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Simultaneous determination of Maillard reaction impurities in memantine tablets using HPLC with charged aerosol detector

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ABSTRACT

A gradient high performance liquid chromatographic (HPLC) method using charged aerosol detection (CAD) was developed for the simultaneous determination of impurities formed by the Maillard reaction in memantine tablets. These impurities were a memantine-lactose adduct (ML), a memantine-dimethylamino glycine adduct (DMAG), a memantine-galactose adduct (MGAL), and a memantine-glucose adduct (MGLU). The chromatographic separation was performed on a Synergy Hydro RP column (100 mm × 3 mm, 2.5 μm particles) from Phenomenex with gradient elution using mobile phases consisting of 0.6% (v/v) of heptafluorobuturic acid (HFBA) in two acetonitrile–isopropyl alcohol–water mixtures. The method validation for the impurities included linearity, accuracy by spike recovery, precision, limits of detection and quantitation, and robustness. The method was sensitive for these non-chromophoric impurities down to 0.4–0.6 μg/mL (0.02–0.03% of the memantine drug substance). The effect of mobile phase HFBA concentration on chromatographic resolution and peak shape was investigated, and the effect of sample diluent acidification on method accuracy via spike recovery was studied. The operational simplicity of the CAD detector for routine quality control has been demonstrated.

1. Introduction

The reaction between amino compounds and reducing sugars is known as a Maillard reaction (MR), and the chemical pathways of the MR are very complicated. Hodge [1] presented it as a multi-staged reaction series in which each stage depends on a number of controlling factors such as temperature, pH, and nature of reactants. High temperature and high pH support a quick completion of the reaction. However, degradation products formed by the MR have also been observed under less extreme conditions in pharmaceutical products containing both lactose, an excipient commonly used as a filler in solid dosage formulations [2], and drug substances containing amino groups, such as fluoxetine hydrochloride [3], aminophylline, amlodipine, acyclovir [4] and baclofen [5]. Formation of MR impurities was also reported in memantine tablets [6].

Long-term stability studies (25 °C/60% RH storage condition) were conducted for memantine tablets formulated with lactose at less than a 1:20 drug to lactose ratio, as well as other common tablet excipients. During the storage, a primary amino group of memantine (1-amino-3,5-dimethyladamantane) underwent the MR with lactose, a reducing sugar, resulting in four MR related impurities; a memantine-lactose adduct (ML), a memantine-dimethylamino glycine adduct (DMAG), a memantine-galactose adduct (MGAL), and a memantine-glucose adduct (MGLU). These four impurities were characterized by HPLC-mass spectrometry and subsequently identified in memantine tablets using authentic compounds. A schematic diagram showing the MR between lactose and memantine is presented in Fig. 1.

Quantitation of the MR impurities, especially those lacking an appreciable chromophore, has traditionally proven difficult. Analytical techniques such as HPLC with mass spectrometric detection [4,5,7–10] and HPLC with evaporative light scattering detection (ELSD) [11,12] have been used to separate and quantitate these types of impurities. Although mass spectrometry is highly sensitive and has advantages with respect to detection of non-chromophoric compounds, it is an expensive and complex technique for use in a routine quality control laboratory environment. ELSD is considered a "universal detector," but its sensitivity, dynamic range, and precision are limited. One more alternative detection technique, fluorometry, has been commonly used in the pharmaceutical industry to detect non-chromophoric compounds or to improve trace level method sensitivity over standard UV detection. However, this detection technique often requires a derivatization reaction in order to increase sensitivity or selectivity. A number of HPLC methods with fluorimetric detection based on the

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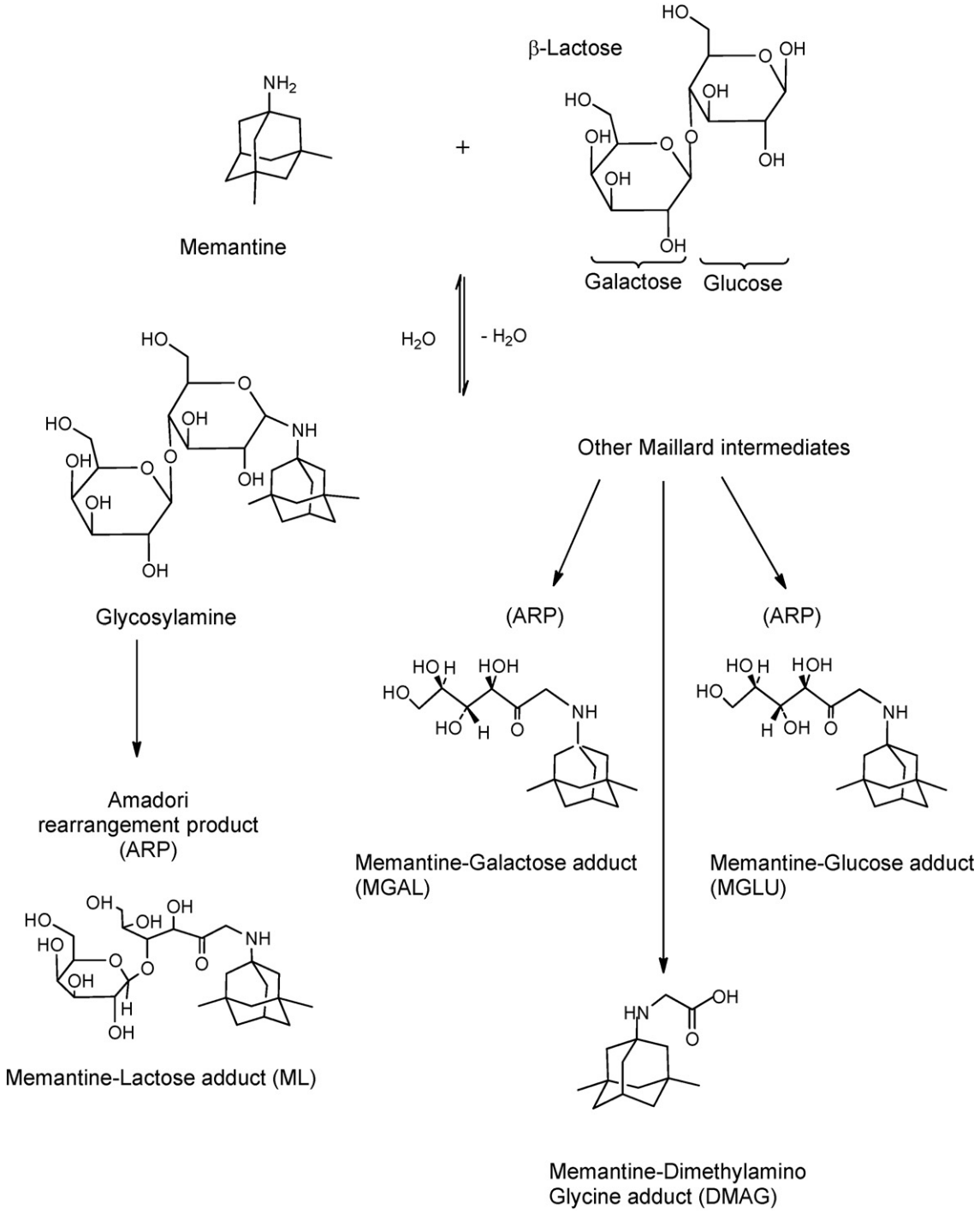

Fig. 1. Schematic diagram showing Maillard reaction between lactose and memantine.

derivatization technique were developed for amantadine and its derivative memantine [13–16].

Another "universal" detector that is gaining acceptance for the analysis of non-chromophoric analytes is the Corona® Charged Aerosol Detector (CAD). CAD is a mass-based detector which passes nebulized column effluent through a drying tube and then into a corona discharge zone. The corona forms charged analyte molecules, which are then accelerated into an electrometer for detection. The detector response is proportional to the amount of analyte present [17] and is less dependent on molecular structure than a UV detector response, especially for compounds of similar structure. The CAD provides a wide dynamic range, sensitivity down to nanogram levels, and is compatible with gradient elution. A comparison between the performances of CAD and ELSD "universal" detectors demonstrated that CAD has significant advantages over ELSD in terms of linearity, precision and sensitivity [18–23], and the CAD is better suited for the detection of impurities and degradation products.

This paper describes a sensitive and selective reversed phase gradient HPLC method with CAD detection for the quantification of four MR impurities in memantine tablets using a simple sample preparation technique. There are relatively few publications describing the use of HPLC-CAD in pharmaceutical applications, but its use has been growing. Nováková

et al. developed and validated a HPLC-CAD method for the determination of statins in tablets [24]. Diaz-Lopez et al. developed a HPLC-CAD method for the quantification of a pegylated phospholipid, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000], associated to polymeric microcapsules of perfluorooctyl bromide [25]. Duan et al. used HPLC-CAD for the mass-balance evaluation of the forced degradation of digitoxin [26]. Inagaki et al. described the direct detection method of oligosaccharides using HPLC with CAD [27]. Blazewicz et al. developed novel liquid chromatography methods with CAD for the determination of pancuronium and its impurities, atracurium, cisatracurium and mivacurium with their impurities in pharmaceutical preparations [28,29]. Holzgrabe et al. developed and fully validated a reversed phase ion-pair HPLC method with CAD for the pharmaceutical quality control of L-aspartic acid [30]. To our knowledge, the approach described here is the first to utilize HPLC with a CAD detector for the detection and quantitation of non-chromophoric low level impurities such as ML, DMAG, MGAL and MGLU in lactose containing solid dosage formulations.

2. Experimental

2.1. Chemical and reagents

Memantine HCl was obtained from Merz & Co. (Frankfurt, Germany). The ML, MGLU and MGAL impurities were provided by Clauson–Kaas (Farum, Denmark). The DMAG impurity was received from OlainFarm (Olaine, Latvia). HPLC grade acetonitrile and isopropanol were purchased from EMD (Gibbstown, NJ, USA). HPLC grade methanol was obtained from Burdick & Jackson (Muskegon, MI, USA). Deionized water was obtained from a Millipore Corporation Milli-Q system, Millipore (Bedford, MA, USA). Sequanal-grade heptafluorobutyric acid (HFBA) was purchased from Pierce (Rockford, IL, USA). Formic acid (purity ≥98.0%) was purchased from Fluka (Buchs, Switzerland). Memantine tablets were produced by Allergan, Inc.

2.2. Sample preparations

Standard solutions of the MR impurities were prepared by dissolving the compounds in methanol followed by dilution in methanol:water (50:50, v/v). The nominal concentration of the working standard was 0.016 mg/mL.

Memantine tablets stored for 3 years at 25 °C/60% RH storage condition were dissolved in methanol:water (50:50, v/v) acidified by formic acid. Tablets were first transferred to a 50 mL volumetric flask, and then approximately 25 mL of water was added to the flask. The solution was left standing for 15 min at room temperature to allow tablets to disintegrate. The solution was then swirled without agitation in order to avoid foaming. After the tablets were visibly disintegrated, 0.25 mL (0.5% of the total dilution volume) of formic acid was added to the solution followed by dilution to volume with methanol:water (50:50, v/v). The resultant solution was mixed by stirring for 30 min. The nominal concentration of memantine in the sample solution was 2 mg/mL. Finally, an aliquot of the diluted sample was filtered through a 0.45 μm PTFE Acrodisc syringe filter directly into an HPLC vial for analysis.

2.3. Instrumentation and conditions

HPLC analyses were carried out using a Waters 2695 HPLC system (Waters Corporation, Milford, MA, USA) connected to a CAD detector (ESA, Chelmsford, MA, USA). The CAD thermal organizer was not included in the system. Data acquisition and integration were performed by using the Waters Empower software. The analytical column was a Synergy-RP (100 mm × 3 mm, 2.5 μm particles) from Phenomenex (Torrance, CA, USA), and it was maintained at 40 °C. The autosampler was held at ambient room temperature. The column flow rate was set to 0.4 mL/min, and the injection volume was 50 μL.

Table 1
HPLC gradient program.

Time	Mobile phase A	Mobile phase B	Gradient curve
Initial	100%	0%	N/A
10.0 min	65%	35%	Convex
30.0 min	65%	35%	Isocratic
30.1 min	0%	100%	Immediate increase
35.0 min	0%	100%	Isocratic
40.0 min	100%	0%	Linear

The chromatographic separations were carried out using gradient elution, as described in Table 1. Mobile phase A consisted of a mixture of HFBA:Solution A (0.6:99.4, v/v), where Solution A was a mixture of acetonitrile:isopropyl alcohol:water (5:5:90, v/v/v). Mobile phase B consisted of HFBA:Solution B (0.6:99.4, v/v); where Solution B was a mixture of acetonitrile:isopropyl alcohol:water (30:27:43, v/v/v). The mobile phases were filtered through 0.45 μm Millipore HVLP membrane filters prior to use.

The following operating parameters for the CAD were set: the nitrogen gas pressure at the detector inlet was set to 35 psi, the detector response range was 100 pA, and the filter was set to "None." Nitrogen with a purity of NLT 99.99% was used as the nebulizing gas.

2.4. Quantitaton of impurities

Quantitation of the MR impurities in memantine tablets was performed using single point working standards of the impurities.

3. Results and discussion

3.1. Method optimization

3.1.1. Optimization of chromatographic conditions

A mobile phase containing 0.6% (v/v) of HFBA in a water, acetonitrile and isopropanol mixture was found to be optimal for this method. At the beginning of the method development, mobile phases containing methanol and water with 0.2% (v/v) of trifluoroacetic acid (TFA), an anionic ion-pairing reagent, were used. The TFA was chosen because of its volatility and compatibility with CAD operational principles [31]. However, baseline separation of the MR impurities could not be obtained, and the method sensitivity was poor due to high background noise. It has been reported [17,31] that mobile phases containing methanol may increase the background noise of the CAD. For this reason and to improve the chromatographic separation, the first mobile phase optimization step was to replace methanol with acetonitrile without impacting the overall chromatography, which did reduce the background noise. Further refinement steps led to a mobile phase containing a mixture of acetonitrile and isopropyl alcohol, which was selected because of the lower polarity and improved selectivity. However, the percentage of isopropanol in the mobile phase was limited by its high viscosity, which leads to an increased column back pressure. With the isopropanol present, the resolution between the ML impurity and the MGAL impurity was significantly improved relative to that obtained with acetonitrile alone.

To further enhance the method sensitivity and impurity resolutions, the TFA in the mobile phase was replaced with a less volatile but more hydrophobic, longer alkyl chain HFBA. Several concentrations, including 0.4%, 0.6% and 0.8% (v/v) HFBA, were evaluated, and a signal-to-noise ratio increase was observed for the 0.4% and 0.6% (v/v) HFBA mobile phases compared to the 0.2% TFA

mobile phase. At a concentration of 0.8% (v/v) HFBA, though, the background noise became unacceptable. Concurrently, the resolutions increased between the DMAG impurity and memantine and between the very closely eluting MGAL and MGLU impurities with increasing HFBA concentration. The final HFBA concentration was set to 0.6% (v/v) in the mobile phase, as it provided the optimal balance between sensitivity and impurity resolution.

The Waters 2695 HPLC provides a wide variety of gradient curves to adjust the rate of change between the individual mobile phase channels, with linear being the most commonly used. In order to investigate the ability of different curves to improve the separation between the analytes and matrix components, linear and convex curves were evaluated for the first segment of the gradient program. As the name indicates, a linear curve mixes the two channels in a 1:1 ratio throughout the program segment. The convex curve accelerates the percentage of mobile phase B relative to A in the beginning of the segment and slows as the segment ends. The convex curve was applied to accelerate the elution of placebo matrix components during first 10 min and thus to reduce the overall duration of the chromatographic run. In order to achieve sufficient resolution between each of the analytes and formulation peaks, an isocratic elution was applied to the second segment, from 10 to 30 min. Because the convex curve was only applied to accelerate the elution of placebo matrix components during first 10 min, this profile can be changed to a linear gradient without negatively affecting the separation of MR impurities.

All CAD operating parameters were held constant during the chromatographic separation. The optimization of detection parameters was limited to only two variable settings, namely the response range and a filter setting. The range was set to "100 pA" to select the full-scale range for the detector and to ensure that the chromatographic peaks remained on scale. Additionally, the signal filter was set to "None" in order to collect the unsmoothed signal for better low level impurity detection.

3.1.2. Optimization of sample diluent

The initial spike recovery assessment of the MGLU, MGAL, DMAG and ML impurities from the formulation matrix was conducted with a methanol:water (50:50, v/v) sample diluent. In this diluent, all of these impurities, which contain a secondary amine functional group (estimated pK_a of the protonated amine > 10) [32], would carry a positive charge. Additionally, the DMAG impurity contains a carboxylate functional group (estimated pK_a ~ 4.8) [33] that would be ionized in the diluent to carry a negative charge. Thus DMAG would be overall neutral while the MGLU, MGAL, and ML impurities would carry a net positive charge in the methanol:water (50:50, v/v) sample diluent. As a result, the spike recovery for the MGLU, MGAL, and ML impurities in methanol:water was poor, as shown in Table 2.

Given that the tablet formulation contains colloidal silicon dioxide, which is negatively charged [34], the most likely cause for the poor recovery of the three impurities is electrostatic attraction between the positively charged impurities and the negatively charged silicon dioxide, which was filtered away during sample preparation. Acidifying the methanol:water sample diluent substantially increased the recovery of MGLU, MGAL, and ML as shown in Table 2. The acidified sample diluent suppressed the negative charge on the silicon dioxide during the sample preparation, thereby lowering the electrostatic attraction between the positively charged impurities and silicon dioxide. Since the DMAG impurity was uncharged in the neutral methanol:water (50:50, v/v) sample diluent, its recovery was fairly good without acidification. After acidification, the DMAG carried a positive charge, but due of the negative charge suppression on the silicon dioxide, the recovery of DMAG was not significantly affected. Therefore, the behavior of the DMAG impurity in this study is consistent with the hypothesis that electrostatic attraction played a role in affecting recovery.

In order to confirm the specificity of the method for the MR impurities, placebo samples were prepared in the acidified methanol:water (50:50, v/v) diluent, and no interfering peaks at the retention times of the MR impurities were observed. Additionally, no chromatographic differences (including peak areas) were observed between impurity standards prepared with methanol:water and acidified methanol:water diluents. Therefore, the acidification of the sample diluent did not induce matrix or standard degradation that would potentially interfere with the quantitation of the MR impurities.

3.2. Method validation

3.2.1. Linearity

Linearity of the detector for the ML, MGLU, MGAL and DMAG impurities was demonstrated in the concentration ranges shown in Table 3 by plotting the peak area of the analyte versus its concentration. A linear least-squares regression was performed, and the correlation coefficients (R) for all the regressions were at least 0.996, thus demonstrating a good linear response for the impurities across the concentration range of interest. A summary of linearity data is presented in Table 3.

3.2.2. Accuracy and precision

The method accuracy was assessed by spiking an accurately known quantity of the MGLU, MGAL, ML and DMAG impurities into the sample matrix and determining their recoveries. The spike recovery studies were performed at three concentration levels for each impurity, and triplicate sample preparations were made at the each concentration level. Results are shown in Table 4.

Table 2
Spike recovery with and without acidification of the sample preparation.

MR impurity	Level of spiked impurity as % of memantine drug substance	Concentration of spiked impurity, μg/mL	% Recovery with the acidification of sample preparations	% Recovery without the acidification of sample preparations
ML	0.1	1.9	89	69
	1.9	38	86	81
MGLU	0.05	1.0	109	33
	1.0	21	102	37
MGAL	0.06	1.1	77	28
	1.1	23	99	39
DMAG	0.06	1.2	106	93
	1.2	25	139	133

Table 3
Linearity data for ML, DMAG, MGLU, and MGAL.[a]

Compound	Concentration range, μg/mL	Y-intercept ($\times 10^5$)	Slope ($\times 10^6$)	Correlation coefficient, r
ML	1.9–38	1.44	2.36	0.996
DMAG	1.3–53	1.65	3.03	0.998
MGLU	1.1–43	1.10	2.60	0.999
MGAL	1.2–47	2.53	2.34	0.996

[a] Each linearity solution was prepared in triplicate ($n = 3$) using methanol–water (50:50, v/v) as a diluent. Each linearity plot passed through the origin within 95% confidence interval.

Table 4
Method accuracy and intra-assay precision data.

MR impurity	Level of spiked impurity as % of memantine drug substance	Concentration of spiked impurity, μg/mL	%RSD ($n = 3$)	Mean % recovery at each concentration level	Overall mean % recovery
ML	0.09	1.9	5.4	84	88
	1.1	23	2.2	92	
	1.9	38	1.1	89	
DMAG	0.07	1.3	3.3	120	126
	1.1	21	0.9	134	
	2.7	53	0.1	124	
MGLU	0.05	1.1	3.2	85	100
	0.9	17	1.0	109	
	2.2	43	0.8	106	
MGAL	0.06	1.2	11	92	95
	0.9	19	0.2	99	
	2.4	47	1.2	93	

Table 5
Method precision data ($n = 3$).

MR impurity	Level as % of memantine drug substance[a]	%RSD
ML	0.81	1.9
	0.79	
	0.78	
DMAG	0.28	0.0
	0.28	
	0.28	
MGLU	0.24	2.4
	0.24	
	0.23	
MGAL	0.48	1.2
	0.47	
	0.48	

[a] Memantine concentration in the sample preparation solution equals to 2 mg/mL.

Method intra-assay precision was also determined as the percent relative standard deviation (%RSD) of the spike recovery results at each concentration level (Table 4).

Single day method precision was tested by analyzing three preparations of memantine tablets and determining the %RSD of the impurity results. The data are summarized in Table 5.

Day-to-day method precision was demonstrated by analyzing memantine tablets on two different days, three preparations on each day, and determining ratios of the means for day-to-day data sets. Comparison of the mean values obtained for each impurity showed no significant difference between the two data sets, and therefore sufficient method ruggedness was demonstrated. A summary of the results is shown in Table 6.

3.2.3. Method detection limit (LOD) and quantitation limit (LOQ)

LOD and LOQ were determined by analyzing placebos spiked with impurities at known low concentrations that yielded signal-to-noise ratios of at least 3:1 and 10:1, respectively. The measured LOD and LOQ values are presented in Table 7. Fig. 2 shows chromatograms of placebo spiked with impurities at low concentrations and the detector sensitivity solution.

Given the maxim daily dose of 20 mg, the ICH reporting, identification and qualification thresholds were 0.1%, 0.2% and 0.5% of the drug substance label strength, respectively. The method's LOQs for the various impurities are adequate to meet the ICH requirements.

3.2.4. Effects of column temperature and HFBA concentration in mobile phase

To understand the effect of column temperature on method performance, particularly the resolution between the critical-pair of the MGLU and MGAL impurities, a controlled study varying the column temperature above and below the nominal values was performed. A sample prepared from aged memantine tablets was analyzed using column temperatures of 35 °C, 40 °C and 45 °C. As shown in Table 8, the temperature variation shifted the retention times for the analytes, as anticipated, but the resolution between the MGLU and MGAL was not affected.

As for the effect of HFBA concentration in the mobile phase on the separation and detector response, the experiments conducted during method development and detailed in Section 3.1.1 shows that varying HFBA concentration leads to improved sensitivity and selectivity. However, at levels above 0.6% (v/v), the detector background noise becomes unacceptably high. Therefore, the HFBA concentration in the mobile phase is a critical parameter for optimizing method performance.

3.3. Real sample analysis

This analytical method was applied to the quantitation of MR impurities in aged memantine tablets from the long-term stability program. Tablets were stored for 3 years under nominal controlled temperature and humidity storage conditions of

Table 6
Day-to-day method precision data ($n = 3$).

MR impurity	Level as % of memantine drug substance[a]		Mean level as % of memantine drug substance		Ratio of means Day1/Day2
	Day 1	Day 2	Day 1	Day 2	
ML	0.81	0.79	0.79	0.80	0.99
	0.79	0.81			
	0.78	0.80			
DMAG	0.28	0.30	0.28	0.29	0.95
	0.28	0.29			
	0.28	0.29			
MGLU	0.24	0.22	0.24	0.22	1.06
	0.24	0.20			
	0.23	0.25			
MGAL	0.48	0.48	0.48	0.50	0.96
	0.47	0.47			
	0.48	0.54			

[a] Memantine concentration in the sample preparation solution equals to 2 mg/mL.

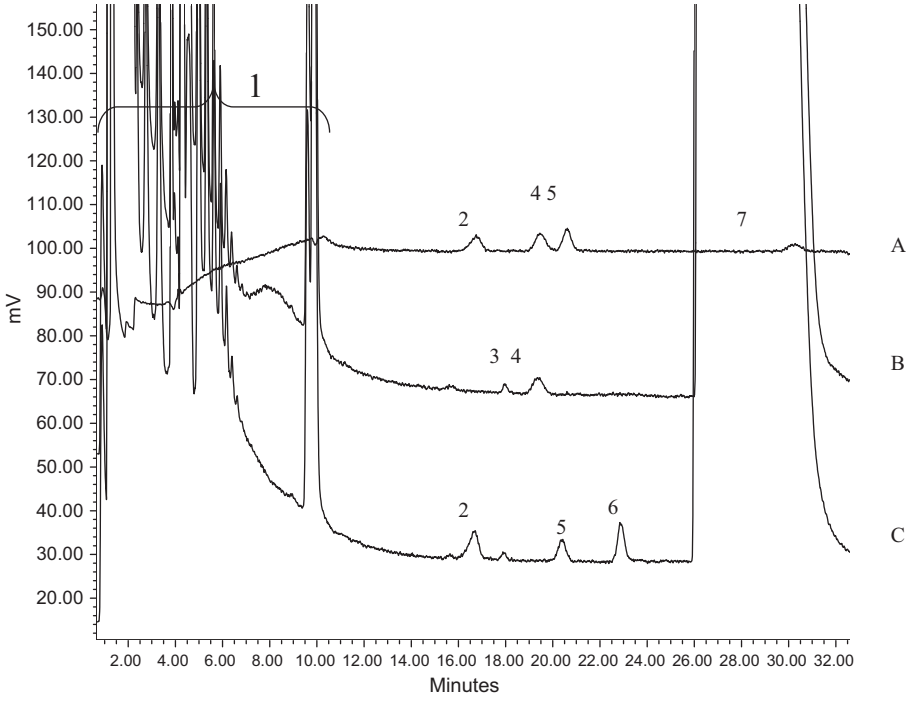

Fig. 2. Chromatograms of placebo spiked with impurities at low concentrations and the detector sensitivity solution: (A) detector sensitivity solution with the concentration of impurities at 0.05% of drug substance; (B) placebo spiked with drug substance and MGLU at 0.05% of drug substance; (C) placebo spiked with drug substance, along with ML, MGAL and DMAG at 0.09%, 0.06% and 0.07% of drug substance, respectively. The elution order was the following (retention time shown in parentheses in minutes): 1 –matrix components (0–11); 2 – ML (16.6); 3 – drug substance related unspecified impurity; 4 – MGLU (19.5); 5 – MGAL (20.4); 6 – DMAG (22.7); 7 – drug substance (26.3).

Table 7
LOD and LOQ values.

MR impurity	LOD/LOQ	Level as % of memantine drug substance	Impurity concentration, μg/mL
ML	LOD	0.03	0.66
	LOQ	0.11	2.2
DMAG	LOD	0.02	0. 38
	LOQ	0.07	1.3
MGLU	LOD	0.03	0.62
	LOQ	0.10	2.1
MGAL	LOD	0.03	0. 56
	LOQ	0.09	1. 9

25 °C/60% RH. The MR impurities were quantitated against external bracketing standards, and the following levels of impurities were detected in memantine tablets as % of the drug substance label concentration: ML = 0.70%, DMAG = 0.30%, MGLU = 0.25% and

Table 8
Effect of column temperature on analyte retention times and resolution between MGLU and MGAL.

HPLC column temperature	35 °C	40 °C	45 °C
ML retention time, min	18.3	16.7	15.6
MGLU retention time, min	21.5	19.4	17.9
MGAL retention time, min	22.7	20.5	18.9
DMAG retention time, min	25.8	23.2	21.1
Resolution between MGLU and MGAL	1.4	1.5	1.5

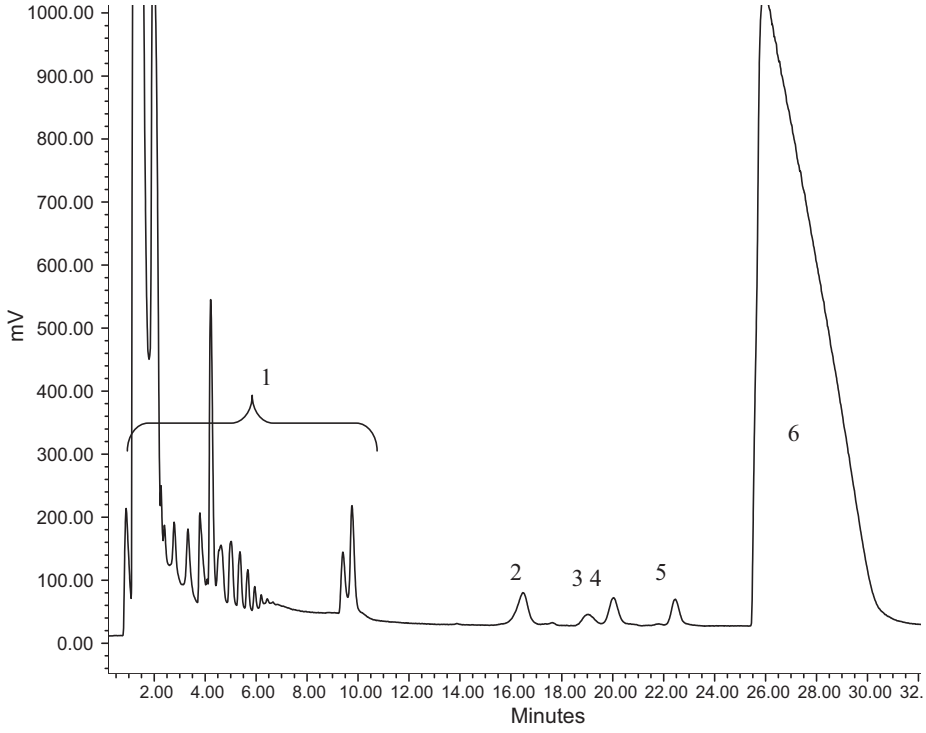

Fig. 3. Chromatogram of the memantine tablet stored for 3 years at 25 °C/60% RH storage condition. Sample contains low levels of MR impurities. 1 – placebo components; 2 – ML; 3 – MGLU; 4 – MGAL; 5 – DMAG; 6 – memantine.

MGAL = 0.55%. Fig. 3 is a chromatogram of the memantine tablet sample, which had been stored for 3 years at 25 °C and 60% RH.

4. Conclusions

A new gradient HPLC method with CAD detection was developed and validated for the simultaneous determination of four primary, non-chromophore-containing Maillard reaction impurities in memantine tablets: ML, DMAG, MGLU and MGAL. The method was linear over the range of typical impurity levels with good accuracy, precision, and robustness. HFBA added to the mobile phase improved the resolution and peak shapes of the impurities Detection of the impurities by CAD provided sufficient sensitivity to detect these types of compounds at levels as low as 0.02–0.03% of the drug substance label concentration. It was also determined that acidification of the sample diluent was required during sample preparation to ensure acceptable recovery of the analytes from the complex tablet matrix. With the successful development, optimization and validation of this robust and simple HPLC-CAD procedure, routine quality control analysis of memantine tablets for these MR impurities is now possible.

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References

[1] J.E. Hodge, Chemistry of browning reactions in model systems, J. Agric. Food Chem. 1 (1953) 928–943.
[2] A. Wade, P.J. Weller (Eds.), Handbook of Pharmaceutical Excipients, Second ed., American Association/The Pharmaceutical Press, Washington/London, 2000.
[3] D.D. Wirth, S.W. Baertschi, R.A. Johnson, S.R. Maple, M.S. Miller, D.K. Hallenbeck, S.M. Gregg, Maillard reaction of lactose and fluoxetine hydrochloride, a secondary amine, J. Pharm. Sci. 87 (1998) 31–39.
[4] S.S. Bharate, S.B. Bharate, A.N. Bajaj, Interactions and incompatibilities of pharmaceutical excipients with active pharmaceutical ingredients: a comprehensive review, J. Excipients Food Chem. 1 (2010) 3–26.
[5] F. Monajjemzadeh, D. Hassanzadeh, H. Valizadeh, M.R. Siahi-Shadbad, J.S. Mojarrad, T. Robertson, M.S. Roberts, Assessment of feasibility of Maillard reaction between baclofen and lactose by liquid chromatography and tandem mass spectrometry, application to pre formulation studies, AAPS PharmSciTech 10 (2009) 649–659.
[6] Stable pharmaceutical composition of memantine and process of preparation thereof, IP.com Prior Art Database, IPCOM/000168000, 2008.
[7] S.M. Monti, A. Ritieni, G. Graziani, G. Randazzo, A.L. Mannina, V. Segre, Fogliano LC/MS analysis and antioxidative efficiency of Maillard reaction products from a lactose-lysine model system, J. Agric. Food Chem. 47 (1999) 1506–1513.
[8] U. Tagami, S. Akashi, T. Mizukoshi, E. Suzuki, K. Hirayama, Structural studies of the Maillard reaction products of a protein using ion trap mass spectrometry, J. Mass Spectrom. 35 (2000) 131–138.
[9] C.M. Utzmann, M.O. Lederer, Independent synthesis of aminophospholipid-linked Maillard products, Carbohydr. Res. 325 (2000) 157–168.
[10] A. Munanairi, S.K. O'Banion, R. Gamble, E. Breuer, A.W. Harris, R.K. Sandwick, The multiple Maillard reactions of ribose and deoxyribose sugars and sugar phosphates, Carbohydr. Res. 342 (2007) 2575–2592.
[11] O. Higuchi, K. Nakagawa, T. Tsuzuki, T. Suzuki, S. Oikawa, T. Miyazawa, Aminophospholipid glycation and its inhibitor screening system: a new role of pyridoxal 5′-phosphate as the inhibitor, J. Lipid Res. 47 (2006) 964–974.
[12] J.A.B. Baptista, R.C.B. Carvalho, Indirect determination of Amadori compounds in milk-based products by HPLC/ELSD/UV as an index of protein deterioration, Food Res. Int. 37 (2004) 739–747.
[13] T.H. Duh, H.L. Wu, C.W. Pan, H.S. Kou, Fluorimetric liquid chromatographic analysis of amantadine in urine and pharmaceutical formulation, J. Chromatogr. A 1088 (2005) 175–181.
[14] B. Narola, A.S. Singh, P.R. Santhakumar, T.G. Chandrashekhar, A validated stability-indicating reverse phase HPLC assay method for the determination of memantine hydrochloride drug substance with UV-detection using precolumn derivatization technique, Anal. Chem. Insights 5 (2010) 37–45.
[15] I.A. Darwisha, A.S. Khedra, H.F. Askala, R.M. Mahmoudb, Simple fluorimetric method for determination of certain antiviral drugs via their oxidation with cerium (IV), Farmaco 60 (2005) 555–562.
[16] Y. Higashi, S. Nakamura, H. Matsumura, Y. Fujii, Simultaneous liquid chromatographic assay of amantadine and its four related compounds in phosphate-buffered saline using 4-fluoro-7-nitro-2,1,3-benzoxadiazole as a fluorescent derivatization reagent, Biomed. Chromatogr. 20 (2006) 423–428.
[17] M. Swartz, M. Emanuele, A. Awad, D. Hartley, Charged aerosol detection in pharmaceutical analysis, an overview, LC GC April (2009).

[18] P.H. Gamache, R.S. McCarthy, S.M. Freeto, D.J. Asa, M.J. Woodcock, K. Laws, R.O. Cole, HPLC analysis of nonvolatile analytes using charged aerosol detection, LC GC February (2005).
[19] M. Pistorino, B.A. Pfeifer, Polyketide analysis using mass spectrometry, evaporative light scattering, and charged aerosol detector systems, Anal. Bioanal. Chem. 390 (2008) 1189–1193.
[20] B.A. Olsen, B.C. Castle, D.P. Myers, Advances in HPLC technology for the determination of drug impurities, Trends Anal. Chem. 25 (2006) 796–805.
[21] L. Wang, W.-S. He, H.-X. Yan, Y. Jiang, K.-S. Bi, P.-F. Tu, Performance evaluation of charged aerosol and evaporative light scattering detection for the determination of ginsenosides, Chromatographia 7 (2009) 603–608.
[22] N. Vervoort, D. Daemen, G. Török, Performance evaluation of evaporative light scattering detection and charged aerosol detection in reversed phase liquid chromatography, J. Chromatogr. A 1189 (2008) 92–100.
[23] K. Takahashi, S. Kinugasa, M. Senda, K. Kimizuka, K. Fukushima, T. Matsumoto, Y. Shibata, J. Christensen, Quantitative comparison of a corona-charged aerosol detector and an evaporative light-scattering detector for the analysis of a synthetic polymer by supercritical fluid chromatography, J. Chromatogr. A 1193 (2008) 151–155.
[24] L. Nováková, S.A. Lopéz, D. Solichová, D. Šatínský, B. Kulichová, A. Horna, P. Solich, Comparison of UV and charged aerosol detection approach in pharmaceutical analysis of statins, Talanta 78 (2009) 834–839.
[25] R. Diaz-Lopez, D. Libong, N. Tsapis, E. Fattal, P. Chaminade, Quantification of pegylated phospholipids decorating polymeric microcapsules of perfluorooctyl bromide by reverse phase HPLC with a charged aerosol detector, J. Pharm. Biomed. Anal. 48 (2008) 702–707.
[26] L. Duan, K. Li, Y. Cheng, X. Ding, Mass balance evaluation for forced degradation of digitoxin using HPLC-CAD, PPD poster, http://www.ppdi.com/resource_library/posters/Mass_Balance_Evaluation.pdf.
[27] S. Inagaki, J.Z. Min, T. Toyo'oka, Direct detection method of oligosaccharides by high-performance liquid chromatography with charged aerosol detection, Biomed. Chromatogr. 21 (2007) 338–342.
[28] A. Błazewicz, Z. Fijałek, M. Warowna-Grześkiewicz, Determination of pancuronium and its impurities in pharmaceutical preparation by LC with charged aerosol detection, Chromatographia 72 (2010) 183–186.
[29] A. Błazewicz, Z. Fijałek, M. Warowna-Grześkiewicz, M. Jadach, Determination of atracurium, cisatracurium and mivacurium with their impurities in pharmaceutical preparations by liquid chromatography with charged aerosol detection, J. Chromatogr. A 1217 (2010) 1266–1272.
[30] U. Holzgrabe, C.J. Nap, S. Almeling, Control of impurities in L-aspartic acid and L-alanine by high-performance liquid chromatography coupled with a corona charged aerosol detector, J. Chromatogr. A 1217 (2010) 294–301.
[31] P.R. Brown, E. Grushka, Advances in Chromatography, vol. 41, Marcel Dekker, New York, 2001.
[32] H.K. Hall Jr., Correlation of the base strengths of amines, J. Am. Chem. Soc. 79 (1959) 5441–5444.
[33] J.F. Dippy, S.R.C. Hughes, A. Rozanski, The dissociation constants of some symmetrically disubstituted succinic acids, J. Am. Chem. Soc. 498 (1959) 2492–2498.
[34] K.W. Goyne, A.R. Zimmerman, B.L. Newalkar, S. Brantley, J. Chorover, Surface charge of variable porosity Al_2O_3 (s) and SiO_2 (s) adsorbents, J. Porous Mater. 9 (2002) 243–256.