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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**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.

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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 antibiotic 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 kanamycticus, gentamicin from Micromonaspora purpurea, sisomicin from Micromonaspora inyosensis [1, 2]. Semisynthetic aminoglycosides like netilmicin from Sisomicin, tobramycin from Streptomycyes tenebrarius and amikacin from kanamycin [3]. Aminoglycosides molecules contain aminomycicyclitol 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. Resemblance 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 excessively 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 spectrometry (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 these 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 trimethylsilyl (TMS) derivatives. The TMS derivatives of neomycin, kanamycin and sisomicin was achieved by using a mobile phase containing 0.1M sodium tetraborate (pH 9.0) and water (25:75) with Phenomenex C18 column under isocratic condition using 205 nm wavelength [19].

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.

- Mustafà S and Devi K reported a method to detect Kenamycin using a mobile phase containing 0.1M sodium 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 (60:40) with Agilent SB C18 column [21].
- Kim B, Lee S and Lee H reported a post-column derivatization liquid chromatographic method for the determination of aminoglycosides using derivatization agent known as phenyl isothiocyanate. Analytical column Capcell pak C18, Mobile phase combination of Acetonitrile and 0.1 % TFA at 240 nm wavelength were used during the analysis [22].
- Kabanyi L, Rao C V N reported an RP-HPLC method for the determination of Kenamycin 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-C18 column with water-acetonitrile (57:43, v/v) as mobile phase and detection carried out at 230 nm [27].

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

- 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. Fluorometric 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 NH₄OAc (pH 4.0)/Heptfluorobutric acid
ODS C 18 column was used during the analysis [30].

benzotrifluoride in presence of trimethylamine at 70 °C. Kromasil Solution were derivatized by using 4-chloro 3,5 din itro-
samples with solid phase extraction and pre-column derivatization.

chromatography method for the determination of amikacin in water

5μm) was used during the analysis [29].

heptanesulfonate. Derivatization procedure was performed by using

mobile phase consisting of a mixture of acetoni trile, water and

Gentamicin using various column like Aqua C18 5μm, Luna C18 5μm,

chromatographic method for the analysis of amikacin  with pulsed

dicarbaldehyde at room temperature [33].

Derivatization procedure was performed by using

Mobile phase was prepared by mixing methanol, water, and glacial acetic acid (70:25:5 v/v/v) with Sodium 1-

Galanakis E G, Megoulas N C, Soluch P reported a no vel method

Zhu Yu C, Zhao He Y reported an analytical method for the

determination of Tobramycin using UV detector. An isocratic mobile

Meicheng Y, Zhou L developed a liquid chromatographic method

using pre column derivatization for the content of gentamicin sulfate and

with body phase consisting of a mixture of acetoni trile, water, and 50 mmol heptahalobutyrinic acids [46].

Chuong M C, Chin J recommended a HPLC method for the assay of

Gentamicin using various column like Aqua C18 5μm, Luna C18 5μm,

and mobile phase consisting of a mixture of acetoni trile, water and 50 mmol heptahalobutyrinic acids [46].

• 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-

phthaldehyde (OPA) solution. Detection wavelength was carried out at 330 nm during the analysis [42].

• Thoughtful 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 ultraviolet absorption of plasma before derivatization with the fluorescence derivatizing reagents 1-methoxy-caronylindolizine-3.5
dicarbalddehyde at room temperature [33].

• Ovals 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-aminoquinolinyl-N-

hydroxysuccinimidyl carbamate (AQG). 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].

• Nicol 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 I 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].

• 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 Altitima C18 column [50].

• 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 LCChrosorb RP-18) column and a mobile phase composed of 0.02 M sodium hexane sulfonate and 0.025 M tribasic sodium phosphate in acetone-trile-water (8:92, v/v) at pH 6.0 with detection by ultraviolet absorbance at 195 nm [49].

• 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].

• 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: acetonicitrile (0.025:95.5, v/v/v) and (B) trihydroxoaetic acid: water: acetonicitrile (1:95.5, v/v/v) was used during the study [45].

• 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].

• Plouza T, Trenery V C reported a robust method to confirm and quantify the levels of dihydrostreptomycin, streptomycin, apramycin, neomycin and gentamicin (C1, C2 and C1α) 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 heptahalobutyrinic 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 method for the analysis of amikacin. Proposed method was performed by using Discovery column. The detection 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, Medley 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].

Claret L, 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 acid [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 orthophthalaldehyde, 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 formulations. 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 K 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 (42:6:5:51:5; 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 JAIJ proposed LC-MS/MS method for the determination of Tobramycin in M-media. Method performance was achieved by using a PFP column (2.0 × 50 mm, 3 µl) 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 database of various 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 chromatophore 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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