Review

# Review of operating principle and applications of the charged aerosol detector

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## ARTICLE INFO

## ABSTRACT

Recently a new detection method, based upon aerosol charging (the charged aerosol detector (CAD)) has been introduced as an alternative to evaporative light-scattering detector (ELSD), chemiluminescent nitrogen detector and refractive index detector for detection of non-ultraviolet and weakly ultraviolet active compounds and for UV-absorbing compounds in the absence of standards. The content of this review article includes description of operation principle, advantages and disadvantages of CAD system, and short reports of selected applications of this detector. The main advantages of CAD detector are unique performance characteristics: better sensitivity than ELSD system, a dynamic range of up to 4 orders of magnitude, ease of use and constancy of response factors. Both detectors are mass dependent and the response generated does not depend on the spectral or physicochemical properties of the analyte. This attractive feature of a detection technique generating universal response factors is the potential use of a single, universal standard for calibration against which all other compounds or impurities can be qualified. CAD also has the same limitation as ELSD, namely, the response is affected by mobile-phase composition. This problem has been resolved by using inverse gradient compensation as is done for high pressure liquid chromatography and supercritical fluid chromatography. CAD has been applied for the analysis of structurally diverse compounds used in the pharmaceutical, chemical, food, and consumer products industries and in life science research. They include nonvolatile and semivolatile neutral, acidic, basic, and zwitterionic compounds, both polar and nonpolar (e.g. lipids, proteins, steroids, polymers, carbohydrates, peptides).

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## 1. Introduction

For analytes with one or more UV-absorbing chromophores, ultraviolet (UV) detection is probably the most widely used detection method in liquid chromatography due to its high sensitivity, broad linear range, relatively low cost, ease of use, and the fact that it is compatible with most solvents used as the mobile phase in isocratic or gradient elution mode [1]. As an alternative to UV/Vis detection in many applications, in particular for the analysis of compounds lacking strong UV chromophores such as many amino acid derivates, carbohydrates, lipids, polymers and surfactants, which also include some drug substances and natural products, mass spectrometry (MS), evaporative light-scattering (ELSD), chemiluminescent nitrogen (CLND), and refractive index (RID) detectors could be used. Mass spectrometry is considered to be a specific and universal detection method but, as the response depends on the ionization process, quantitative analysis using MS coupled with liquid chromatography is currently less robust [2] and the high price of the instruments limits its use for routine analysis [3]. In some applications ELSD detectors exhibit significant limitations in precision, sensitivity, dynamic range and the nature of calibration curves [4–6]. Like ELSD, the relatively new condensation nucleation light-scattering detector (CNLSD system) is appropriate for detecting any compounds, provided their volatility is low enough, and has recently become commercially available. It reportedly offers better sensitivity than ELSD [5,7,8]. CLND systems may have poor precision, require high maintenance and are not compatible with nitrogen-containing mobile phases such as those containing acetonitrile and triethylamine [4]. RID detectors have significant limitations in sensitivity and are not compatible with gradient elution [9]. Nevertheless, these limitations do not effect most of the application and can be successfully used for analysis. However, a new detection method, based on aerosol charging (the charged aerosol detector), has recently been introduced as an alternative to ELSD, CLND and RID systems for HPLC detection of non-UV active and weakly UV active compounds and for UV-absorbing compounds for which the standards are not available. The main positive characteristics of CAD system are: universal detection of nonvolatile analytes, a response independent of chemical properties, a broad dynamic response range with high sensitivity from low ng to high μg amounts of analytes, good precision for a diverse range of analytes, and simple and reliable operation [10]. However, as CAD system is an aerosol-based detector, it has the same main limitation as ELSD detector – the response of the detector varies with the mobile-phase composition [11]. Another drawback of this type of detector is that no spectral information is acquired so it is not possible to identify a certain peak or perform peak purity analysis as in UV-diode array detectors or MS detectors [1].

The comparison of the main characteristics of CAD and ELSD systems is compiled in Table 1.

## 2. Operating principle of CAD system

The operating process of CAD system is illustrated in Fig. 1 and is broadly comparable to that of the ELSD and CNLSD. In CAD, CNLSD and in ELSD the eluent of a chromatographic system is nebulized, using a flow of nitrogen, and the resulting aerosol is transported through a drift tube where the volatile components and solvents are evaporated. In the last step in CAD the dried particle stream is charged with a secondary stream of nitrogen that has passed a high-voltage platinum wire and the resulting charged particle flux is measured by an electrometer. In case of ELSD the signal is proportional to the number of photons scattered from the residual solid fraction that has been introduced into a detection cell [3,5]. Because the mobile phase is converted to gas before the detection

**Table 1**
Comparison of the main characteristics between CAD and ELSD systems.

| | CAD system/ELSD system |
|---|---|
| Operating principle | Both detectors are aerosol-based HPLC detectors. The operating principle is the same in the first phase (nebulizing the column eluent, evaporating the mobile phase from the droplets), but different in the detection (ELSD systems measure light scattering of the particles, CAD system measures charged particle flux). |
| Response | Both detectors detect semivolatile compounds regardless of their spectral or physicochemical properties. The CAD system gives parabolic calibration curve and when the concentration level is very low or when the concentration range is small, the calibration curve is close to linear. The nature of ELSD response is polynomial and a sharp decrease in signal at lower concentrations is an expected result. |
| Dynamic Range | CAD system shows a dynamic range of up to 4 orders of magnitude, ELSD system may show some limitations. |
| Sensitivity | According to the published applications better with CAD system. |
| Main limitations | The response of both detectors varies with the mobile-phase composition (this could be eliminated with mobile-phase compensation). No spectral information of both detectors is acquired. |

of the solutes in CAD, it belongs to the category of so-called "open cell detectors" [12].

Operation is simple, requiring only setting of few controllable parameters, among them the gas input pressure, the temperature or the temperature range and signal output range [13]. However, this could actually limit the room for optimization of detection [14]. CAD detector has been coupled with HPLC [3,5,10], with packed column supercritical fluid chromatography (pSFC) [15] and with micro high-temperature liquid chromatography (μHTLC) [16].

## 3. The response of CAD system

### 3.1. Mass-dependent detector

Like ELSD, CAD system is a mass-dependent detector and the generated response does not depend on the spectral or physicochemical properties of the analyte as in a specific UV detector, which is a concentration-dependent detector. Theoretically this means that CAD and ELSD systems as bulk property detectors generate a similar response for identical amounts of different analytes. For example, only a slight variation of the response for equal amount of compounds analyzed, was observed by Gamache et al. over a test set of 17 chemically different compounds under isocratic elution conditions. However this variation was about 7% relative standard deviation (RSD) between all responses of all 17 chemically different compounds, which indicates that CAD response depends upon analyte volatility [10]. The relationship between signal and amount of analyte is nonlinear in CAD, as in ELSD, in which the relationship between area response and analyte mass can be described by:

$$A = aM^b \tag{1}$$

where $A$ is the area response of the detector, $M$ the mass of the analyte, and $a$ and $b$ are values that depend on the analyte and chromatographic conditions.

Eq. (1) can be transformed into:

$$\log A = b \log M + \log a \tag{2}$$