods applied derivatization technique for improvement of their chromatographic performance. Derivatization techniques with simple chromatographic procedure methods have the advantage of reducing analysis time and lower cost of instruments and maintenance. But these derivatization procedures have shown the disadvantage like lack of stability of the solution. Resemble of the similar molecular structure of these aminoglycosides antibiotics makes the separation of these molecules makes quite critical and major challenging. Some of the detection technique methods like mass spectrometry, gas chromatography was used to analyse these antibiotics. Also there is no definite analytical method that has been reported for the detection of impurities or related compounds present in this aminoglycosides antibiotics [5]. Aminoglycoside antibiotics molecules are polar, resistant to acids, bases, heat and not extensively bound to protein [6]. Although plenty of work has been performed to this various class of compounds, there is still huge potential for further research of this compound.

Chromatographic methods used for the analysis of aminoglycosides

Chromatographic technique used for qualitative use

Aminoglycoside molecules have been analyzed in tissues and urine by various techniques like microbiological, radioenzymatic assay (REA), radioimmunoassay (RIA) method and by paper chromatography. These methods are still extensively used but often lack quantitative or qualitative performance. Some of the biological methods like microbiological assays methods which performed based on agar diffusion of the drug and concentration-dependent growth inhibition (inhibition zone) of the test organism inoculated in the agar. But this assay method requires longer time period (24–72h) for its incubation, after which inhibition of bacterial growth can be measured. Numerous factors like incubation temperature, pH and depth of the agar on plate and ion concentration of test strain, incubation time influence the performance of these methods. Additionally, different agar pH needs to be used for the analysis of various kinds of aminoglycosides molecules. Although microbiological methods are useful, simple and relatively cheap but looks like they are inaccurate and subject to interferences caused by nonspecific inhibitors or other antimicrobial drugs [7].

RIA methods look more promising as compared to the microbiological assay method. RIA methods are very sensitive and specific, but other aminoglycosides might cause interferences during analysis. Aminoglycosides like gentamicin, tobramycin, amikacin, netilmicin, and sisomicin analysed by using RIA technique. Analysis using an RIA method requires complicated parameter optimization and specialization for the analysis. Selection and preparation of suitable procedure is difficult and time-consuming [8].

Chromatographic technique used for quantitative use

Chromatographic methods for the analysis of aminoglycoside were needed for qualitative and quantitative determinations. However, due to structural similarity, separations between the aminoglycosides are quite difficult and challenging.

Some of the chromatographic analysis performed by using various chromatographic technique like Gas chromatography, Liquid chromatography, Liquid chromatography with mass spectroscopy (LC MS) etc. were discussed in the various section of this paper.

Gas chromatography (GC)

Gas chromatography (GC) is mostly used technique for the analysis of volatile, heat-stable compounds. However, direct analysis of theses aminoglycosides using GC is quite challenging because of the hydrophilic, basic and non-volatile nature of these aminoglycosides molecules. Derivatization technique was used to improve the chromatographic nature of these types of molecules [9].

Trimethyl silyldiethyl amine (TMSDEA) has been used as a derivatizing agent, for the detection of some class of this aminoglycosides molecules. Derivatizing agent like Trimethyl silyldiethyl amine (TMSDEA) are less sensitive and unstable. Consequently, due to this nature of this agent, it produces nonlinear, poor repeatability and low yield. Freeze drying of samples prior to derivatization need to be used to eliminate variations in sample moisture content and solubility. Sealed sample vials, removal of metal parts from the chromatographic system, and on-column injection have been tried to improve repeatability and quantification. Results obtained from this method were remaining poor [10, 11].

The components of Kanamycin A, B, and C have been separated as their trimethylsilyl (TMS) derivatives. The TMS derivatives of neomycin, kanamycin also has been identified by mass spectrometry (MS). Derivatization results in silylation of all amino and hydroxyl groups. Various components of aminoglycosides and its stereoisomers have been separated by GC with derivatization technique [12].

Derivatization procedure using trimethylsilylimidazole (TMSI) for silylation of hydroxyl groups and heptafluorobutyric imidazole (HFBI) for heptafluorobutyrylation of amino groups has been reported.

Preu M, Guyot, Petz M have developed a gas chromatography–mass spectroscopy method for the analysis of aminoglycosides antibiotics using experimental design for the optimization of the derivatization reactions. Here the analytes were derivatized using two-step procedure involving trimethylsilylation of the hydroxyl groups with trimethylsilyimidazole and acylation of the amino group with heptafluro-butyrylimidazole [13].

Mineo H, Kaneko S, Koizumi I reported a gas chromatography with FID detector for the determination of 7 penicillins, 3 tetracycline, 23 antibiotics in meat [14].

Using the derivatization technique, Mayhew and Gorbach detected various aminoglycosides like gentamicin, tobramycin, netilmicin and amikacin in serum. Results are satisfactory in accuracy and precision. TMS–heptafluorobutyryl (HFB) is considered as another suitable derivatizing agent used to analyse the aminoglycosides through GC technique [15].

Stead D discuss about the use of various analytical technique like X-ray crystallography, nuclear magnetic resonance (NMR), Mass spectroscopy (MS) for the analysis of aminoglycosides [16].

A. P Topolyan has proposed a method for the derivatization of aminoglycosides antibiotics with Tris (2,6-dimethoxy phenyl) carbenium ion by MS technique to detect the presence of sisomicin, tobramycin molecules [17].

Liquid chromatography (LC)

High-Performance liquid chromatography (HPLC) is considered as an advance form of chromatographic technique. Different substantial chromatographic parameters like Specificity, Precision, Linearity. Accuracy and Robustness were assessed to check the method performance of the HPLC technique [18]. Due to this it was considered as one of the widely used technologies.

The most significant characteristics of this aminoglycosides molecule are the lack of presence of the chromophore group in their molecular structure. Due to this the analysis of these aminoglycosides compounds was quite challenging.

In HPLC technique, the choice of detector is quite important in order to look at the capability of the elution of all the aminoglycoside components peaks in an appropriate wavelength.

Because of the polar nature of the aminoglycoside molecule different types of C18 analytical column were used along with ion pair buffer to perform the analysis in HPLC UV detector

During the survey of several articles, it was found that the derivatization technique required to analys these aminoglycosides antibiotics with HPLC UV detector.

The most commonly used derivatization reagents are *ortho*-phthalaldehyde (OPA) and 1-fluoro-2,4-dinitrobenzene (FDNB) for the analysis of these class of compounds.

Various articles were referred to identify the method used for the analysis were presented below.

- Mustafa S and Devi K reported a method to detect Kenamycin using a mobile phase containing 0.1M disodium tetraborate (pH 9.0) and water (25:75) with Phenomenex C18 column under isocratic condition using 205 nm wavelength [19].

- Hao-Ran J, Xiang-peng Li reported a pre-column derivatization HPLC method for the quantitative and qualitative analysis of Kenamycin. Chromatographic condition was established by using the Kromasil C18 column, Mobile Phase: Methanol: Water (40:60), flow rate 0.5 ml/min, UV detection at 390 nm [20].

- Jin-feng W, Hua-xin reported an HPLC method using Nano quantity analyte detector (NQAD). Chromatographic separation was achieved by using a mobile phase 0.2% Trifluoroacetic acid: Methanol (80:20) with Agilent SB C18 column [21].

- Kim B, Lee S and Lee H reported a post-column derivatization liquid chromatographic method for the detection of aminoglycosides using derivatization agent known as phenyl isothiocyanateas. Analytical column Capcell-pak C18, Mobile phase combination of Acetonitrile and 0.1 % TFA at 240 nm wavelength were used during the analysis [22].

- Kalyani L, Rao C V N reported an RP-HPLC method for the determination of Kenamicin using a combination of Methanol: Acetonitrile: Acetate buffer with pH 5.1 (75:20:0.05 v/v/v) as mobile phase. Waters X Terra column and 212 nm were used a wavelength nanometer during the analysis [23].

- Korany M, Haggag R reported a novel liquid chromatographic technique method using pre-column derivatization reaction to determine amikacin. The separation was achieved by Spherisorb C18 ODS column using Mobile phase composed of Acetonitrile: 0.1M Sodium acetate buffer (pH 5.0, 25:75 v/v). Detection was carried out at 330 nm [24].

- Dan H, Yang L reported a post-column derivatization method for the determination of amikacin using Waters SunFire C18 column. Detection was carried out 360 and 440 nm [25].

- Vimal D proposed an RP HPLC method for the estimation of amikacin. The separation was achieved by C18 column and Acetonitrile: water (10:90 v/v) as mobile phase. Detection was carried out at 212 nm [26].

- Feng C H, Lin S developed a simple and sensitive liquid chromatographic method for the determination of amikacin in human plasma. The amikacin is derivatized with 1-naphthyl isothiocyanate (NITC) and it was analysed by HPLC on a LiChroCART RP-Cls column with water-acetonitrile (57:43, v/v) as mobile phase and detection carried out at 230 nm [27].

- Chauhan B, Jalalpure S developed an ultra-high performance liquid chromatography (UHPLC) method for the determination of amikacin sulfate in human serum using derivatization with FMOCCl and glycine. Chromatographic condition was achieved by using mobile phase composed of Acetonitrile: water in the ratio 70:30 (v/v) and Shim-Pack XR-ODS III, Shimadzu) C18 column. Fluorimetric detection at excitation and emission wavelength of 265 nm and 315 nm, respectively was used for the proposed chromatographic method [28].

- Kim M, Liu Y developed a tandem mass spectroscopy method for the detection of amikacin using a mobile phase composed of MeOH/10 mmol NH_4OAc (pH 4.0)/Heptafluorobutyric acid

(5/95/0.2) and methanol. Betasil phenyl column (100 x 2.1 mm, 5µm) was used during the analysis [29].

- Li D, He S presented a rapid and sensitive high-performance liquid chromatography method for the determination of amikacin in water samples with solid phase extraction and pre-column derivatization. Solution were derivatized by using 4-chloro 3,5 dinitro-benzotrifluroride in presence of trimethylamine at 70 °c. Kromasil ODS C 18 column was used during the analysis [30].

- Chuong M C, Chin J recommended a HPLC method for the assay of Gentamicin using various column like Aqua C18 5µm, Luna C18 5µm, Nucleosil C18 5µm. Mobile phase was prepared by mixing methanol, water, and glacial acetic acid (70:25:5 v/v/v) with Sodium 1-heptanesulfonate. Derivatization procedure was performed by using *ortho*-phthaladehyde (OPA) solution. Detection wavelength was carried out at 330 nm [31].

- Adams E, Vaerenbergh G V, Roets E reported a liquid chromatographic method for the analysis of amikacin with pulsed electrochemical detection [32].

- Oguri S, Miki Y reported a selective and reproducible high performance capillary electrophoretic (HPCE) method for the quantification of amikacin in human plasma. This method involves ultrafiltration of plasma before derivatization with the fluorescence derivatizing reagents 1-methoxy-caronylindolizine-3.5 dicarbaldehyde at room temperature [33].

- Ovalles J F, Brunetto M R, Gallignani M proposed a simple and sensitive RP HPLC method for the determination of amikacin (AMK) by using derivatization technique. This method is based on the pre-column derivatization of AMK with 6-aminoquinolyl-N-hydroxysuccinimidyl carbamate (AQC). Detection was performed by UV absorption instead of fluorescence [34].

- Galanakis E G, Megoulas N C, Soluch P reported a novel method for the direct determination of the aminoglycosides antibiotics (amikacin, kanamycin) based on the reverse phase liquid chromatographic (LC) with ELSD detector [35].

- Nicoli S, Santi P reported a simple technique for the determination of amikacin by using HPLC UV technique. UV detection was carried out 365 nm [36].

- Zawilla N H, Li B, Hoogmatens J reported an improved reversed-phase liquid chromatographic method with ECD for the analysis of amikacin. Proposed method was performed by using Discovery column [37].

- Serrano M J, Silva M reported a simple and sensitive method for the quantification of amikacin in the urine sample by using HPLC with chemiluminescence detection [38].

- Brajnoski G, Hoogmartens J, Allegaert K proposed a sensitive method for the determination of amikacin by using electrochemical pulse detection [39].

- Zhu Yu C, Zhao He Y reported an analytical method for the determination of kanamycin A, amikacin and tobramycin residues in milk by capillary zone electrophoresis with post column derivatization and laser-induced fluorescence detection [40].

- Laki M, Hajdu M developed a new, fast high-performance liquid chromatographic-UV method for quantitative analysis of gentamicin carrier samples drawn in drug release studies. The mobile phase consisted of methanol-water-acetate buffer (0.02 M ammonium acetate solution, adjusted with ammonia to pH = 9), a reverse phase, Zorbax Rx-C18 column has been used during the analysis [41].

- Kuehl P, De S developed a stability-indicating HPLC assay method with UV detection for the simultaneous quantification of Gentamicin Sulfate and L-leucine from NanoGENT dry powder for inhalation. Mobile phase was prepared by mixing methanol, water, and glacial acetic acid (70:25:5) with Sodium 1-heptanesulfonate. Derivatization procedure was performed by using *ortho*-pthaladehyde (OPA) solution. Detection wavelength was carried out at 330 nm during the analysis [42].

- Joseph A, Rustum A developed a RP-HPLC method for the determination of gentamicin sulfate using pentafluorophenyl column and a charged aerosol detector. Mobile phase comprising of (A) heptafluorobutyric acid: water: acetonitrile (0.025:95:5, v/v/v) and (B) trifluoroacetic acid: water: acetonitrile (1:95:5, v/v/v) was used during the study [43].

- Isoherranen N, Soback S developed a method to determine gentamicin and its components using derivatization technique with UV detector. 1-fluoro-2,4-dinitrobenzene was used as derivatization agents. Symmetry TM C18 reversed-phase column was used during the study [44].

- Meicheng Y, Zhen L developed a liquid chromatographic method using pre column derivatization for the content of gentamicin sulfate and neomycin sulphate. 9-fluorenylmethyl chloroformate (FMOC-Cl) was used for derivatization during the analysis [45].

- Plozza T, Trenerry V C reported a robust method to confirm and quantify the levels of dihydrostreptomycin, streptomycin, apramycin, neomycin and gentamicin (C1, C2 and C1a) present in animal tissue using liquid chromatography-tandem mass spectrometry. The compounds were separated using C18 column and mobile phase consisting of a mixture of acetonitrile, water and 50 mmol heptafluorobutyric acids [46].

- Caudron E, Bagriche S. developed a simple HPLC method for the determination of gentamicin sulfate and colistin sulfate by ion pairing reverse phase chromatography at UV detection 215 nm. Separation was achieved by using Waters X Terra C 18 column. Combination of Acetonitrile: Water was used as mobile phase [47].

- Hussain A, developed a simple high performance liquid chromatographic technique for the estimation of Streptomycin. It was achieved by using intersil ODS-3 C-18 column and detected carried out by UV-Visible Detector at 240 nm. A gradient combination of a mixture of Methanol and Buffer was used as a mobile phase [48].

- T J Whall developed an isocratic high performance liquid chromatographic method for the determination of streptomycin and dihydrostreptomycin. The method employs a microparticulate reversed-phase (µBondapak C18 and LiChrosorb RP-18) column and a mobile phase composed of 0.02 M sodium hexane sulfonate and 0.025 M tribasic sodium phosphate in acetonitrile-water (8:92, v/v) at pH 6.0 with detection by ultraviolet absorbance at 195 nm [49].

- Bruijnsvoort V M, Ottink M J, Jonker M K developed a LC-MS/MS method for the determination of streptomycin (STR) and its derivative dihydrostreptomycin. Proposed method was achieved by using Analytical Alltima C 18 column [50].

- Edder P, Cominoli A, Corvi C reported a simple and reliable procedure for the analysis of streptomycin by using β napthoquinone 4-sulfonate as post derivatization and fluorescence detection [51].

- Holzgrabe U, Nap J C, Kunz N proposed a method to control the impurities in Streptomycin sulfate by HPLC coupled with mass detection and corona charged aerosol detection. This was performed by using the Supelcosil ABZ alkylamide column [52].

- Adams E, Rafiee M, Roets E proposed a liquid chromatographic method for the analysis of streptomycin sulfate. Proposed method was achieved by using analytical column Supelcosil LC-ABZ column [53].

- Ashraf S, Ahmad Z R developed a simple and sensitive ultra-high performance liquid chromatographic method (UPLC) with electron spray ionization (ESI) tandem mass spectrometry. Separation of both the analytes was carried out by using BEH Hillic column and triple quadruple mass spectrometer in positive ESI mode [54].

- Ruckmani K, Shaikh Z developed a novel method for the determination of Tobramycin using UV detector. An isocratic mobile phase consists of buffer 0.05 M diammonium hydrogen phosphate, pH adjusted to 10.0 using tetramethylammonium hydroxide. Analysis was carried out by using Purosphere RP column. The detection was carried out using variable wavelength UV-Vis detector set at 210 nm [55].

- Russ H, Mecleary developed a HPLC method for the determination of tobramycin in ophthalmic suspension. Proposed method was achieved by using chromatographic parameters include a mobile phase of acetonitrile/buffer (55/45; v/v) and a Nova-Pak C18 column, maintained under ambient conditions. The wavelength of detection was set at 365 nm [56].

- Zhu L, Wang J developed simple and direct method for the detection of Tobramycin using refractive index (RI) detector. ZORBAX SB-C18 column used was during analysis [57].

- Clarot I, Paris S I developed a simple HPLC method with evaporative light scattering detection for the detection of Tobramycin. Chromatographic separation was carried out in gradient mode using a Zorbax SB C18 column with mobile phase's combination of acetonitrile and water with trifluoroacetic [58].

- Kubo H, Kobayashi Y, Nishikawa T proposed a simple and accurate liquid chromatographic method for the determination of kanamycin and dibekacin in serum. The determination of kanamycin and dibekacin was performed by a combination of reverse-phase, ion-pair chromatography, post column derivatization with *ortho*-phthalaldehyde, and fluorescence detection [59].

- Manyanga V, Elkady E have proposed a reversed phase liquid chromatographic method with pulsed electrochemical detection for tobramycin in bulk and pharmaceutical formulation. Chromatographic condition was achieved using a Discovery C18 RP column with a mobile phase, containing sodium sulfate (35 g/l), sodium octanesulphonic acid (1 g/l), tetrahydrofuran (14 ml/l) and 0.2 M phosphate buffer pH 3.0 [60].

- Mashat M, Chrystn H proposed a reversed-phase liquid chromatography method involving pre-column derivatisation with fluorescein isothiocyanate for determination of tobramycin in urine samples. The chromatographic separation was carried out on a Phenomenex Luna C18 column at ambient temperature using mobile phase of acetonitrile–methanol–glacial acetic acid–water (420:60:5:515, v/v/v/v). The tobramycin–FITC derivative was monitored by fluorescent detection at an excitation wavelength 490 nm and emission wavelength 518 nm [61].

- Huang L, Haagensen JAJ proposed LC-MS/MS method for the determination of Tobramycin in M_9 media. Method performance was achieved by using a PFP column (2.0 × 50 mm, 3 µm) eluted with water containing 20 mmol ammonium formate and 0.14% trifluoroacetic acid and acetonitrile containing 0.1% trifluoroacetic acid in a gradient mode [62].

DATA SOURCE

English language article published from 1980 to 2019 were identified through searches of the Pistoia Alliance database, science direct data base, Analytics, Reference standard data base various bibliographies using the key word like Aminoglycosides, chromatography, names of aminoglycosides molecule, liquid chromatography technique. The search include various chromatographic condition uses to analyse the aminoglycoside molecules through various research and review articles. Search dates February 2019 to November 2019

CONCLUSION

This article provides knowledge for the analysis of aminoglycoside molecule by liquid chromatographic technique. The wider use of this class of compounds requires suitable methods for their detection and use in routine analysis. The proposed methods must be accurate, sensitive, and robust against interferences. However, the chemical features of aminoglycoside molecules such as polarity, solubility, lack of volatility, and lack of chromophore make method development difficult and challenging.

Selection of derivatizing agents and chromatographic techniques plays a substantial role on the separation and selectivity of the method. Developed method need to validated as per the regulatory guideline and it is utilized to ensure that quality is built to support drug development process.

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AUTHORS CONTRIBUTIONS

All the author has contributed equally.

CONFLICT OF INTERESTS

Declared none

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