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(Review)

Recent Advances in Aminoglycoside Antibiotics Analytical Determination

Michael Gamal Fawzy [1, *], Mohamed Ashraf [2], Hossam S. El-Sawy [2]

[1] *Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Egyptian Russian University, Cairo 11829, Egypt.*

[2] *Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Egyptian Russian University, Cairo 11829, Egypt.*

*Corresponding author: Michael G. Fawzy, E-mail address: michael.g.fawzy@eru.edu.eg, Tel.#: +2012-8891-9729

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Abstract

Aminoglycoside antibiotics have been widely used for several decades due to their potent antimicrobial activity against various Gram-negative bacteria. However, the emergence of antibiotic resistance and associated adverse effects have necessitated the development of reliable methods for the determination of aminoglycoside antibiotics in different matrices. This review article provides an overview of the current state of aminoglycoside antibiotic determination, highlighting the analytical techniques employed, including chromatographic methods and immunoassays. The article discusses the advantages and limitations of each method, emphasizing their applicability in different sample types such as biological fluids, food, and other samples. In addition to the present situation, this review highlights the potential future developments in aminoglycoside antibiotic determination. These include the emerging trends in miniaturized and portable analytical devices, advancements in sample preparation techniques, and the integration of multiple detection methods for improved sensitivity and selectivity. Overall, this review article provides a comprehensive analysis of the current methods used for aminoglycoside antibiotic determination, while also discussing the future directions in this field. The information presented

herein will be valuable for researchers, regulatory authorities, and stakeholders involved in the development and implementation of effective strategies for determination and analysis of aminoglycosides.

Keywords: Aminoglycoside antibiotics; Analytical techniques; Liquid Chromatography; Immunological methods; Spectrophotometric methods; Spectrofluorimetric methods

1. Introduction

A class of drugs known as aminoglycoside antibiotics (AGs) has a wide range of medical uses. Gram-negative bacteria, and less frequently Gram-positive bacteria, are the primary causes of infections treated with AGs. A. Schatz and S. Waksman found the first AG in 1943. They discovered streptomycin's antibacterial qualities after isolating it from Streptomyces griseus germs for the first time. In 1952, they were awarded the Nobel Prize for their discovery. AGs are divided into two categories according to their source: natural antibiotics (such as neomycin, gentamycin, kanamycin, streptomycin, tobramycin, and sisomycin) and semi-synthetic antibiotics (such as amikacin, dibekacin, isepamycin, netilmycin, and arbekacin) [1].

Antibiotics classified as aminoglycosides share a common set of pharmacokinetic characteristics. They are applied to veterinary care as well as human treatments. AGs have a wide range of therapeutic applications, including the treatment of infections of the skin, bones, joints, and urinary tract. In addition to their usage in ophthalmology, AGs are also utilized in the gastrointestinal tract to sterilize it before surgery. Additionally, they are added to farm animal feed as a supplement and utilized as a pest deterrent in gardening [2,3]. AGs have limited absorption after oral administration because of the polycationic nature of their molecules. Consequently, AGs are applied topically (creams), subcutaneously (injections), and directly to the eyes and ears (drops). The way that AGs work is by attaching themselves to the A-site of the bacterial ribosome, also known as the protein ribosome, and preventing protein translation, which eventually causes the death of the bacteria [1].

Even though aminoglycosides have a strong antibacterial efficacy, they are also considered toxic compounds with low therapeutic indices. For instance, the ratio of plasma tobramycin concentration that is hazardous to that that is within the therapeutic range is almost 50% [4]. Additionally, AGs have the ability to build up in parenchymal tissues, such as the renal cortex,

where they attach to glycoproteins such as megalin, impairing the function of the urinary system. AG side effects include neurological and digestive system damage, as well as oto- and nephrotoxicity. Furthermore, because AGs can cross the placenta, they may harm the foetus. As a result, the type of AG and its dosage need to be carefully regulated. These medications run the risk of being overused in commercial animal farms because of their low cost. In large-scale farms in particular, antibiotics are not only used to cure animals but also as growth promoters and prophylactic measures.

The use of AGs in veterinary applications accounts for about 3.5% of all antibiotic usage [5]. The improper handling of AGs might lead to negative environmental effects because they are non-metabolizable substances that are eliminated in their unaltered molecular form [6]. Certain bacterial types, particularly enteric bacteria, become more resistant to antibiotics when high volumes of AGs are released into the environment [7]. AG half-lives are 2–3 hours in plasma and 30–700 hours in tissues [8]. AGs can be present in food that comes from animals since they build up in animal tissues. Since large-scale breeding farms are located in North Carolina (USA), where agricultural antibiotic abuse has been widely reported and resulted in the discovery of substantial levels of antibiotics in farm wastewater, soil, and animal tissues, awareness of this issue has increased. As a result, several nations have passed laws limiting the amount of antibiotic residue that can be found in food that comes from animals [5]. Furthermore, the biggest restaurant chains, including KFC, Subway, and McDonald's, are now asserting that the food they serve is antibiotic-free. Surface waterways and soil pollution levels rise due to the excretion of agricultural pollutants in their unaltered forms and the influx of wastewater containing AGs from hospitals and the pharmaceutical industry.

The proper management of these contaminants is a serious issue that calls for specialized treatment facilities as well as specific legislation. Fig. 1 provides a schematic representation of the movement of AGs in their surroundings.

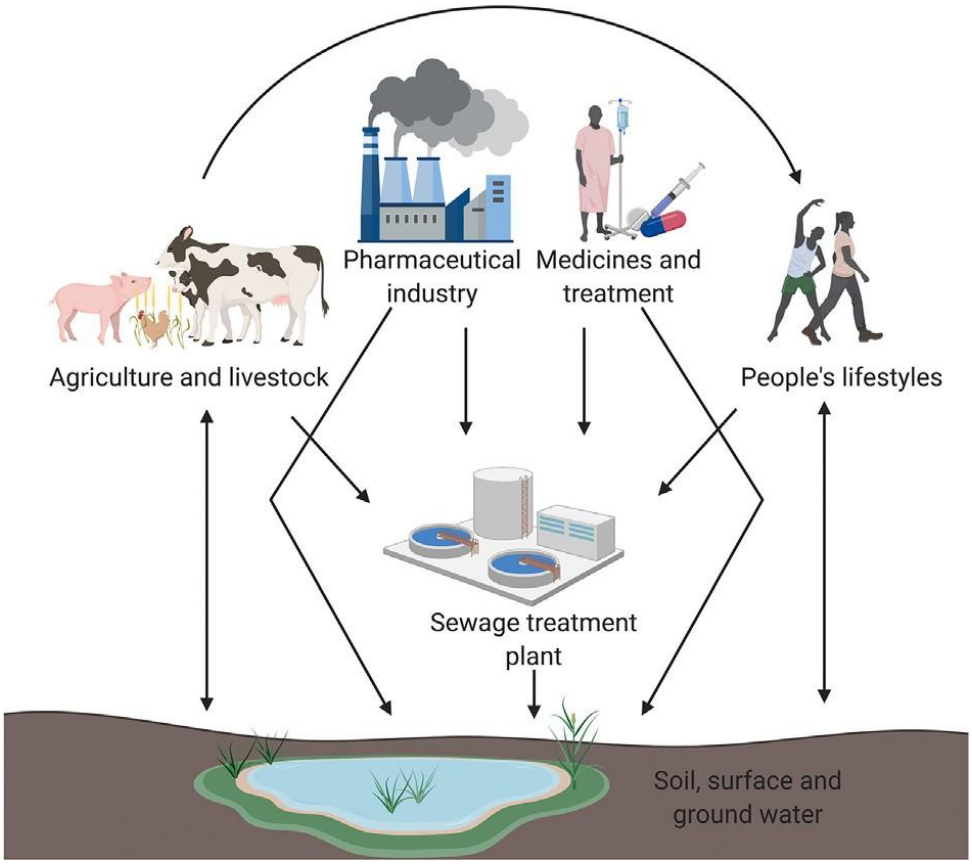

Fig. 1. Aminoglycoside antibiotic mobility in the environment [9].

AGs, which can be (i) streptidine (e.g., streptomycin), (ii) 4,5-di-substituted deoxystreptamine (e.g., neomycin), or (iii) 4,6-di-substituted deoxystreptamine (e.g., kanamycin), are weak bases made up of two or more molecules of aminosugars (D-glucosamine, D-kanosamine) joined by a glycosidic bond with cyclitol (see Fig. 2).

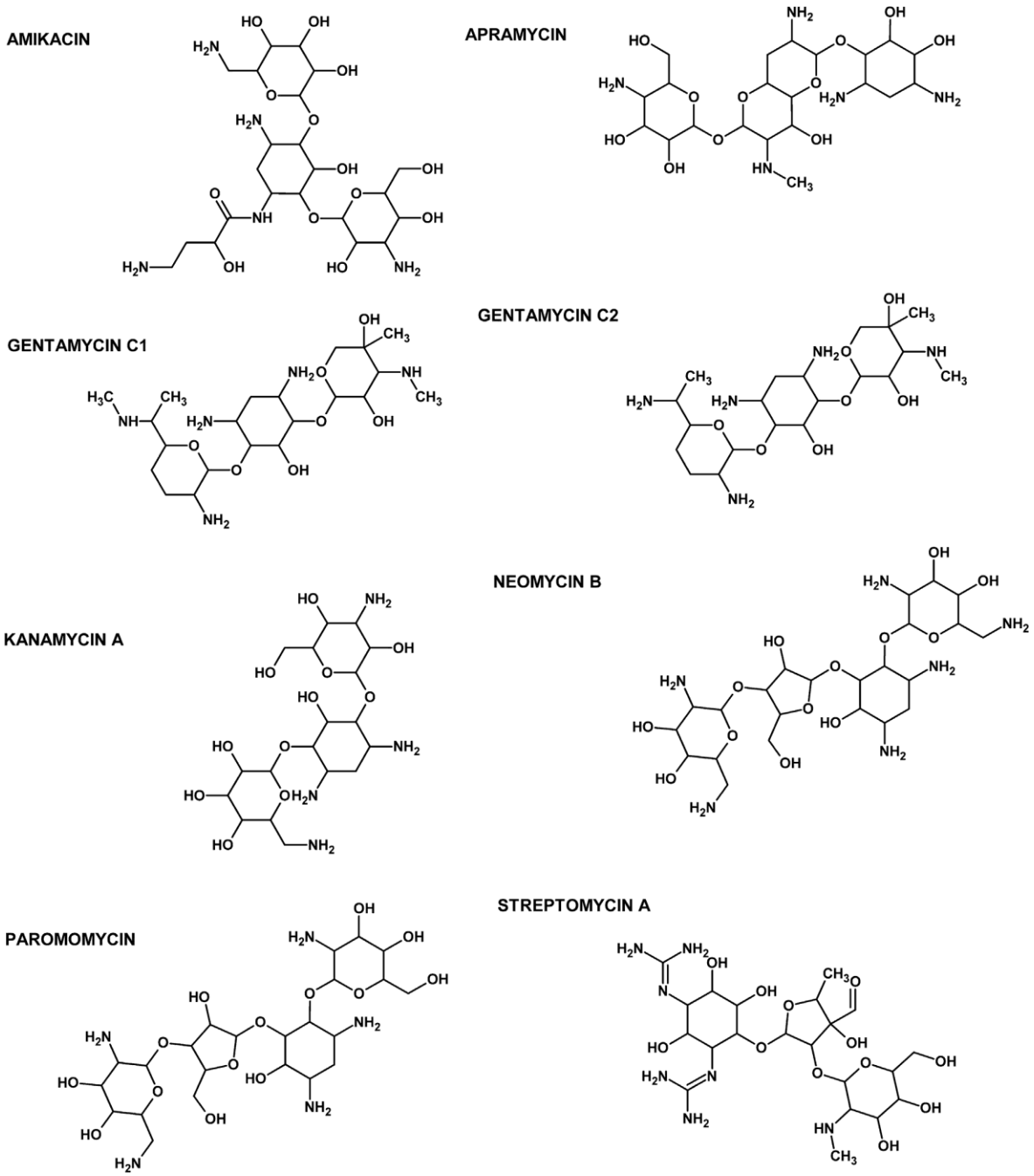

Fig. 2. Selected aminoglycoside antibiotics chemical structures [9].

They have high polarity/hydrophilicity (logP values between 4 and 9), are insoluble in non-polar organic solvents, extremely soluble in water, and moderately soluble in methanol. Certain AGs exist as complexes, which are made up of multiple distinct chemical molecules. Gentamycin, for instance, is made up of four major compounds: gentamycin C1 (477.6 g/mol), gentamycin C1A (449.5 g/mol), and gentamycin C2 (which comes in the form of two stereoisomers, A and B, 463

g/mol). Neomycin is another example; it comes in two stereoisomers, B and C, of which only B has been used therapeutically [8]. A complex process in sample preparation and final determination, aminoglycoside analysis is caused by their high polarity, polycationic nature, and lack of chromophores.

2. Liquid chromatography

Prior to their determination, liquid chromatography (LC) is still the gold standard for separating AGs. This is because, in addition to being a tried-and-true method with a wealth of literature at its disposal when faced with the challenge of analyzing a specific type of sample, it also has the capability of simultaneously analyzing multiple AGs, a feature that is possibly unique to capillary electrophoresis when it comes to the analysis of aminoglycosides in complex matrices. Because of their high resolution, selectivity, and sensitivity, LC-based techniques appear to be the most widely utilized, albeit the best approach will always depend on the analytical task at hand and the type of sample.

Sample preparation is an essential stage in the analytical process because of the many problems with aminoglycoside determination, which can result in erroneous and irreproducible results due to their complex physicochemical properties and the common matrices. The sample preparation procedure is typically restricted to dissolving the sample in deionized water or using the mobile phase for additional LC analysis in the case of relatively simple matrices, such as pharmaceutical formulations. Specifically, these methods are applied to eye drops, tablets (after crushing), and certain kinds of medicated animal feed [10–13]. For creams and ointments, there is typically a need for an extra de-fatting phase. For this, a variety of non-polar organic solvents are employed, such as DCM [11]. The processes involved in sample preparation are typically more involved when dealing with matrices, such as foods derived from animals. For example, because honey is mostly composed of sugars, the presence of enzymes and polyphenols may complicate sample preparation and analysis [14]. The significant levels of proteins, lipids, salts, vitamins, and minerals found in milk and foods containing animal matter may also make it difficult to isolate and identify AGs. Fig. 3 displays a generic sample preparation scheme. However, it should be mentioned that the best method of sample treatment for determining AGs inevitably depends on a number of variables, including the intended application, the sample matrix's complexity, the analytes' concentration, etc. Because of this, there is no one-size-fits-all solution. The specific

factors that need to be taken into account while choosing the sample treatment technique are described in the sections that follow.

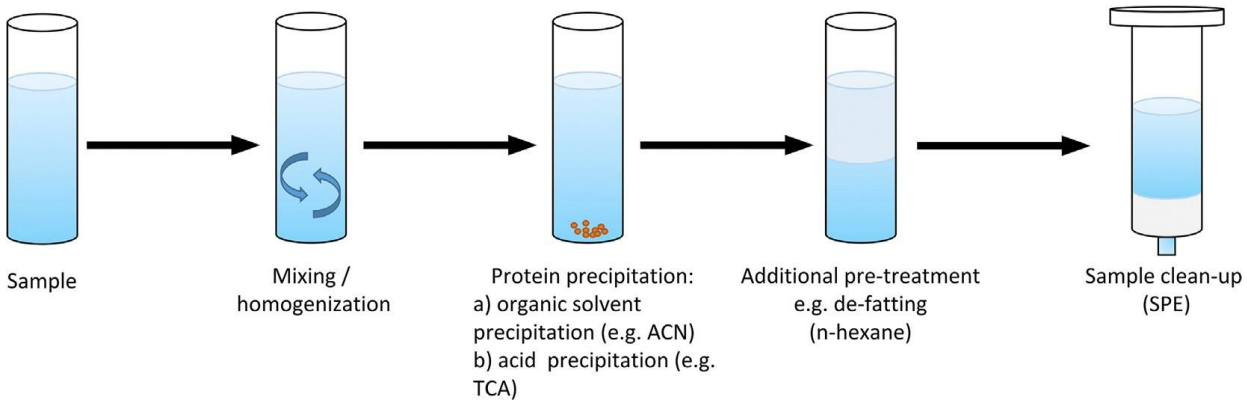

Fig. 3. Sample treatment for succeeding aminoglycosides analysis [9].

2.1.Sample pre-treatment

Typically, sample homogenization or grinding is the first step in the sample preparation technique. When there are significant numbers of proteins, they are precipitated out using acetonitrile or organic solvents such methanol [15–18]. However, it should be mentioned that AGs lose some of their solubility during protein precipitation since they are weakly soluble in combinations with high concentrations of organic solvents. Conversely, in acidic aqueous solutions, AGs exhibit excellent solubility and great stability. In light of this, acid precipitation appears to be a more secure option for protein removal when determining AGs. Because of their great efficacy at comparatively low concentrations, chlorinated or fluorinated organic acids, such as trichloroacetic acid (TCA), trifluoroacetic acid (TFA), or heptuloric acid (HFBA) [18–27], are frequently utilized for this purpose. Because of its inexpensive cost and quick acting properties, TCA appears to be the most widely used precipitating agent. 2 × 5% TCA solutions are typically employed [28]. Aside from EDTA, which is used to break down AGs complexes with polyvalent ions, precipitating solutions may also contain pH control compounds (NH4Ac, KH2PO4), ionic strength adjusting substances (NaCl), or pH control compounds (NH4Ac, KH2PO4) [22, 28-30]. Samples are centrifuged, filtered, and defatted as needed following protein precipitation [23, 26]. Lastly, the sample solutions' pH can be adjusted to the appropriate level [25, 28, 29].

2.2.Sample purification and amelioration

After the sample is pre-treated, it goes through a purification and enrichment step using a number of methods, primarily SPE. Commonly employed are hydrophilic-lipophilic balance mode (HLB) solid phase extraction (SPE) sorbents, C18 sorbents (in conjunction with ion-pairing reagents), and cationic exchangers (mostly weak cationic exchangers, WCX). Choosing the right sorbent type can be difficult because different AGs have varied acid/base dissociation constant values. This is especially true when processing many analytes at once. Because AGs are poly-cationic and apt to bind to functional groups, ion exchange sorbents are commonly used. Numerous sample types, such as animal tissues (kidney, liver, and muscle), milk, eggs, honey, royal jelly, and animal feeds, can be purified using this form of sorbent [14, 24, 29, 31]. For extraction techniques utilizing WCX cartridges, a pH range of 6 to 8 is necessary.

In these circumstances, the negatively charged functional groups of sorbents draw in molecules of protonated AGs. AG elution is facilitated by the sorbent surface becoming neutral at pH values below 3. At least for some analytes, the recoveries may be significantly impacted by the ionic strength of the pre-extraction mixture [29]. Further problems could arise if many AGs are to be extracted simultaneously since, depending on the type of cartridge used, the signal for specific AGs may be suppressed in some matrices [31]. Strong cation exchange functionality (PCX) polymeric cation exchangers, on the other hand, have been demonstrated to yield superior results when used with specific AGs when compared to standard WCX cartridges [14], while strong cation exchange (SCX) cartridges work better overall when used for the extraction of weakly basic compounds, like gentamycin [24].

Hydrophilic-lipophilic balance (HLB)-based sorbents exhibit AGs extraction efficiency fluctuating with sample extract pH, much like ion exchange sorbents do. This problem could be remedied, for example, by developing modified sorbents or multi-step extraction techniques [21]. The latter approach was used in a study wherein a small internal diameter PTFE tube was used to synthesize urea-formaldehyde resin [25]. Using the resultant monolithic microcolumn as a sorbent, the levels of tobramycin, neomycin, and streptomycin in fresh meat extracts were measured. An alternative method involved grouping four monolithic poly (methacrylic acid-co-ethylene methacrylate) fibres and using them to extract six AGs from samples of milk and honey. The extraction process was significantly simplified as a result of the polymeric nature of the fibres and

the carboxyl functionality they possessed on their surface, which led to the observation of two different sorption mechanisms: hydrophobic contacts and cation-exchange mechanisms [19].

Another option for cleaning up samples is to use non-polar octa-decyl (C18) cartridges. AGs have a weak interaction with hydrophobic C18 sorbents because of their hydrophilic nature; hence, the latter can be utilized to extract non-polar components from sample extracts. Dispersive SPE (DSPE) is one method that can be used to do this clean-up [3], and QuECh-ERS procedures [32] can incorporate it because it is a quick process. On the other hand, because AGs are polycationic, they can be made more hydrophobic by forming ion pairs with substances like perfluorinated organic acids (HFBA, or heptalofuorobutyric acid). These ion pairs can be separated from extracts using methods that are frequently applied to other non-polar materials. Specifically, reversed-phase liquid chromatography [33] and SPE are both applicable.

The previously reported developments in AGs extraction and sample clean-up make use of magnetically active sorbents and molecularly imprinted polymers (MIPs). MIPs are specialized, highly selective sorbents created during the molecular polymerization process under spatial constraints. By interacting with the monomer functional groups through ionic, hydrogen, or covalent interactions, the template (analyte) molecule forms complexes. The form of such a complex is trapped or imprinted in the three-dimensional polymer structure upon cross-linking. A molecular imprint is left behind after the template/analyte is removed from the polymer. High affinity for molecules with shapes resembling those of the template (analyte) molecules is demonstrated by the resultant substance. The analyte-sorbent interactions are comparatively strong in the case of MIPs. Consequently, while preparing samples, two or three-step washing techniques (using MeOH or DCM) are feasible. Reducing interferences induced by matrix components, both polar and non-polar, is possible with thorough washing. Regretfully, SupelMIP® SPE-AG from Supelco is the only kind of such sorbent that is now offered for sale. AGs were determined in animal tissues, fish, eggs, processed food, honey, milk, and milk-based food products using sample clean-up techniques using MIPs [27, 34]. The MIP sorbents provide for improved recoveries overall when compared to conventional SPE and can be reused numerous times without losing sorption efficiency [35]. Ferromagnetic particles, most often Fe3O4, coated in a coating of the sorptive substance are the basis of magnetically active sorbents. For dispersive solid-phase extraction, such sorbents are employed (DSPE). Because of their high specific surface area and

tiny particle size, these sorbents provide higher extraction efficiency. Sorbent particles' magnetic activity makes it easier for them to separate from the sample matrix. Unfortunately, there is a dearth of information in the literature about the uses of these sorbents and they are not yet commercially accessible. The creation of poly (vinyl alcohol)-coated core-shell magnetic nanoparticles (Fe3O4) for the DSPE extraction of three AGs from honey [36] and the application of a similar method in which the Fe3O4 nanoparticles modified with carbohydrates with functional groups selected to mimic AGs structure and properties [37] are two promising applications, nevertheless. The two scenarios' comparatively high recovery values (83% - 101% and 94% - 109%, respectively) demonstrate the promise of this method for extracting AGs from a range of matrices.

2.3.Aminoglycosides separation and detection for LC-/CE-based analysis

AGs' high polarity and polycationic nature can lead to a number of issues when separating them chromatographically in their original forms. The absence of chromophoric or fluorogenic moieties further complicates the identification of these compounds when taking into account potential detection methods. While there is some use for direct AGs detection with UV or fluorescence detectors in pharmaceutical formulation control, it is not recommended [38–40]. Due to the significant danger of potential matrix-related interferences, a wider use of this type of detection for underivatized AGs does not appear to be feasible. Moreover, these techniques are not applicable to all AGs. For instance, it has been demonstrated that amikacin and tobramycin may be examined via direct UV detection, but gentamycin cannot be [40]. A potential solution to this issue is derivatization. By decreasing the polarity of the analytes, it not only simplifies detection but also makes chromatographic separation of the analytes easier. In reversed phase, derivatization products are typically easily separated. 1-naphthyl isothiocyanate (NITC), 9-fluorenylmethyloxycarbonyl (FMOC), 6-aminoquinolyl-N-hydroxysuccinimidyl carbamate (AQC), o-phthalaldehyde (OPA), and 1-fluoro-2,4-dinitrobenzene (FDNB) are the most widely used derivatization agents for AGs [15, 16, 20, 41, 42]. However, it must be emphasized that choosing a derivatization agent might be challenging. Multiple derivatives can be produced from a single analyte by certain derivatizing agents (e.g., FMOC) reacting with the main and secondary amino groups of AGs with varying selectivity and efficiency (Fig. 4).

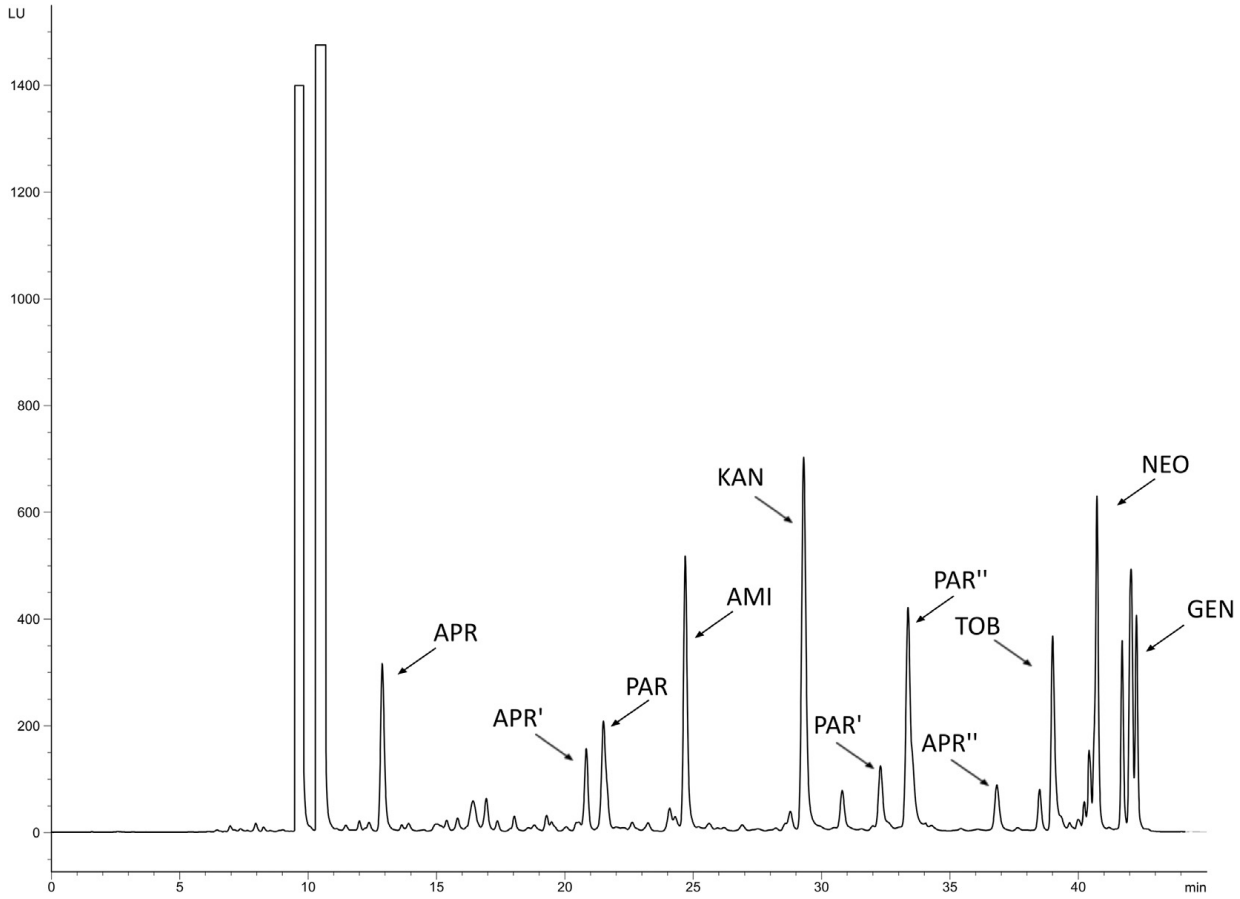

Fig. 4. An illustration of a chromatogram following the derivatization of the AGs combination with FMOC is shown in [9]. The compounds shown in the chromatogram are: APR; apramycin, PAR; paromomycin, AMI; amikacin, KAN; kanamycin, TOB; tobramycin, NEO; neomycin, and GEN; gentamycin.

Matrix effects levels will rise and quantitation will be hampered as a result. Another potential source of problems is the stability of derivatization products. For example, because the derivatives of OPA are not very stable, it is advised to employ it in post-column mode [43, 44]. particular derivatization agents demand very strict reaction conditions, like high temperatures (derivatization with FDNB requires about 85º C), which could be a limiting factor in particular circumstances [42]. Furthermore, the makeup of the sample matrix has a significant impact on derivatization efficiency. All things considered, derivatization techniques are more frequently employed to investigate samples with simpler matrices (such as those found in medicines) or when a single AG needs to be identified [15, 16, 20]. It appears that the use of reversed-phase separation conditions in conjunction with derivatization reactions is waning. The most recent developments

in the identification of AGs centre on the creation of methods using ion-pairing liquid chromatography (IPLC) or hydrophilic interaction (HILIC). These methods require the application of alternative detection techniques, such as charged aerosol detection (CAD), evaporative light scattering detection (ELSD), mass spectrometry (single or tandem MS), or pulsed amperometric detection (PAD), but they also enable the determination of AGs in their native forms. The publications that are cited mostly deal with HILIC and IPLC. It is crucial to give careful thought to the detector selection when creating a method for measuring amino-glycosides that uses a separation technique like LC or capillary electrophoresis, which are covered in Section 3 of this review. It may be more affordable to use detectors like ELSD, UV, FLD, or CAD for the analysis of simpler matrices and the determination of a single analyte. Tandem mass spectrometry appears to be the preferred technique, nevertheless, when the opposite is true or the analytes are present in the sample at trace concentration levels.

2.4.Ion-pairing liquid chromatography (IPLC)

The molecules of AGs have several amino groups in their structures, which causes them to produce polyvalent cations in the solution. Anions of perfluorinated organic acids are one example of a negatively charged moiety with which these cations may interact. As previously mentioned, the resultant ion-pairs are noticeably less polar than AGs. By using LC columns filled with non-polar sorbents (such as C8, C18, etc.), this phenomenon can be used to boost AGs retention and separation selectivity during LC separation. The shortened lifespan of chromatographic apparatus and columns, as well as detection issues when mass spectrometry is used ion suppression, are the principal disadvantages of IPLC. IPLC is widely used because it effectively separates additive grains (AGs) in multi-component mixtures, making it competitive with other LC-based techniques, despite certain drawbacks. Higher resistance to low pH circumstances can be demonstrated by their specific versions, which can help reduce column lifetime issues.

The most often utilized ion-pairing (IP) reagents that offer the optimum separation of acid-base grains (AGs) are volatile perfluorinated organic acids, such as trifluoroacetic acid (TFA), pentafluoropropionic acid (PFPA), and heptafluorobutyric acid (HFBA). Concentrations of IP agents are added to the mobile phase in increments of 0.1% to 1% (v/v) [10, 11, 33, 45, 46]. Since non-volatile ion-pairing reagents, including alkylsulfonic acids, are incompatible with most AGs

analysis detectors (MS, evaporative light scattering (ELSD), and charged aerosol detectors (CAD), they are not employed in modern analytical chemistry.

The choice of detectors for determining AGs using IPCL may vary according on the sample matrix's complexity. Generally, (ELSD) and (CAD) [10, 11, 13] are an excellent choice for well-defined and generally simple matrices, including pharmaceutical formulations. Their features include low operating costs, a consistent reaction to all AGs, good sensitivity (LODs start at about 10 ng injected on column), and a simple, robust design. Lack of selectivity and a non-linear (sigmoidal) response curve are the drawbacks. Modern computer technology makes it easy to tackle the non-linearity problem but also necessitates the employment of more complex sample preparation procedures due to the lack of selectivity. Using tandem mass spectrometry at the detection step can significantly increase the performance of IPLC methods [3, 21, 23, 26, 27, 46]. Improved selectivity, higher sensitivities, and the ability to analyze multiple residues can be attained at the cost of increased instruments, manpower, and maintenance. Despite analytes' non-baseline separation, mass spectrometric detection frequently enables accurate analyte determination. In IPLC-MS/MS, the selection of the ion-pairing reagent needs to be well thought out. Although TFA has been effectively employed to identify 15 AGs [26], it is generally considered a nuisance when used in conjunction with mass spectrometry. Although its superiority over HFBA has not yet been conclusively proven, pentafluoropropionic acid (PFPA) could be utilized as a substitute since it induces less ion suppression and has a lower affinity to the stationary phase than HFBA [46].

2.5.Hydrophilic-interaction-LIC (HILIC)

When it's necessary to separate polar, water-soluble chemical compounds—like aminoglycoside antibiotics—HILC can be employed. The interactions between analytes and the quasi-stationary phase—which is thought to consist of a layer rich in water encircling appropriate stationary phase particles—are thought to form the basis for the separation mechanism. Because it depends on a number of variables, such as the mobile phase's composition (percentage and kind of organic component), the stationary phase's characteristics, pH, the kind and concentration of the buffer, temperature, and more, the retention behaviour of the analyte is fairly unpredictable.

HILIC employs stationary phases such as amino-modified silica gels, pentafluorophenyl, bare, diol, and cyanopropyl. These phases can be used to successfully separate a variety of types of

chemicals; however, for AGs, new stationary phases (such ZIC-HILIC and its variations) that were created especially for HILIC separations typically yield significantly superior results (Fig. 5). Since zwitterionic groups (phosphorylcholine, sulfobetaine) are covalently attached to the surface of silica particles, ZIC-HILIC stationary phases combine hydrophilic partitioning with weak ionic interactions. The separation of AGs appears to be a good fit for phosphorylcholine-modified silica gels [47].

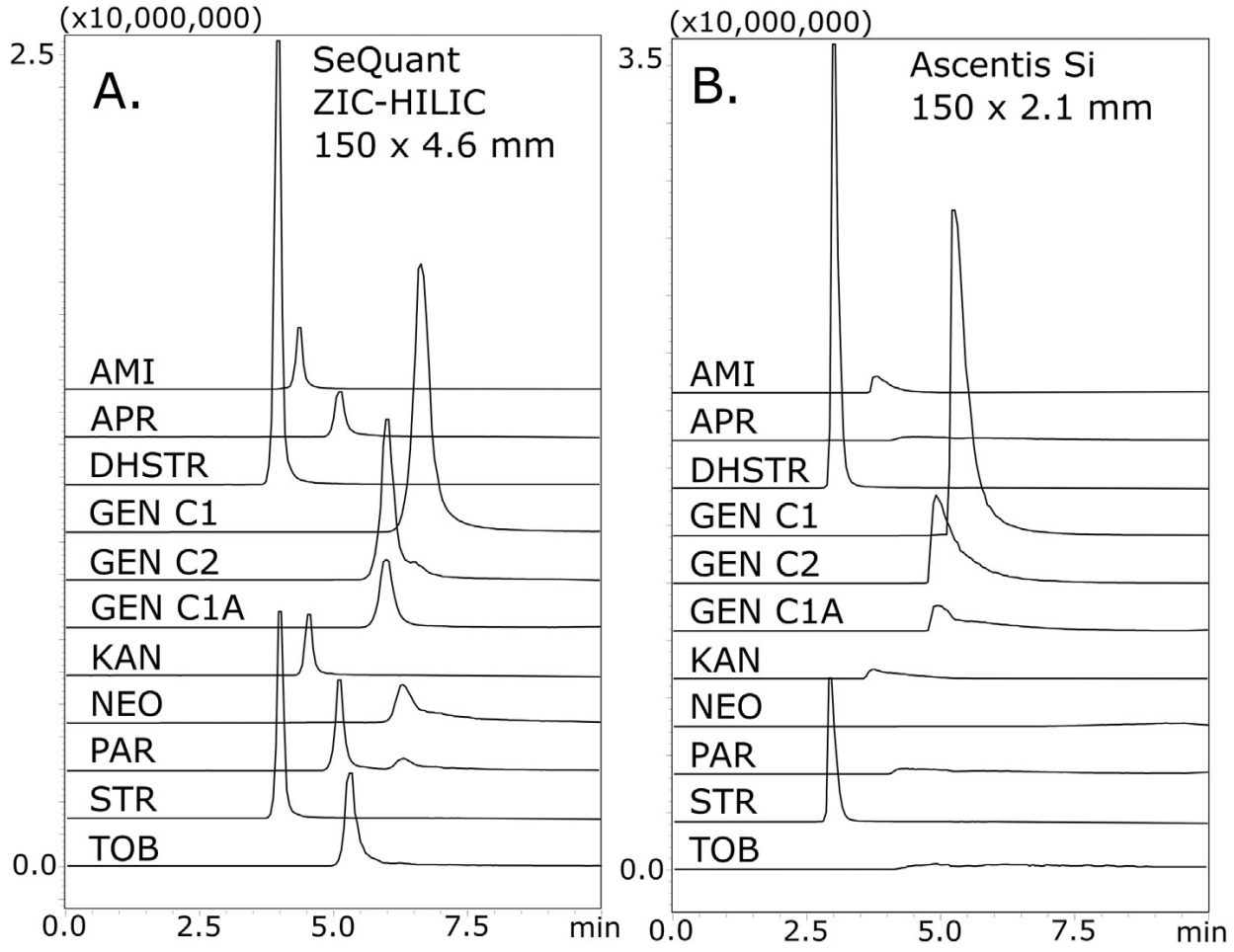

Fig. 5. SeQuant ZIC-HILIC (A) and Ascentis Si (B) LC columns were used to compare the chromatographic separation of 11 AGs under HILIC conditions [9]. The AGs are: AMI - amikacin, APR - apramycin, DHSTR - dihydrostreptomycin, GEN - gentamycin, KAN - kanamycin, NEO - neomycin, PAR - paromomycin, STR - streptomycin, TOB – tobramycin.

When it comes to the composition of the aqueous mobile phase, buffers with concentrations less than 60 mM (or water acidified with formic acid, for example) are often preferable for the

identification of no more than five AGs in the sample. Baseline separation of AGs is very challenging under these circumstances. The buffer's concentration raises the separation resolution. Buffer values greater than 150 mM are required to achieve adequate separation for a simultaneous multi-AG combination. Furthermore, 0.05–2% (v/v) FA is added to the mobile phase (both the buffer and the organic components) in the majority of protocols. This improves peak shape, particularly their distinctive “tailing” under HILIC conditions, by weakly reducing the interaction of AGs with the stationary phase through ionic interactions with amino groups [2, 19, 22, 23, 28, 30, 31, 34, 36].

An attempt to concurrently identify 9 AGs using HILIC-ELSD [12] serves as an example of how difficult, if not impossible, it is to perform baseline separation of numerous (more than 8) AGs under HILIC conditions. It was not possible to achieve baseline separation of analytes despite a lengthy chromatographic run (120 min). The entire separation time was 240 minutes, and the authors' attempt to resolve overlapping peaks using 2D-LC with IPLC as a second separation dimension was only partially successful.

These restrictions can be removed by combining HILIC with mass spectrometric detection, as it eliminates the need for hazardous mobile phase additives (such as perfluorinated IP reagents). The problem of non-baseline separation of analytes can be solved by mass spectrometric detection in general and tandem mass spectrometry in particular due to their selectivity, which also offers significantly shorter run times (e.g., 9 min when fast HILIC- MS/MS was applied for the determination of 11 AGs in milk-based food products [34]). The effect of the buffer or the organic modifier (notably, methanol was found to be superior to the commonly used acetonitrile in certain applications [28]) on the shape of the peaks and the response of the detector should be the focus of attention. ZIC-HILIC columns have been demonstrated to outperform Obelisc R, a different type of zwitterionic column, and are frequently employed to produce an acceptable separation of AGs. In contrast to the sulfonic groups found in the ZIC-HILIC columns, the stationary phase of the latter is distinguished by the presence of carboxyl acid functional groups [28]. Graphitized LC columns are another method that might be used [24], but they have certain drawbacks as well, like variable analyte retention periods and a laborious column deactivation procedure. In a study comparing three different HILIC-ESI settings for the identification of multiresidue medicines, including 11 AGs and colistins in animal muscle and milk samples, it was shown that the symmetry

and retention of the neomycin peak with the ZIC-HILIC column weren't adequate. However, issues with spectinomycin and neomycin retention were noted when using a graphitized column. The authors have selected the bare silica Poroshell HILIC column as the best option [29].

3. Alternate analytical procedures

The gold standard for identifying aminoglycosides in a range of matrices is still liquid chromatography. However, using it frequently calls for the employment of highly skilled workers and the use of somewhat expensive tools. This is also true for some capillary electrophoresis-based techniques, such CE-ESI-MS/MS, but other cutting-edge approaches, like immunoassays and microfluidic devices, may make it easier to create portable, less costly tests. Though it is unlikely that these will ever approach the power and adaptability of the well-established LC-based methods, they could significantly expand access to AGs analysis, especially for those in resource-constrained environments and the farming and food processing sectors.

3.1.Capillary electrophoresis (CE)

In aqueous solutions, aminoglycosides frequently form complexes and ionic species. They can therefore be used in electrophoretic separations. CE is a potent separation method that has been effectively applied to the identification of this class of chemicals. The primary benefit of CE is its high resolving power, with instrument affordability and fast separation periods playing a secondary role. Improving selectivity and detection sensitivity is the main task while using CE. Due to the incompatibility of non-volatile buffers used in CE with mass spectrometry, it is frequently difficult or impossible to combine the high resolving power with sensitive and selective detection such as MS. Furthermore, the sample throughput is severely limited by the very short lifetime of the columns (Huidobro et al. [48] advised that the capillary should be changed after just 8 cycles to ensure repeatable findings). Since liquid chromatography and capillary electrophoresis use almost identical sets of detectors, detection issues resulting from AG characteristics are documented in CE cases as well. These issues also have comparable remedies. FLD detection can be used with o-phthalaldehyde (OPA) derivatization [49]. Laser-induced fluorescence detection (LIF) can be used to detect kanamycin, bekanamycin, and paromomycin using a different reagent called 6-carboxyfluorescein succinidyl ester (CFSE) [50]. For the purpose of determining AGs, indirect UV detection has been described [52], as well as direct UV detection at 195 ± 5 nm without [48] or after complexation with borates [51]. However, because of the relatively poor sensitivity

(LOD > 10 mg/mL) of this detection technique, the application of CE in conjunction with both direct and indirect UV detection plays a minimal role in the assessment of underivatized AGs [48,51, 53]. Other types of detectors, such as electrochemical detectors, are required to assess underivatized AGs with better sensitivity. In this situation, amperometric detectors (AD) with transition metal electrodes like Cu and Ni are used [54, 55]. Electrode fouling is the primary issue with CE-AD methods in AGs analysis [56]. Generally speaking, Cu-based electrodes are preferred due to the low stability of Ni-electrodes. To further enhance CE-AD performance, a number of electrode modifications have been suggested [56, 58]. One such modification is the use of a chemically modified copper electrode (Cu-CFE, or Cu microparticle-modified carbon fibre microdisk array electrode), which yielded consistent results and low LOD values per millilitre [59]. In a study where CE was combined with capacitively coupled contactless conductivity detection (C4D) to measure tobramycin in human plasma, Mukhtar et al. [60] similarly found very good findings (LOD ¼ 10 ng/mL). The increased popularity of CE-C4D methods can be attributed to their comprehensiveness and versatility in handling all types of ionic analytes [61].

The application potential of CE in the determination of AGs has significantly expanded during the last 20 years due to improvements in analytical instrumentation capabilities. Combining CE with extremely sensitive and selective mass spectrometric detectors is one of the most promising methods [62]. Though theoretically feasible, this method does not appear to be workable at this time. As was previously indicated, non-volatile buffers are incompatible with mass spectrometry and are necessary to fully realize the promise of CE. While it is feasible to substitute the aforementioned buffers with their volatile counterparts, the resulting approach would either have low sensitivity or low resolution. Two interesting papers [63, 64] have been published thus far that successfully describe the determination of AGs utilizing CE-MS/MS apparatus. As an alternative, a variety of online pre-concentration methods, including field-enhanced sample injection (FESI) and field-amplified sample stacking (FASS), could be used to increase CE sensitivity [49, 55]. Results of kanamycin determination (UV detection) with and without online FASS pre-concentration were compared by Long et al. [49]. With FASS, the method sensitivity was twenty times higher. Ge et al. [55] employed FESI to hyphenate the transient moving substitution boundary (MSB) in order to determine the presence of streptomycin, neomycin, and kanamycin (AD detection). When compared to previously published CE-AD approaches, the

sensitivity of the method was improved by two to three orders of magnitude with the application of online pre-concentration procedures.

3.2.Immunological procedures

When used to determine AGs, immunological techniques such as fluoroimmunoassay (FIA) [28], radioimmunoassay (RIA) [66], and enzyme-linked immunosorbent assay (ELISA) [67, 68] are known for their high sensitivity and low limit of detection (LOD) values, which can be as low as a few ng/mL or even pg/mL. However, false-positive results are often obtained because of their high sensitivity [69]. Furthermore, these techniques are only appropriate for screening and semi-quantitative testing because to their low repeatability, which typically requires LC measurements for confirmation [70]. Competitive ELISA, which may be implemented as either indirect or direct competitive ELISA, is currently the immunological technique most frequently utilized in AGs analytics.

The enzymatic reaction product is identified in both situations using spectrophotometric, fluorescence, or chemiluminescence measurement. Compared to its IC-ELISA counterparts, direct competitive ELISA (DC-ELISA) methods often require less labor, resources, and time; however, this comes at the expense of more false-negative results and no signal amplification. For instance, Jin et al.'s [71] DC-ELISA method for neomycin detection ensured LOD ¼ 2.73 ng/mL (for milk samples). By contrast, the corresponding IC-ELISA technique created by Xu et al. [67] demonstrated a LOD ¼ 0.08 ng/mL. Nonetheless, there are instances in which DC-ELISA techniques can be enhanced and match IC-ELISA techniques in terms of performance. Gold nanoparticles treated with horseradish peroxide were employed by Jiang et al. [72] to measure the levels of tobramycin and kanamycin in milk. The method's LOD was five times better than that of the traditional DC-ELISA. While the ELISA procedures are often quite sensitive and very simple to perform, even by inexperienced workers, the main issue with determining AGs with this technique is the cross-reactivity (CR) phenomenon, which results in poor test selectivity [73]. Highly specific anti-bodies are needed to prevent cross-reactivity, which increases the cost, complexity, and time necessary to execute ELISA [74]. In order to prevent or reduce AG cross-reactivity, researchers currently using both IC-ELISA and DC-ELISA are concentrating on creating highly-selective antibodies.

3.3.Spectrophotometric and spectrofluorimetric approaches

AGs can be easily and non-separatively analyzed using spectrophotometric and spectrofluorimetric techniques. The application of these approaches is restricted to the routine control of a single ingredient in pharmaceutical formulations due to their lack of selectivity. Analytical processes typically involve a derivatization stage using different reagents. There are a few exceptions to the general rule that derivatization is the primary approach utilized in spectroscopic methods for AGs determination, such as the use of direct fluorimetry for the rapid assessment of apramycin in pharmaceuticals and milk samples [76]. Micelle-enhanced natural apramycin fluorescence made it possible to achieve sensitivity that was on par with techniques involving derivatization. Water, serum, and milk samples with LOD less than 0.1 ng/mL were employed by Ghodake et al. [77] for the colorimetric measurement of streptomycin using an AgNP probe coated with gallic acid. Ma et al. [78] used colorimetric sensors based on single-stranded DNA and golden nanoparticle (AuNP) to measure the tobramycin in milk and egg samples, with detection limits of 11 ng/mL. Techniques for determining AGs using fluorescent quantum dots (QD) sensing have recently been developed. Following MIP SPE extraction, some applications demonstrate the potential of QD-based processes in the selective identification of specific AGs in somewhat complicated matrices [79, 80].

Additionally, system automation may benefit greatly from the development of smaller, AG-specific biosensors that allow for the online identification of pollutants. For this reason, Tang et al. [45] created an evanescent wave aptasensor called FQ-EWA, which is based on target binding assisted fluorescence quenching. A fluorophore-labeled DNA aptamer was used to establish selectivity towards a specific AG (kanamycin). Interestingly, the FQ-EWA exhibited comparatively great endurance, allowing for over 60 cycles of detection-regeneration. This highlights the possible applications of AGs-specific biosensors, such as electrochemical sensors, which are covered in the subsequent subsection on electrochemical techniques. The continuous efforts to use the calorimetric methods in conjunction with the widely used smartphones, which combine a convenient interface, detector (CCD camera), processing capacity, and network connectivity, have the potential to make them point-of-need approaches [81]. These advancements have the potential to significantly reduce expenses and enhance accessibility to in-field AGs analysis.

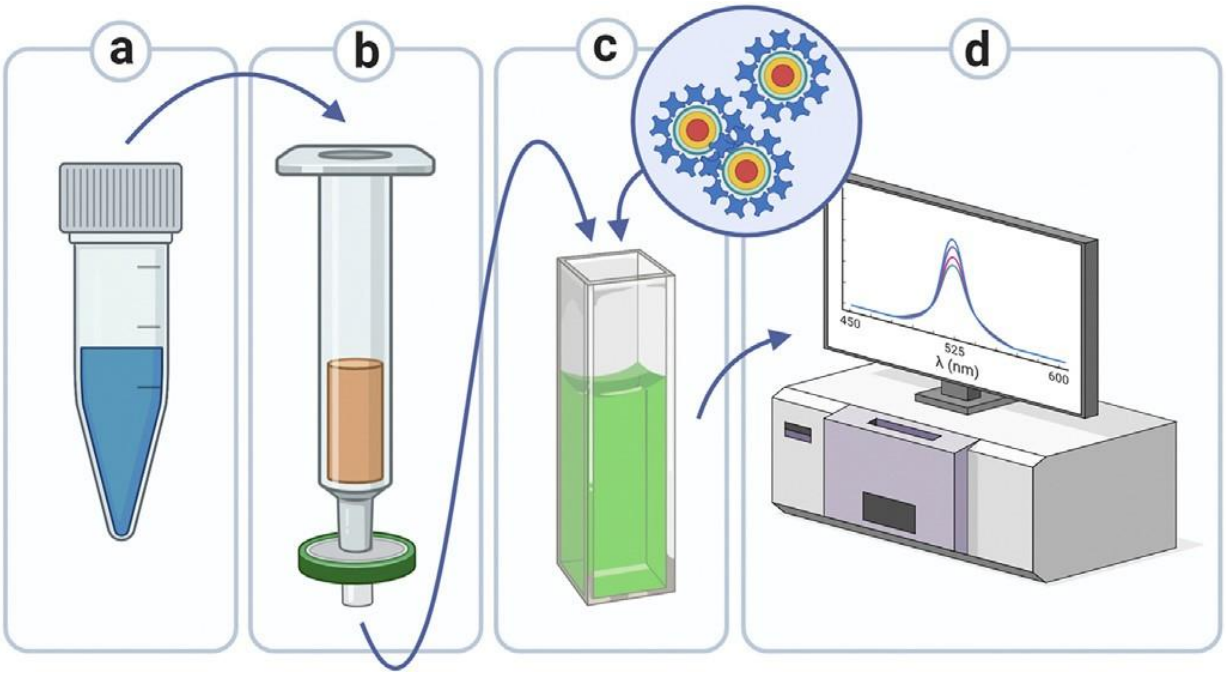

Fig. 6. Using the thioglycolic acid-CdTe quantum dots photoluminescence as a basis, one may determine the presence of kanamycin in vaccine samples [79]. A syringe filter and a SPE cartridge were used to load aliquots of reconstituted vaccine samples (a) and pack them with kanamycin-MIP (b). The aliquots were first cleaned and then eluted with acidic water. Next, they were placed onto a TGA-CdTe quantum dots dispersion probe (c), and photoluminescence measurements were performed using a luminescence spectrophotometer (d).

3.4.Electrochemical means

Numerous electrochemical techniques can also be used to identify aminoglycoside antibiotics. Although there aren't many reports on the application of more conventional methods like potentiometry or various voltammetry flavors for the determination of AGs, there is a growing trend in the use of these and other electrochemical sensing methods in the development of aptamer-based AGs biosensors, or aptasensors. Using an ion-selective electrode (ISE) made of plasticized membranes containing ionophores based on ion pairs of both aminoglycosides with tetraphenylborate and Acid Chrome Black Special (ABS), potentiometric measurement of gentamycin and kanamycin was demonstrated [90]. The selectivity constants (gentamycin/kanamycin) were nearly equal to unity, and the limit of detection (LOD) for both antibiotics was in the 0.5 mg/mL range. Because the electrodes have such large selectivity constant values, they are totally nonselective, which restricts their use to measuring the overall

concentrations of gentamycin and kanamycin or to pharmaceutical formulations containing single AGs. Tobramycin was detected electrochemically using a voltammetric sensor that included an electrode modified with a decreased graphene oxide/graphene oxide hybrid [91]. Two concentration ranges were used to observe the linear response: 3.2 - 23.4 mg/mL and 23.4 - 420.3 mg/mL. The sensor was effectively utilized to determine the amount of tobramycin in human saliva, with an estimated limit of detection (LOD) of 0.9 mg/mL. Researchers looking for simple, fast, reagentless, and selective ways to determine agricultural glycosides (AGs) are becoming increasingly interested in electrochemical aptasensors as they align more closely with the principles of Green Analytical Chemistry than the more traditional approaches. In summary, these sensors are comprised of an aptamer that is specific to the target antibiotic, which is attached to the electrode's surface. Such a sensor is in the "off" state when there are no antibiotic molecules present, which indicates that the aptamer chain or molecule has a particular conformation and that the sensor as a whole possesses particular electrochemical characteristics. When the antibiotic molecules are introduced, they bind to the aptamers, changing their conformation and the sensor's overall electrochemical properties in quantifiable ways. In recent years, a number of publications reporting such aptasensors have been published. The reader interested in this issue is urged to read one of the good evaluations available, such as the comprehensive piece by Mehlhorn et al. [92], as the body of literature on this topic is too enormous to include in this work.

3.5.Qualitative analysis

Identification of aminoglycosides, structural confirmation, and comprehension of interaction or transformation mechanisms are all part of quantitative approaches. Nuclear magnetic resonance (NMR), namely 15N-NMR, H-NMR, and 13C-NRM, can be used to determine the structural makeup of AGs and characterize the interactions between AGs and RNA [93–96]. As early as the 1960s and 1970s, attempts were made to characterize AGs using X-ray diffraction spectroscopy. It can only be achieved for a limited number of AGs (such fortimicin) because of their amorphous structure and difficulties in creating crystals of diffraction-quality [97]. Currently, the structures and kinds of interactions of AG crystal complexes with RNA and enzymes are determined using X-ray crystallography [98]. There have also been several published research on the structural analysis of AGs utilizing mass spectrometry. Mass spectrometry has been used to analyze the structure following chemical alterations [102], to look into bacterial resistance [101],

and to learn more about the interactions between aminoglycosides and other substances (RNA and enzymes) [99, 100]. Research on bacterial resistance mechanisms and drug design benefit greatly from the use of NMR, mass spectrometry, and X-ray diffraction spectroscopy.

4. Recent examples of amikacin quantification approaches

Chromatography is the only technology that can accurately quantify AMK due to the inherent drawbacks of single component analysis and the complexity of biological samples. The liquid chromatographic techniques previously stated have only been reported for the determination of AMK; hence, a dependable method for the determination of AMK drug as well as the most commonly prescribed medication, "cephalosporins," must be developed. As previously mentioned, AMK is utilized in conjunction with other antibacterial agents, particularly inhibitors of β lactamase production. As a result, AMK determination techniques in the context of concurrently delivered medications are also required [103]. Because AMK lacks a chromophore, derivatization is necessary before LC–UV analysis. Here, the amine of amikacin was derivatized using the Hantzsch reagent, a mixture of acetylacetone, formaldehyde, and acetate buffer. Since this reagent imparts chromophore in structure, it may be used as a pre-column derivatization reagent for the measurement of AMK. The methodology was refined and verified for statistically significant results. The method that was developed was also used to identify amikacin in actual biological samples [103]. The determination of amikacin sulphate (AMK) in various pharmaceutical preparations and in the presence of its synthetic precursor, kanamycin sulphate, in pure form was also done using this method [104].

El-Say et al. [105] discuss one of the pre-column derivatization approach's most recent applications. AMK plasma concentration was measured using isocratic HPLC chromatography. The Waters Alliance 2595 HPLC equipment, located in Milford, Massachusetts, USA, was outfitted with an autosampler, quaternary pump, vacuum degasser, variable wavelength ultraviolet-spectroscopic detector, and Empower 3 data processing software. The chromatographic separation procedure was performed at room temperature using a Symmetry C18 column (100 x 4.6 mm − 3.5 μm; Waters) with the UV detector set at 330 nm. The mobile phase was pumped through the apparatus at a flow rate of 1 mL/min and consisted of acetonitrile and 0.1% acetic acid in a 70:30 v/v ratio. Using a vortex shaker, combine 0.25 mL acetonitrile with 0.25 mL aliquots of the plasma samples for 1 minute. Centrifuge the mixture at 5000 rpm for 10 minutes to extract

AMK from the samples. The organic solvent was then evaporated at 50°C while the samples were dried completely under a nitrogen stream. Following a pre-derivatization with 20 µL p-chloranil and 20 µL borate buffer at pH 9.0 for 10 min at 65 °C, the residue was dissolved in 60 µL of the mobile phase. 30 µL of this volume was then utilized for injection. To create the calibration curve, a 100 µg/mL AMK stock solution in acetonitrile was produced. Working solutions with concentrations ranging from 1 to 600 µg/mL were created by diluting the stock solution with acetonitrile. The same HPLC technique that was previously mentioned was used to analyze samples of the working standard, and the concentration of the plasma samples was determined using the equation derived from the calibration curve. The internal standard utilized in this investigation was paracetamol. The chromatographic conditions used in this investigation were determined to be exact, dependable, accurate, selective, and sensitive based on internal testing.

5. Conclusion

Aminoglycoside antibiotics are essential antibacterial drugs used in various human activities, but their low therapeutic indices and low therapeutic indices make them a concern for their use. To ensure food and drug quality and prevent environmental pollution, analytical tools are needed for controlling these antibiotics. Determining aminoglycosides is challenging due to their high polarity, polycationic character, and lack of chromophores. Sample preparation and final determination stages depend on the sample and the final determination technique. Solid-phase extraction is commonly used for pharmaceutical analysis, while molecularly imprinted polymer-based materials are promising due to their high selectivity against aminoglycoside antibiotics. Liquid chromatography is the most powerful tool for determining aminoglycosides due to its variety of separation modes and compatibility with selective and sensitive detectors. Recent developments in bioassays, quantum dot-based colorimetric applications, and aptasensors show potential for low-cost, user-friendly point-of-need tests. However, biosensors may fall short when analyzing samples containing multiple antibiotics. Future method development should prioritize multi-residue extraction protocols and validation for complex animal-derived food matrices like meat, milk, eggs, and honey, where protein and lipid interference remain a key challenge for accurate aminoglycoside quantification.

- **Conflict of Interest**

  The authors declare that they have no competing interests.

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