Talanta 85 (2011) 2301–2306

Contents lists available at ScienceDirect

Talanta

journal homepage: www.elsevier.com/locate/talanta

Comparison of two aerosol-based detectors for the analysis of gabapentin in pharmaceutical formulations by hydrophilic interaction chromatography

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ARTICLE INFO

Article history:
Received 31 December 2010
Received in revised form 3 April 2011
Accepted 5 April 2011
Available online 12 April 2011

Keywords:
CAD
ELSD
UV
HILIC
RP
Gabapentin

ABSTRACT

Comparison of hydrophilic interaction chromatography (HILIC) columns coupled with an evaporative light scattering detector (ELSD) or charged aerosol detector (CAD) was done for the detection of gabapentin in pharmaceutical formulations. The chromatographic separations were achieved on four HILIC columns: ZIC HILIC, ZIC *p*HILIC, Luna HILIC, and Atlantis HILIC. Experimental factors such as mobile phase composition, acetonitrile content, and mobile phase pH were evaluated. Validation of method was done in terms of linearity, sensitivity, accuracy, and precision. The performance of ELSD detection method is comparable to that of CAD. The intra-day and inter-day variations were below 1.7% and 3.2% for CAD and 2.8%, and 3.4% for ELSD, respectively. In addition, detection sensitivities of ELSD, CAD, and UV detectors were also compared for HILIC and reversed phase (RP) modes and the highest sensitivities were obtained in the HILIC mode when connected with CAD and ELSD. The developed HILIC aerosol based detection methods were successfully applied to the analysis of gabapentin in commercial tablets and capsules.

1. Introduction

Gabapentin, 2-(1-(aminomethyl)cyclohexyl)acetic acid (Fig. 1), is an anti-epileptic drug which is commonly used for the treatment of neuropathic pain, partial seizures, anxiety disorder, bipolar depression, and hot flashes [1–4]. It is reported to have milder side effects and lack significant drug interactions compared to older generation anti-epileptics [5,6]. Gabapentin is a highly polar compound which has no significant volatility, and it is easily soluble in aqueous solutions. Due to the high polarity and absence of significant UV-absorbing chromophores, the analysis and detection of gabapentin were mostly achieved by derivatization methods with a separation procedure on a reversed phase high performance liquid chromatography (RP-HPLC) column followed by UV or fluorescence detection [7–11]. Other analytical methods such as gas chromatography (GC), HPLC coupled with mass spectrometry (MS) detection [12,13], and capillary electrophoresis with UV detection [14] have also been reported as methods for the analysis of gabapentin in various sample matrices.

ELSD and the more recently developed CAD have been widely applied for the detection of compounds lacking in UV-absorbing chromophores in the pharmaceutical field [15–24]. Both of the detection procedures are based on the nebulization of column eluents following an evaporation step to produce dried analyte particles. In case of ELSD, the formed particles scatter the incident laser light and the scattered photons are directly detected by a silicon photodiode. However for CAD detection, the dried particles first should be charged by a stream of nitrogen gas with positive charge, and consequently, the resulting charged analytes are measured through an electrometer [25]. Since both CAD and ELSD are aerosol-based detectors, some studies were done to evaluate the performance of CAD versus ELSD by comparing validation parameters including sensitivity, linearity, accuracy, and precision [26]. CAD performed better than ELSD in the RP-HPLC mode [27], normal phase HPLC (NP-HPLC) mode [28], and supercritical fluid chromatography (SFC) mode [29]. However, there is no detailed validation between CAD and ELSD in Hydrophilic interaction chromatography (HILIC) mode.

HILIC is an alternative of conventional RP-HPLC and NP-HPLC. In HILIC mode, because the mobile phase is commonly composed of a high percentage of acetonitrile and low amount of water or volatile buffer solutions, the separation is achieved on a polar stationary phase. For the analysis of polar compounds, the HILIC mode can effectively solve problems often found in RP and NP modes such as less retention and peak deformation in RP and poor reproducibility in NP mode [19]. Thus it is suitable for the analysis of polar compounds including peptides [30], carbohydrates [31], and some pharmaceuticals [32–35].

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doi:10.1016/j.talanta.2011.04.012

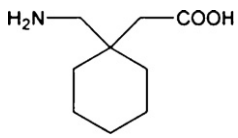

Fig. 1. Chemical structure of gabapentin.

Bare silica or polar functional group-modified silica gel is commonly used as stationary phase in HILIC mode. Retention order, detector response or detection selectivity with these stationary phases were compared in the literature. Mitchell et al. [36] compared the sensitivity of ELSD, CAD and MS in HILIC and RP-HPLC mode. The detector response of ELSD for the selected compounds was slightly better in HILIC mode than RP-HPLC mode while the average response of CAD was 10 times more sensitive in HILIC mode than RP-HPLC mode. However, the research discussed above was accomplished using a single diol HILIC column and the only validation parameter was sensitivity. Huang et al. [37] compared four HILIC columns coupled to CAD to detect inorganic pharmaceutical counterions. In their work, Atlantis HILIC and ZIC HILIC were found unsuitable for coupling with CAD because slight column bleeding under their mobile phase conditions caused serious background noise. Guo and Gaiki [38] also studied four types of stationary phase for the retention behavior of small polar compounds in the HILIC mode but the detection was achieved only with a UV detector.

In the present study, the performance of four HILIC columns coupled with ELSD or CAD was investigated for the determination of gabapentin in pharmaceutical formulations. To the best of our knowledge, this is the first comparison of analytical methods using multiple HILIC columns coupled to CAD or ELSD with a detailed validation and, also, the first successful application of HILIC mode for gabapentin analysis with aerosol based detectors.

2. Experimental

2.1. Chemicals and reagents

HPLC grade acetonitrile, methanol, and purified water were purchased from Duksan Pure Chemicals (Ansan, Korea). Ammonium acetate and acetic acid were purchased from Sigma (St. Louis, MO, USA). Gabapentin was purchased from ILDONG Pharmaceutical Co., Ltd. (Seoul, Korea). The commercial drug tablets and capsules were provided by Shin Poong Pharmaceutical Co., Ltd. (Ansan, Korea) and Korea United Pharm Inc. (Yongi, Korea).

2.2. Instrumentation

A Series 200 HPLC system (PerkinElmer, USA) was used in all experiments. The system consisted of a PerkinElmer Series 200 pump and an auto-sampler. Data collection and processing were achieved by Totalchrom Workstation software. Detection was accomplished using corona CAD plus (ESA, Chelmsford, MA, USA) and ELSD 2000 (Alltech Associates, Deerfield, IL, USA).

2.3. Chromatographic conditions

Four HILIC columns, Luna HILIC (100 mm × 2.0 mm, 3 μm, Phenomenex), Atlantis HILIC Silica (100 mm × 2.0 mm, 3 μm, Waters), ZIC HILIC (100 mm × 2.1 mm, 3.5 μm, SeQuant), and ZIC *p*HILIC (150 mm × 2.1 mm, 5 μm, SeQuant) were used for HPLC separations. The column temperature was set to 25 °C and the injection volume was 5 μL. The inlet nitrogen pressure of CAD was maintained at 35 psi according to the operating manual. The ELSD was operated in "impactor off" mode with a gain value set to 8. For each column, the composition and flow rate of mobile phase were first varied under isocratic elution to adjust the retention time and peak shape. And then, the parameters of detectors such as drift tube temperature and inlet nitrogen gas flow rate of ELSD, range set-up of CAD were varied to achieve the best signal to noise ratio.

2.4. Standard solutions and sample preparation

A stock solution of gabapentin was prepared in water to give a final concentration of 1 mg/mL. Standard solutions were made by serial dilution in a mixture of acetonitrile/water (75:25, v/v). Four quality control (QC) solutions were prepared daily by diluting the stock solution at 20, 75, 175, and 300 μg/mL. To prepare the commercial drug sample stock solution of 1 mg/mL, drug tablets and capsules were accurately weighed and crushed to make homogeneous mixtures. The appropriate amount was transferred to a 25 mL volumetric flask and adjusted to volume with acetonitrile/water (75:25, v/v) followed by sonication for 10 min.

3. Results and discussion

3.1. HILIC method development

Four HILIC columns with three different types of stationary phase were selected for the current work. Atlantis HILIC and Luna HILIC represented the bare silica and diol stationary phase, respectively. ZIC HILIC and ZIC *p*HILIC were applied as zwitterionic stationary phase. The retention mechanism of HILIC mode is complicated and commonly believed to be the partitioning of analyte between a water-enriched layer around the stationary phase and the mobile phase elute, and an additional secondary interaction via weak electrostatic interaction with the charged stationary phase in case of ZIC HILIC and ZIC *p*HILIC. For the current study, the retention behavior of gabapentin on each HILIC column and the responses of CAD and ELSD were compared under various mobile phase conditions.

3.1.1. The effect of organic solvent content on retention and baseline noise

Similar to RP-HPLC mode, acetonitrile is most often employed as the organic solvent in HILIC mode, but the elution order is reversed

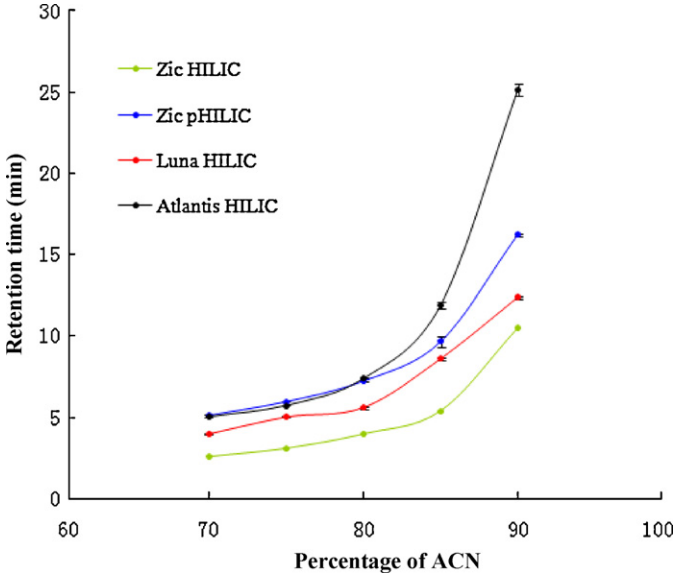

Fig. 2. Acetonitrile effect on the retention of gabapentin over HILIC columns by ELSD detector. The acetonitrile content was varied from 70 to 90%; other conditions are shown in Table 1. Error bars were shown by standard error.

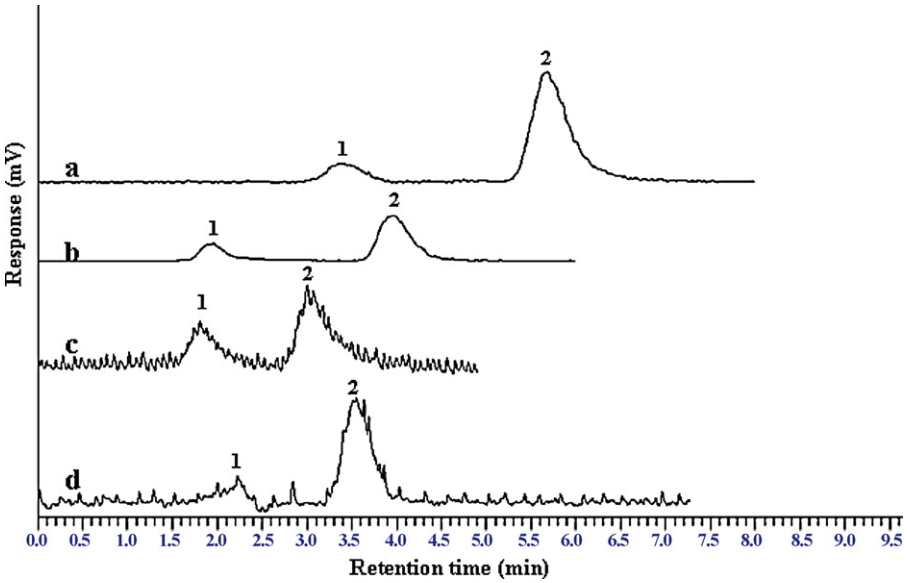

Fig. 3. CAD detection of gabapentin over (a) ZIC *p*HILIC, (b) Luna HILIC, (c) Atlantis HILIC, (d) ZIC HILIC. Peak 1, solvent peak. Peak 2, gabapentin. Chromatographic conditions are shown in Table 1 except Atlantis HILIC with a flow rate of 0.3 mL/min. All chromatograms were drawn on the same scale.

in comparison with RP since a higher amount of acetonitrile in HILIC would induce a longer retention time. As shown in Fig. 2, the retention times changed dramatically with the increasing of acetonitrile, which reflected that the acetonitrile content was the most significant parameter for adjusting the retention of gabapentin for the tested HILIC columns.

Since column bleeding was reported on some silica based HILIC columns [39], we evaluated the bleeding of the columns at relatively low and high aqueous mobile phase compositions using both CAD and ELSD. For CAD detection, the background signals of Luna HILIC and ZIC *p*HILIC were barely affected by high water content. Previously, it was predicted that the cross-linked diol bonded phase of Luna HILIC could minimize silica dissolution and column bleeding and that the polymer-based stationary phase of ZIC *p*HILIC could be stable in a high water content [37]. However, serious baseline noise from column bleeding was observed in Atlantis HILIC and ZIC HILIC columns when detected by CAD (Fig. 3). Therefore, the application of Atlantis HILIC and ZIC HILIC coupled with CAD were excluded, and the results in Tables 2–4 were shown as "NA" (not available). The baseline noise could be improved with 90% acetonitrile in the mobile phase but the retention time was too long to be used for the rapid analysis of gabapentin and peak broadening also occurred, obstructing the sensitive and accurate quantification of gabapentin. Interestingly, very smooth baselines were achieved with Atlantis HILIC and ZIC HILIC columns when ELSD, which is also a mass-dependent detector [40] and therefore, might be affected by the column bleeding, was coupled as shown in Fig. 4. Therefore, ELSD was considered to be the choice of detection for Atlantis HILIC

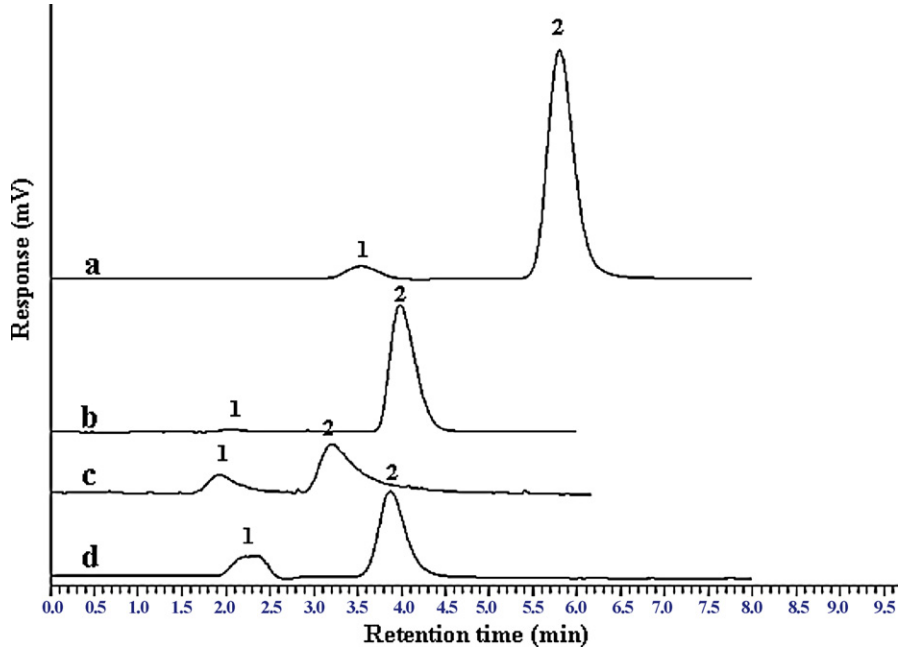

Fig. 4. ELSD detection of gabapentin over (a) ZIC *p*HILIC, (b) Luna HILIC, (c) Atlantis HILIC, (d) ZIC HILIC. Peak 1, solvent peak. Peak 2, gabapentin. Chromatographic conditions are shown in Table 1 except Atlantis HILIC with a flow rate of 0.3 mL/min. All chromatograms were drawn on the same scale.

Table 1
ELSD conditions used for each tested column.

Columns	Mobile phaseflow rate (mL/min)	Mobile phase composition (v/v)	Drift tube temperature (°C)	Inlet nitrogen flow rate (L/min)
ZIC HILIC	0.2	80:20 (ACN:AmAC[a])	45	1.0
ZIC *p*HILIC	0.15	75:25 (ACN:AmAC)	55	1.1
Luna HILIC	0.2	70:30 (ACN:Water)	55	1.2
Atlantis HILIC	0.2	75:25 (ACN:AmAC)	60	1.5
RP-C18	1.1	55:45 (Methanol:Water)	85	2.3

ACN: acetonitrile.
AmAC: ammonium acetate.
[a] The concentration was 5 mM.

and ZIC HILIC columns in this study. The exact mechanism for the different baseline responses in CAD and ELSD is not clear although the difference appears to occur at the final detection procedure as described above. Further study is in progress to elucidate the basis for this phenomenon.

3.1.2. *pH effect on the retention behavior of gabapentin*

Gabapentin, a gamma amino acid with two pK_a values of 3.7 and 10.7, could exist as a cationic, anionic or zwitterionic form in solution depending on the pH, suggesting that pH should affect the retention behavior of gabapentin on HILIC stationary phases. Therefore, the pH effect was investigated. The pH of the mobile phase containing 5 mM ammonium acetate was adjusted to pH 6.5, 5.0, 4.2, 3.5 and 3.2 before mixing with acetonitrile. No significant changes in the retention time were observed on Luna HILIC and Atlantis HILIC. This is probably because there were no additional electrostatic interactions between gabapentin and the columns at the given pH range in which the diol and bare silica stationary phases are not charged.

In principle, charged analytes could go through a second separation mechanism via weak electrostatic interaction in case of ZIC HILIC or ZIC *p*HILIC because sulfobetaine as zwitterionic functional group is covalently bonded to silica gel (ZIC HILIC) or polymer beads (ZIC *p*HILIC). Since both columns possess the same functional group, we just discussed the pH effect on ZIC *p*HILIC column for the current study. As shown in Fig. 5, gabapentin was retained longer with a decreasing pH, which could be explained by the interaction of the cationic form of gabapentin with the negatively charged stationary phase.

3.2. Linearity

Six calibration solutions (20, 50, 100, 150, 200 and 300 μg/mL) were prepared by serial dilution of the stock solution. Calibration curves were constructed by plotting the peak area versus the known amounts of gabapentin. As the responses of CAD and ELSD are non-linear [25], a log–log transformation was applied producing linear curves with correlation coefficients greater than 0.998 for all the tested columns coupled with either CAD or ELSD.

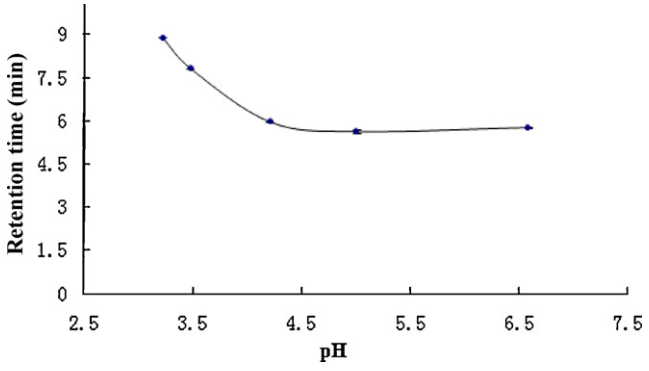

Fig. 5. pH effect on the retention of gabapentin over a ZIC *p*HILIC column. Chromatographic conditions are shown in Table 1. Error bars were shown by standard error.

Table 2
Sensitivity comparison of HILIC mode and RP-HPLC mode coupled with ELSD, CAD, and UV detectors. Data unit was 'ng' which was calculated by each concentration × injection volume.

Columns	CAD		ELSD		UV	
	LOD	LOQ	LOD	LOQ	LOD	LOQ
ZIC HILIC	NA	NA	7.5	20	375	500
ZIC *p*HILIC	10	30	5	15	375	500
Luna HILIC	7.5	20	7.5	20	300	425
Atlantis HILIC	NA	NA	30	50	425	600
RP-C18	20	40	500	600	375	500

NA means "not available" due to the baseline noise.

3.3. Sensitivity comparison

Limit of quantification (LOQ) and limit of detection (LOD), which correspond to the gabapentin concentration at a signal-to-noise ratio of 10 and 3, respectively, were determined as a measure of sensitivity. CAD was reported to be 10 times or more sensitive than ELSD in RP-HPLC mode for the detection of phosphatidic acid [27] and SFC mode for synthetic polymers [29]. In this study, the sensitivities of both detectors were compared for the detection of gabapentin in HILIC mode and RP-HPLC mode. The mobile phase conditions searched for HILIC separation were described in Section 2.3. For CAD detection, the range set-up is a very important parameter for sensitivity and the available values are 1, 2, 5, 10, 20, 50, 100, 200 and 500 pA. Higher sensitivity could be obtained with lower values, however, the background noise increased as well. The value 100 pA was chosen because of the best signal to noise ratio. Different from CAD, the response of ELSD depends on both the drift tube temperature and inlet nitrogen gas flow rate. Therefore, the two factors were optimized for the individual column at a fixed mobile phase composition and flow rate (Table 1) in order to get the best response. For RP-HPLC mode, the analysis was done on a GraceSmart RP-18 packed column (250 mm × 4.6 mm, 5 μm, Alltech). Similar with HILIC mode, the mobile phase conditions were first searched to adjust the retention and peak shape, and then the range of CAD was tested and optimized to 100 pA; ELSD conditions were varied according to the mobile phase and shown in Table 1.

In HILIC mode, Luna HILIC and ZIC *p*HILIC columns showed similar responses for the two detectors; however, in RP-HPLC mode, the LOD for CAD detection was lower than that of ELSD by more than 25-fold (Table 2). The response of CAD and ELSD is related to the size of the dried analyte particles, which could be affected by the mobile phase. Since the organic-rich mobile phase and lower flow rate found in HILIC mode are generally known to enhance the aerosol detector response [20,40], HILIC is predicted to be more sensitive than the RP mode. In addition, ELSD or CAD requires no derivatization, which is usually a pre-requisite for UV detection of

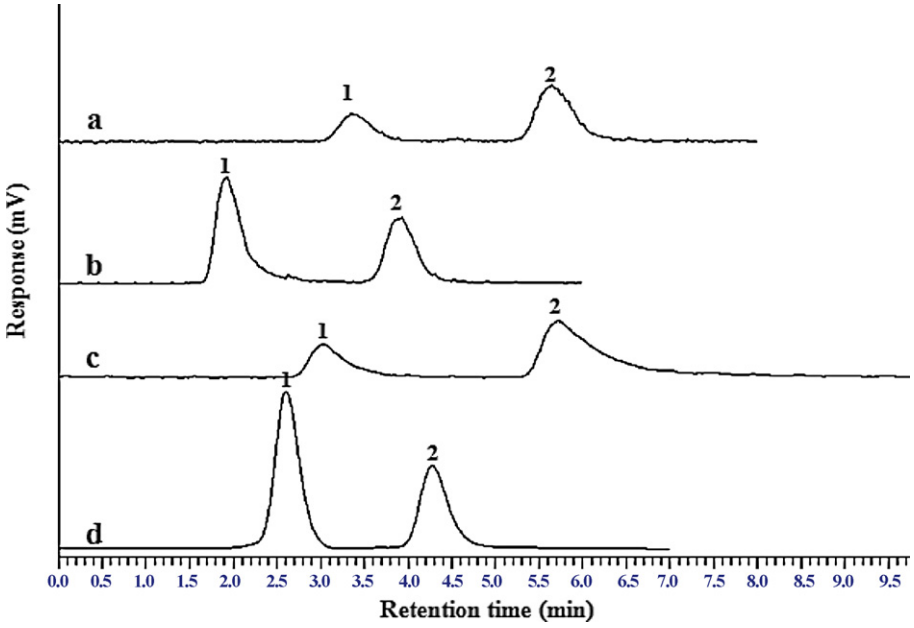

Fig. 6. Analysis of gabapentin in commercial drugs detected by (a) ZIC *p*HILIC with CAD detection for a capsule, (b) Luna HILIC with CAD detection for a tablet, (c) Atlantis HILIC with ELSD detection for a capsule, (d) ZIC HILIC with ELSD detection for a tablet. Peak 1, impurities from solvent and excipients. Peak 2, gabapentin. Chromatographic conditions are shown in Table 1.

non-ultraviolet absorbing compound in pharmaceutical formulations. Herein, the sensitivity of CAD, ELSD, and UV (PerkinElmer, USA) detection methods was compared. The UV wavelength was set to 210 nm according to the literature [41,42]. The LODs of CAD and ELSD detection were found to be as low as 5 ng on column which is ~50 times lower than that of UV (Table 2). Comparing with the reported direct UV detection methods, which obtained LOD values as 100 ng [42] and 600 ng [41], the developed HILIC aerosol detection methods were much more sensitive.

3.4. Precision

Intra- and inter-day precisions were evaluated with quality control samples. The intra-day variation was measured in five replicates in one day and the inter-day variation was measured for three separate days ($n = 5$). The precision was expressed as % RSD and the results are summarized in Table 3. The intra-day and inter-day variations were below 1.7% and 3.2% for CAD and 2.8%, and 3.4% for ELSD, respectively. Although there was a little peak tailing found in Atlantis HILIC column, it did not affect the precision of its application.

3.5. Accuracy

The method accuracy for each column and detector was tested on the commercial drug tablet as mean recovery. The commercial

Table 3
Precision of HILIC coupled with aerosol detection methods evaluated by quality control solutions.

Columns	Intra-day[a] ($n = 5$)				Inter-day ($n = 5 \times 3$ days)			
	20	75	175	300	20	75	175	300
CAD								
ZIC HILIC	NA	NA	NA	NA	NA	NA	NA	NA
ZIC *p*HILIC	1.6	0.7	1.0	1.0	3.1	3.0	2.5	3.0
Luna HILIC	0.7	1.0	1.5	0.7	1.3	1.2	1.9	1.5
Atlantis HILIC	NA	NA	NA	NA	NA	NA	NA	NA
ELSD								
Zic HILIC	1.9	1.7	1.4	1.0	3.4	3.2	2.2	2.6
Zic *p*HILIC	1.8	1.3	1.3	1.4	3.0	2.7	2.7	2.5
Luna HILIC	2.3	1.2	0.7	2.8	2.1	3.2	1.6	2.4
Atlantis HILIC	2.8	2.5	0.9	1.9	3.2	3.3	1.3	2.6

NA means "not available" due to the baseline noise.

Table 4
Accuracy of HILIC coupled with aerosol detection methods ($n = 3$).

Columns	CAD			ELSD		
	80%	100%	120%	80%	100%	120%
ZIC HILIC	NA	NA	NA	101.0	98.9	104.3
ZIC *p*HILIC	106.6	96.7	106.1	102.2	99.7	98.1
Luna HILIC	97.8	96.4	100.8	99.7	98.9	103.8
Atlantis HILIC	NA	NA	NA	108.6	103.9	103.2

NA means "not available" due to the baseline noise.

Table 5
Analysis of commercial drugs by HILIC coupled with aerosol detection methods ($n = 3$).

Columns	Tablet			Capsule		
	Declared content (μg/mL)	Found	RSD	Declared content (μg/mL)	Found	RSD
ZIC HILIC[a]	75.69	74.58	1.5	100	101.23	1.3
ZIC *p*HILIC[b]	75.69	73.95	1.0	100	97.72	1.1
Luna HILIC[b]	75.69	74.21	1.0	100	102.17	0.9
Atlantis HILIC[a]	75.69	76.12	2.5	100	104.93	2.1

[a] Detected by ELSD.
[b] Detected by CAD.

gabapentin drug preparations with a known concentration were spiked with gabapentin standard solutions with concentrations of 80%, 100%, and 120% of the drug preparation. Each concentration was made in triplicate and injected three times. As shown in Table 4, recoveries around 100% suggest the proposed methods are quite accurate.

3.6. Application of the developed methods

Gabapentin in tablet and capsule formulations from two domestic manufacturers was analyzed by the optimized HPLC methods utilizing HILIC columns coupled to either CAD or ELSD. Chromatograms are shown in Fig. 6. The contents of the commercial gabapentin drugs were calculated using linear regression equations obtained from the calibration curves discussed above. As found in Table 5, the amounts found in commercial drug formulations corresponded well to the declared amount suggesting that the proposed methods are applicable for gabapentin analysis in pharmaceutical formulations.

4. Conclusions

The main purpose of this study is to compare the performance of CAD and ELSD in HILIC mode for the detection of gabapentin in pharmaceutical formulations. Comparing the derivatization and direct UV detection methods, the proposed aerosol-based detection methods were considered to be simple and rapid in sample preparation, and much more sensitive than the reported direct UV detection methods. In RP-LC mode, CAD was much more sensitive than ELSD. But in HILIC mode, different from the reported studies on the comparison between CAD and ELSD in other separation modes, the performance of ELSD was comparable to that of CAD in terms of linearity, sensitivity, precision, and accuracy. In addition, ELSD had the advantage of having a low baseline noise over CAD when Atlantis HILIC or ZIC HILIC was used as the separation column. Therefore, this research not only provides a novel method for gabapentin analysis but also might be useful when CAD or ELSD is used for other polar and non-UV detectable compounds in HILIC mode.

Acknowledgements

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2010-0005326) and was supported by the Industrial Source Technology Development Program funded by the Ministry of Commerce, Industry and Energy (MOCIE) in Korea (Grant No. 10031825).

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