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ORIGINAL ARTICLE

Reagent-free determination of amikacin content in amikacin sulfate injections by FTIR derivative spectroscopy in a continuous flow system

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Abstract The quantitative estimation of amikacin (AMK) in AMK sulfate injection samples is reported using FTIR-derivative spectrometric method in a continuous flow system. Fourier transform of mid-IR spectra were recorded without any sample pretreatment. A good linear calibration ($r > 0.999$, %RSD < 2.0) in the range of 7.7–77.0 mg/mL was found. The results showed a good correlation with the manufacturer's and overall they all fell within acceptable limits of most pharmacopoeial monographs on AMK sulfate.

1. Introduction

Amikacin (AMK) is used to treat infections caused by Gram-negative bacteria. It is a semi-synthetic aminoglycoside derived from kanamycin, formulated as a disulfate salt (Fig. 1). The dosage form is normally supplied as a sterile solution for parenteral use [1].

Aminoglycoside antibiotics determination has been carried out by a wide variety of methods [2–4]. However, a direct UV–vis spectrophotometric estimation is not feasible [5]. The former Pharmacopoeia of United States (USP 24) [6] and later the European Pharmacopoeia (Ph. Eur. 6) [7] and British Pharmacopoeia (BP) [8] reported derivatization procedures of AMK prior to reversed-phase liquid chromatographic (LC) analysis. As it is too time consuming, LC methods based on non-derivatization procedures, such as universal aerosol-based detector [9], ligand displacement reaction [10], charged aerosol [11], evaporative light scattering [12] and resonance Rayleigh

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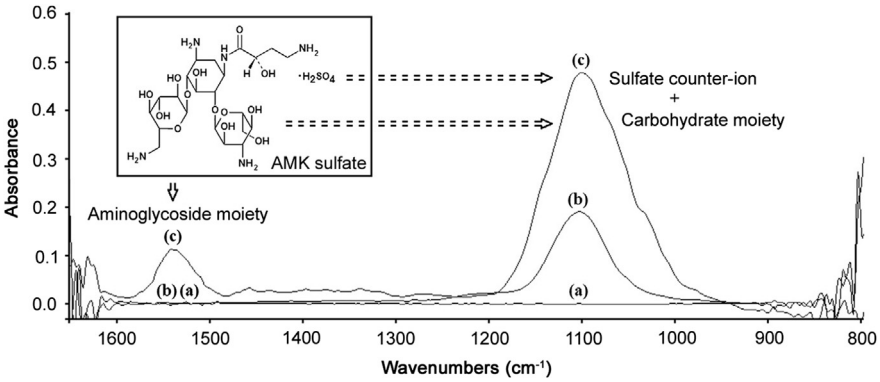

Fig. 1 FTIR spectra of the AMK sulfate injections related substances. Excipients constituted by water, 1.3 mg/mL sodium bisulfite, and 5 mg/mL sodium citrate (a). Aqueous sulfuric acid solution, pH = 4.5 (b). AMK sulfate standard (50 mg/mL) as AMK base (c). All spectra were obtained using water background.

scattering [13] have been proposed. The pulsed electrochemical detection method [14–16] has been adopted in the recent USP monograph [1]. The major drawback of the detection approach coupled to LC is that it requires skills for implementation [17].

Pharmaceutical raw materials are also tested for sulfate content [18]. The actual pharmacopoeial monographs, Eur. Ph. [7] and USP [1] refer to sulfate counter-ion content as a molar ratio between AMK and H_2SO_4. The sulfate ion, outside the allowed range, could indicate that AMK is present as a free base or the sulfate ion, in excess, is present as an impurity [19]. Recently, our research group proposed a Fourier-transform infrared (FTIR) method for determining the sulfate counter-ion content in AMK sulfate injections [19].

FT-mid-IR in conjunction with a continuous flow system (CFS) was extensively used for quantitative estimation of active ingredients in pharmaceutical preparations [19–28]. The spectrum is a marker for identity and purity of the active pharmaceutical ingredient (API) and also useful to detect impurities coming from the excipients.

A direct reagent-free determination of AMK content in parenteral formulations of AMK sulfate by CFS-FTIR-derivative spectrometry (DS) is proposed keeping in view principles of green analytical chemistry [19,29–32]. The advantage of the present method is to simultaneously quantify AMK base and sulfate counter-ion in AMK sulfate injections with a single spectrum.

2. Experimental

2.1. Reagents and samples

All chemicals used were of analytical-reagent grade. Water was obtained from a Milli-Q-TOC purification system (Millipore, Bedford, MA, USA). Reference standards: AMK sulfate stating 786 μg/mg as AMK base, purchased from Sigma-Aldrich (St Louis, MO, USA) and AMK sulfate with 99.95% purity, kindly provided by a pharmaceutical manufacturer of the region. Standard stock solution of AMK sulfate (100 mg/mL) was prepared in water. Pharmaceutical products were acquired from local drug stores and analyzed directly from the ampoules. Commercial samples containing a concentration higher than 50 mg/mL of AMK base were diluted with water to obtain required concentrations.

2.2. Apparatus

A Perkin–Elmer, model Spectrum 2000, FTIR spectrophotometer (Norwalk, CT, USA) was employed for acquisition of spectra. The FTIR equipment was connected to a monochannel flow system through a flow cell. A demountable liquid transmission cell (Wilmad Labglass, Buena, NJ, USA) with ZnSe windows (38 mm × 19 mm size, 2 mm thick, and 0.05 mm optical path-length) was used. An Ismatec IPC peristaltic pump (Glattbrugg, Switzerland) equipped with Tygon tubing was employed for sample and standard propulsion. A Rheodyne manual selecting valve (Alltech, Waukegan, USA) was used for carrying either sample solution or standard solution into the flow cell.

2.3. General procedure

A schematic diagram of the continuous flow system and its operation steps were presented earlier [27]. The system was optimized for leaks, air bubbles, and pump flow rate. Calibration or test sample solutions were continuously pumped in order to reach the flow cell. An injection valve was switched to the solution in turn. The continuous flowing stream of either samples or standards was monitored using the FTIR spectrometer. Each spectrum was automatically converted to its first-order derivative spectrum. The validation of the analytical method was carried out as it was described by us earlier [19].

3. Results and discussion

3.1. Identification, FTIR spectra of AMK sulfate and related excipients in aqueous phase

Infrared spectra of API were recorded under the optimum instrumental conditions. We can see that water showed the characteristic transparency zone localized close to the fingerprint region 1600–900 cm^{-1} (Fig. 1). AMK sulfate has two absorption bands, one broad and intense band observed in the range of 1220–938 cm^{-1} with a maximum at 1100 cm^{-1}, and the other, with lesser intensity in the range of 1590–1480 cm^{-1} with a maximum at 1538 cm^{-1}. The spectra also show that the presence of excipients, at the stated concentrations in the formulation, do not have any additional IR bands in the fingerprint region, except the sulfate from sulfuric acid.

3.2. Selection of the analytical spectral band and the analytical measurement criterion

The two mid-IR bands of AMK sulfate are due to contribution of carbohydrate moiety and hetero-oxy groups of the sulfate