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Development and application of a validated HPLC method for the determination of gabapentin and its major degradation impurity in drug products☆

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Abstract

A simple isocratic reversed-phase HPLC method for the determination of gabapentin and its major degradation impurity, 3,3-pentamethylene-4-butyrolactam, was developed and validated for use in the analysis of pharmaceutical tablets and capsules. Separation was achieved on a Brownlee Spheri-5 Cyano column using an acetonitrile–10 mM KH_2PO_4/10 mM K_2HPO_4 (pH 6.2) (8:92, v/v) mobile phase. The compounds were eluted isocratically at a flow rate of 1 mL/min. Both compounds were analyzed with UV detection at 210 nm. The method was validated according to USP Category I requirements for gabapentin and USP Category II for 3,3-pentamethylene-4-butyrolactam. The validation characteristics included accuracy, precision, linearity, range, specificity, limit of quantitation and robustness. Validation acceptance criteria were met in all cases. This method was used successfully for the quality assessment of four gabapentin drug products.
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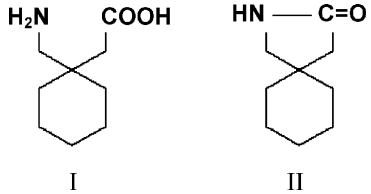
Keywords: Gabapentin; HPLC; Impurity; Degradation; Lactam; Drug products

1. Introduction

Gabapentin [1-(aminomethyl)cyclohexaneacetic acid; structure I] is a γ-aminobutyric acid analog used for treatment of partial seizures in adults and children [1]. It has also been shown to be effective for neuropathic pain [2]. It has a milder side effect profile when compared with older generation anti-epileptics [3]. Gabapentin is structurally related to the neurotransmitter γ-aminobutyric acid (GABA). It was originally designed as a GABA-mimetic agent that freely crosses the blood-brain barrier [4]. Gabapentin has been shown to increase GABA levels in the brain clinically [5]. However, it's mechanism of action is still not clear. Recent articles suggest that gabapentin therapeutic effects are created by an ability to block calcium channels [4] or that gabapentin does in fact mimic the action of GABA on $GABA_B$ receptors [3].

Gabapentin is a white to off-white crystalline solid with a pK_{a1} of 3.7 and a pK_{a2} of 10.7. It is freely soluble in water and in both basic and acidic aqueous solutions [6]. It degrades via intramolecular cyclization to form a γ-lactam: 3,3-pentamethylene-4-butyrolactam (2-azaspiro[4,5]decan-3-one) [lactam, structure II]. This degradation product is a white crystalline solid which melts at approximately 85 °C. By comparison gabapentin's melting point is 165 °C. The lactam has been shown to cause seizures in an animal model [7] focusing greater attention on the need to monitor the lactam degradant in gabapentin pharmaceutical products.



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☆ This scientific contribution is intended to support regulatory policy development. The views presented in this article have not been adopted as regulatory policies by the Food and Drug Administration at this time.

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Various analytical methods for therapeutic monitoring have been reported in the literature for the quantitative determination of gabapentin in human plasma or serum using gas chromatography (GC) [8], capillary electrophoresis (CE) [9], and high-performance liquid chromatography (HPLC) [10–12]. However, all of these methods involve an extraction and derivatization step before quantitative determination of gabapentin. The drawbacks of derivatization are well known and include the possibility of incomplete derivatization, additional chromatographic interferences, increased method complexity, increased costs for additional reagents and increased sample preparation time. Other analytical methods, also used for gabapentin bioanalysis, include tandem techniques such as gas chromatography-mass spectrometry (GC-MS) [13] and liquid chromatography-mass spectrometry (LC–MS) [14,15].

Only a single chromatographic method has been reported in the literature, to date, for the quantitative determination of gabapentin that does not involve a derivatization step or mass spectrometric detection [16]. Even this method was used only for the analysis of gabapentin aqueous solutions, and is only one of two methods which quantitates the lactam [16,17].

Methods for the analysis of gabapentin in pharmaceutical formulations are also quite limited and include spectrofluorometry [18] and colorimetric detection [19], both of which require derivatization, and CE [20]. Only one HPLC method quantitated gabapentin in pharmaceutical formulations but required gabapentin to be derivatized using 2,4,6-trinitrobenzene sulfonic acid, for the analysis of oral suspensions [21].

To the best of our knowledge there are no chromatographic methods in the literature for the analysis of any gabapentin solid dosage form. Hence, an attempt has been made to develop a simple, efficient and selective method for the determination of gabapentin and its major degradation impurity in tablets and capsules. HPLC instrumentation with UV detection, which is readily available in most analytical and pharmaceutical laboratories, was used. In addition, the method requires no extraction or derivatization steps. The total analysis run time is less than 10 min. The method was used successfully to evaluate the potency of four marketed gabapentin drug products as well as the concentration of the lactam degradation impurity.

2. Experimental

2.1. Materials

Gabapentin and lactam certified reference standards were purchased from the United States Pharmacopeia (Rockville, MD). Gabapentin drug substance was purchased from Interchem Corporation (Paramus, NJ). Nylon syringe filters were purchased from Sun SRI (Rockwood, TN). HPLC grade monobasic potassium phosphate and ACS grade phosphoric acid were purchased from Fisher Scientific (Fairlawn, NJ). ACS grade dibasic potassium phosphate was purchased from JT Baker (Philipsburg, NJ). HPLC grade acetonitrile was purchased from Burdick and Jackson (Muskegon, MI). HPLC ready 18 MOhm water was obtained, in-house, from a Milli-Q Gradient A-10 water purification system, Millipore Corp. (Bedford, MA).

2.2. Instrumentation and chromatographic conditions

The HPLC system consisted of a Hewlett Packard 1050 series (Agilent Technologies, Wilmington, DE) equipped with a quaternary pump, online degasser, column heater, autosampler and diode array-detector (DAD). Data collection and analysis were performed using ChemStation software (Agilent Technologies, Wilmington, DE). Separation was achieved on a Brownlee Spheri-5 cyano column 220 × 4.6 mm, 5 μm with a 15 mm × 3.2 mm 7 μm Brownlee cyano guard column (Perkin-Elmer, Shelton, CT). The elution was isocratic with mobile phase of acetonitrile–10 mM KH_2PO_4/10 mM K_2HPO_4 (pH 6.2) (8:92 v/v). The column temperature was maintained at 27 °C. The injection volume was 20 μl with UV detection at 210 nm.

2.3. Preparation of standard solutions

2.3.1. Preparation of gabapentin calibration standards

Gabapentin stock solution I of 10 mg/mL was prepared in water using the USP gabapentin reference standard. Calibration standard solutions at six levels were prepared by serially diluting the stock solution I with the HPLC mobile phase to concentrations of 0.50, 1.00, 2.00., 2.50, 3.75, and 5.00 mg/mL for the analytical range 0.5–5.0 mg/mL.

2.3.2. Preparation of gabapentin quality control standards

Gabapentin stock solution II of 10 mg/mL was prepared in water using the gabapentin reference standard. Quality control (QC) standard solutions were prepared daily by diluting the stock solution II with the HPLC mobile phase for the final QC concentrations of 0.5, 1.5, 2.5, and 5.0 mg/mL. Gabapentin stock solution III of 10 mg/mL was prepared in water using the gabapentin drug substance.

2.3.3. Preparation of lactam calibration standards

Lactam stock solution I of 1 mg/mL was prepared in water using the USP lactam reference standard. Calibration standard solutions at seven levels were prepared by serially diluting the stock solution I with the HPLC mobile phase to concentrations of 2.0, 5.0, 7.5, 10.0, 25.0, 37.5, and 50.0 μg/mL for the analytical range 2–50 μg/mL.

2.3.4. Preparation of lactam quality control standard

Lactam stock solution II of 1 mg/mL was prepared in water using the USP lactam reference standard. Quality control standard solution was prepared by diluting the stock solution II with the HPLC mobile phase to a final concentration of 7.5 μg/mL.

2.4. Sample preparation of the marketed products

2.4.1. Tablets

20 tablets were ground into a fine powder using a glass mortar and pestle. A portion equivalent to about 125 mg of gabapentin was accurately weighed and transferred to a 50 ml volumetric flask. Approximately 40 ml of HPLC mobile phase was added to the flask and the contents were sonicated for 15 min followed by 15 min on a mechanical shaker at 100 rpm. The flask was

adjusted to volume and mixed well. The resulting solution was filtered using a 0.45 μm nylon filter into standard analytical glass vials and injected into the HPLC. Three such samples were prepared from each 20 tablet mixture according to USP criteria and injected twice.

2.4.2. Capsules

20 capsules were weighed and the contents emptied into a glass mortar. The empty capsule shells were weighed to determine the average fill weight in each capsule. The fill material was gently ground using a glass pestle for 1 min to break any aggregated or cemented material. A portion equivalent to 125 mg of gabapentin was weighed accurately and prepared in the same manner as described for the tablets.

2.5. Method validation

The method was validated according to the United States Pharmacopeia requirements. The following validation characteristics were addressed: linearity, range, accuracy, precision, specificity, limit of quantitation and robustness.

2.5.1. System suitability standard

System suitability standard solution which contained 2.5 mg/mL gabapentin and 10 μg/mL lactam was prepared by diluting and mixing the gabapentin and lactam stock solutions with mobile phase. System suitability was determined from six replicate injections of the system suitability standard before sample analysis. The acceptance criteria for gabapentin were less than 2% relative standard deviation (R.S.D.) for peak area, greater than 3000 column plates and peak width at half height of less than 0.25 min. For the lactam acceptance criteria were less than 2% relative standard deviation (R.S.D.) for peak area, greater than 7000 column plates, peak width at half height of less than 0.4 min and resolution between gabapentin and the lactam of at least eight. Resolution was calculated using the following equation:

$$R = 1.18\left[\frac{(t_2 - t_1)}{(W_2 + W_1)}\right]$$

where t_2 and t_1 are the retention times of lactam and gabapentin respectively and W_2 and W_1 are the peak widths at half height. The results were used to monitor critical operational parameters of the chromatographic system to confirm that the resolution and precision were adequate immediately prior to analysis.

2.5.2. Linearity and range

Standard calibration curves were prepared with six calibrators over a concentration range of 0.5–5.0 mg/mL for gabapentin and with seven calibrators over 2–50 μg/mL for the lactam. The data of peak area versus drug concentration were treated by linear least square regression analysis. The standard curves were evaluated for intra-day and inter-day linearity.

2.5.3. Accuracy and precision

Accuracy and precision of the method were determined for the drug substance by analyzing QC standard samples at 4 concentrations of gabapentin (0.5, 1.5, 2.5, and 5.0 mg/mL) and at a single concentration of lactam (7.5 μg/mL). The method precision was established by injecting five standard QC samples at each concentration level for the intra-day precision and on three days for the intermediate precision. Precision was expressed by the %R.S.D. of the analyte peaks. Accuracy was established by evaluating the amount determined from the quality control standards and the lactam and comparing to the respective nominal value expressed as percent recovery. Accuracy of the method was also tested on the drug product at three concentrations with three respective samples. The method of standard additions was utilized. This approach involved the following changes to the procedure in section 2.4: Only 50% of the nominal amount of drug product was placed in the flask. The drug product was then spiked with gabapentin stock solution III and lactam stock solution up to the target concentration. The target concentrations were 2.0, 2.5, and 3.0 mg/mL of gabapentin total and 10, 15, and 20 μg/mL of added lactam, respectively. In addition samples were analyzed containing 50% of the nominal amount of drug product without spiking. Percent recovery was calculated by comparing the known spiked amount of gabapentin or lactam to the amount detected after subtracting the un-spiked (50% product) samples.

2.5.4. Limit of quantitation

The limit of quantitation for gabapentin was calculated as ten times the noise value. The limit of quantitation for the lactam was determined by acceptable accuracy and precision.

2.5.5. Robustness

The robustness of the method was evaluated by analyzing the system suitability standard and evaluating system suitability parameter data after varying, individually, the HPLC pump flow rate (±10%), auto-sampler injector volume (±50%) and column compartment temperature (±4 °C).

2.5.6. Specificity

Specificity of the method was determined by analyzing a sample containing a mixture of the four drug product excipients. Samples containing gabapentin's main degradation product, the lactam, were also injected. In addition gabapentin standards and samples were stressed under individual conditions of 50 °C for 24 h, in 0.1N HCl for 24 h and in 0.1N NaOH for 24 h. All chromatograms were examined to determine if gabapentin and the lactam co-eluted with each other or with any additional degradation or excipient peaks.

3. Results and discussion

3.1. Optimization of HPLC method

Gabapentin is a small, highly polar molecule with an acid pK_a of 3.7 and a base pK_a of 10.7. It can exist in solution as a cation, anion or zwitterion. Thus, it is poorly retained on most reversed-phase HPLC columns. The lactam, on the other hand, is relatively non-polar and exhibits much stronger retention. Therefore, it is difficult to analyze both compounds efficiently

using a simple isocratic system. The optimization goal was to develop a simple chromatographic method for two molecules with very different chemical selectivities with the most efficient analysis time. Typically method development focuses on identifying buffer type and strength, pH and organic modifier and implementing small changes to optimize selectivity and enhance resolution. However, the literature for gabapentin analysis identified a number of HPLC bonded phases previously used, including C18, C8, C4, and phenyl columns [10,14,21,22]. Therefore, we chose to optimize resolution by identifying structural differences between gabapentin and the lactam and utilize those differences to select the appropriate bonded phase. An overview of our method optimization which includes the selection and test results of several columns, with different bonded phases is listed in Table 1.

Initially a C18 column chemistry was selected to exploit the differences in structure and polarity between gabapentin and the lactam to achieve resolution. Ammonium phosphate buffer, pH = 2.5, was used first with methanol as the organic modifier. The initial strategy was correct for optimizing resolution but the C18 column produced long retention times for the lactam. With a relatively high organic content of 27% MeOH the lactam eluted at 71.3 min on a Luna C18 column (2). This may have also been a result of the 5 μ highly uniform spherical particles and most importantly the selectivity of the highly non-polar bonded phase. Selection of a C8 bonded phase column with 5 μ spherical particles using the same conditions resulted in the lactam eluting at 51.1 min. A 10 μ irregular particle phenyl column was chosen to enhance retention of gabapentin and reduce retention of the lactam due to the more moderate non-polar nature of the bonded phase. The excessive resolution between the two compounds was reduced by switching to a column with a larger and less uniform particle size. The column produced a further decrease in analysis time. However, the run time was again prohibitively long at approximately 30 min. The analysis time was decreased to 15 min by reducing the phenyl column length from 300 mm to 150 mm. Still the peak shape was poor for both compounds.

In addition to the analytical column lengths noted above, two shorter columns of 53 and 33 mm in length with modified silica were selected to reduce the analysis time and improve the peak shape. These C18 columns were base deactivated for improved peak shape of basic compounds. Though chromatographic run times were less than 10 min, the gabapentin peak eluted too close to the void volume to be a useful methodology.

Columns with modified C18 phases with enhanced polarity characteristics were selected to optimize efficiency. A C18 column with a polar embedded group designed to give balanced retention of polar and non-polar species was tested. Additionally, a C18 column with hybrid particles of silica and polymer was selected. Both columns yielded relatively long retention times of 16–17 min for the lactam.

In order to better exploit the polarity differences between the gabapentin and the lactam, while maintaining a short run time, two cyano columns were evaluated. Cyano columns are used to exploit their combination of hydrophobic and hydrophilic interactions with amine and amide compounds that have a wide polarity range. Retention of early eluting peaks should be maintained while still allowing for the less polar compounds to elute more quickly. A Phenomenex Luna CN and a Brownlee Spheri-5 were selected and tested, with each eluting the lactam in less than 15 min. When comparing the two cyano columns, the Brownlee cyano generated a shorter run time of 10 min or less. Surprisingly, the Brownlee cyano, although only 220 mm in length, displayed greater selectivity in resolving gabapentin from its early eluting excipient in drug product D which can also be seen in Fig. 1.

In summary, peak symmetry at low pH was poor. Efficiencies were less than 1200 plates for all columns used at pH = 2.5 (Table 1). In addition, gabapentin is most stable in aqueous solutions at approximately pH = 6.0 [16]. The peak shape was improved by switching to a phosphate buffer at pH = 6.2, approximately 2.5 pH units above the pKa_1 and by using acetonitrile as the organic modifier. Use of ternary solvent systems with the organic portion consisting of methanol and

Table 1
Method development

Column	Length × ID (mm) particle size (μ)	Mobile phase	Gabapentin (RT min.)	Lactam (RT min)	Gabapentin plates	Resolution
Phenomenex Luna C18(2)	250 × 4.6, 5 μ spherical	73:27 PO_4 (pH = 2.5):MeOH	7.2	71.3	834	42.8
Beckman Ultrasphere C8	250 × 4.6, 5 μ spherical	73:27 PO_4 (pH = 2.5):MeOH	6.1	51.1	712	34.7
Waters μBondapack Phenyl	300 × 3.9, 10 μ irregular	73:27 PO_4 (pH = 2.5):MeOH	5.2	25.2	1148	20.7
Waters μBondapack Phenyl	150 × 4.6, 10 μ irregular	73:27 PO_4 (pH = 2.5):MeOH	2.7	13.1	525	13.9
Waters X-Terra RP-18 (hybrid, silica/polymer)	100 × 4.6, 5 μ spherical	90:10 PO_4 (pH = 6.9):ACN	1.9	17.8	3080	30.4
Alltech Rocket Platinum EPS C18 (base deactivated, non-acidic silanols)	53 × 7, 3 μ spherical	80:20 PO_4 (pH = 6.9):ACN	2.0	9.0	3242	22.2
Supelco LC-18-DB (base deactivated)	33 × 4.6, 3 μ spherical	82:14:4 PO_4 (pH = 6.9): MeOH:ACN	0.9	9.4	1332	16.7
Phenomenex Synergi Fusion RP (polar embedded C18)	150 × 4.6, 4 μ spherical	64:28:8 PO_4 (pH = 6.9):MeOH:ACN	2.6	16.0	5724	39.6
Phenomenex Luna CN	250 × 4.6, 5 μ spherical	92:8 PO_4 (pH = 6.5): ACN	4.2	10.9	9664	17.9
Brownlee Spheri-5 Cyano	220 × 4.6, 5 μ spherical	92:8 PO_4 (pH = 6.2):ACN	3.9	8.2	7908	16.7

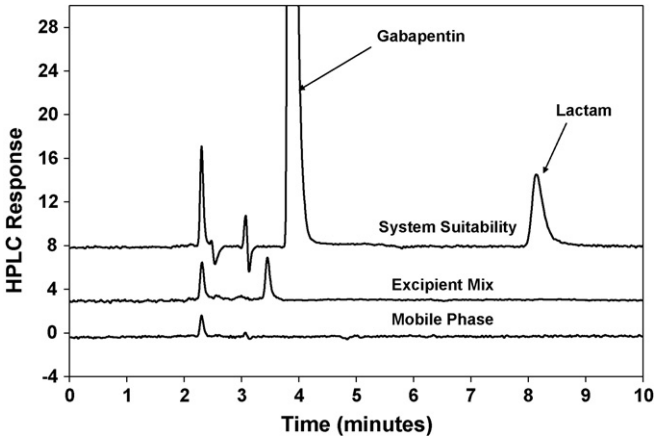

Fig. 1. Chromatography of the mobile phase, excipient mix and system suitability standard.

acetonitrile did not significantly improve the chromatographic method.

3.2. Method validation

The following method validation characteristics were addressed for both gabapentin and lactam: accuracy, precision, specificity, limit of quantitation, limit of detection, linearity, range, and robustness. Therefore, the method validation for gabapentin meets the requirements for USP Category I and the method validation for the lactam meets the acceptance criteria for USP Category II.

3.2.1. System suitability

The system suitability test ensures the validity of the analytical procedure as well as confirms the resolution between different peaks of interest. All critical parameters tested met the acceptance criteria on all days. Adequate resolution of >8 between the gabapentin and the lactam peaks ensured the specificity of the method to analyze both compounds.

3.2.2. Linearity and range

Linearity of the method was confirmed by preparing standard curves for the analytical range of 0.5–5.0 mg/mL for Gabapentin and 2.0–50 μg/mL lactam. The analytical range is 20–200% w/w for gabapentin and 0.08–2.0% (w/w) for lactam. The results, summarized in Tables 2 and 3, show an excellent correlation between analyte peak area and concentration of the drug and lactam within the analytical range with $r^2 \geq 0.9999$.

Table 2
Parameters and linearity data of gabapentin calibration curves

Standard curve	Analytical range (mg/mL)	Calibrators	Slope	*y*-intercept	R^2 value
Validation 1	0.5–5.0	6	508.7	11.10	0.9999
Validation 2	0.5–5.0	6	508.02	10.86	0.9999
Validation 3	0.5–5.0	6	507.72	11.30	0.9999

Table 3
Parameters and linearity data of lactam calibration curves

Standard curve	Analytical range (μg/mL)	Calibrators	Slope	*y*-intercept	R^2 value
Validation 1	2.0–50	7	10.135	−0.1509	1.0000
Validation 2	2.0–50	7	10.413	−3.744	0.9999
Validation 3	2.0–50	7	10.148	−2.870	0.9999

Table 4
Gabapentin accuracy: drug substance ($n = 5$)

	Solutions			
	0.5 mg/mL	1.5 mg/mL	2.5 mg/mL	5.0 mg/mL
Validation set 1	98.0	100.0	99.6	98.2
Validation set 2	97.2	98.7	98.8	97.4
Validation set 3	97.8	99.8	99.2	97.8

Table 5
Lactam accuracy: drug substance (% recovery, $n = 5$)

	Solutions			
	2.0 μg/mL	7.5 μg/mL	25 μg/mL	50 μg/mL
Validation set 1	96.5	94.4	97.9	100.8
Validation set 2	110.1	102.1	99.2	99.9
Validation set 3	105.8	98.3	98.4	97.5

Table 6
Gabapentin precision: drug substance (% R.S.D., $n = 5$)

	Solutions			
	0.5 mg/mL	1.5 mg/mL	2.5 mg/mL	5.0 mg/mL
Validation set 1	1.26	1.02	0.86	0.43
Validation set 2	1.18	0.61	0.55	0.27
Validation set 3	0.19	0.83	0.55	0.23
Intermediate	1.07	0.93	0.79	0.48

3.2.3. Accuracy and precision

Accuracy and precision was established across the analytical range for gabapentin and the lactam. The intra- and inter day accuracy and precision were calculated from the QC samples for gabapentin and the lactam. Results for the intra-day accuracy are summarized in Tables 4 and 5 for the gabapentin and lactam, respectively. Results for the intra- and inter day precision of gabapentin and lactam are summarized in Tables 6 and 7, respectively.

The accuracy results for gabapentin in all drug products showed good recovery and are summarized in Table 8. Results

Table 7
Lactam precision: drug substance (% R.S.D., $n = 5$)

	Solutions			
	2.0 μg/mL	7.5 μg/mL	25 μg/mL	50 μg/mL
Validation set 1	2.82	2.54	0.60	0.36
Validation set 2	2.33	0.93	0.90	0.63
Validation set 3	2.94	0.98	0.34	0.83
Intermediate	3.11	3.19	1.53	1.21

Table 8
Gabapentin accuracy: drug product (% recovery, $n = 3$)

Product	50% Product spiked to		
	2.0 mg/mL	2.5 mg/mL	3.0 mg/mL
A-capsule	97.7	98.1	97.8
B-capsule	103.8	102.3	102.4
C-tablet	98.3	98.7	98.4
D-tablet	100.8	102.2	101.9

Table 9
Lactam accuracy: drug product (% recovery, $n = 3$)

Product	50% Product spiked to		
	10 μg/mL	15 μg/mL	20 μg/mL
A-capsule	99.6	99.9	100.7
B-capsule	96.0	98.0	97.8
C-tablet	96.2	98.6	97.6
D-tablet	96.3	98.7	100.0

for the accuracy of gabapentin tested in drug products A, B, C, and D at three concentration levels by the technique of standard addition ranged from 97.7 to 98.1% for capsule drug product A and 100.8 to 101.9% for tablet drug product D. The recovery was $100 \pm 5\%$ for all samples.

The accuracy results for the lactam in all gabapentin drug products showed good recovery and are listed in Table 9. Results for the accuracy of the lactam tested in drug products A, B, C, and D at three concentration levels by the technique of standard addition ranged from 99.6 to 100.7% for capsule drug product A and 96.3 to 100.0% for tablet drug product D. The recovery was $100 \pm 5\%$ for all samples.

3.2.4. Limit of quantitation

The limit of quantitation of lactam is 2 μg/mL determined by acceptable accuracy and precision at this concentration. The analytical range for gabapentin used in this method is much higher than the limit of quantitation attainable. Therefore, an estimate of the limit of quantitation based on 10× S/N is 0.018 mg/mL. An estimate of the limit of detection based on 3× S/N is 0.005 mg/mL for gabapentin and 0.7 μg/mL for lactam. The greater sensitivity for lactam detection is due to its ultraviolet absorptivity at 210 nm which is approximately one order of magnitude greater than gabapentin.

3.2.5. Robustness

To ensure the insensitivity of the HPLC method to minor changes in the experimental conditions it is important to demonstrate robustness of the method. None of the alterations caused a significant change in resolution between gabapentin and lactam, peak area R.S.D., USP tailing factor, peak width or theoretical plates.

3.2.6. Specificity

A sample chromatogram containing a mixture of excipients from the four drug products is shown in Fig. 1. Only 1 peak was present beyond the void volume and this was resolved from the gabapentin and the lactam peaks. No co-eluting peaks were generated from stress conditions of heat, acid or base. In addition, resolution between gabapentin and the lactam was always greater than eight. Due to the absence of any co-eluting peaks in any of the samples or from any of the stress conditions we determined this method to be specific for gabapentin and the lactam.

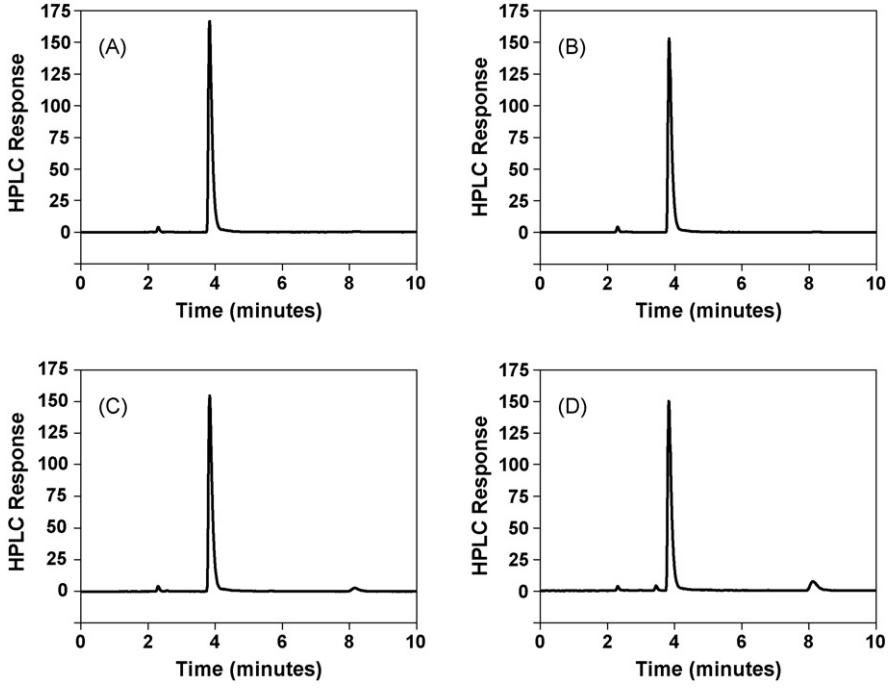

Fig. 2. Chromatography of commercially available gabapentin drug products A, B, C, and D.

Table 10
HPLC results of pharmaceutical formulations of gabapentin

Formulation	Dose strength	Gabapentin potency	Lactam concentration
A-capsule	300	99.6	BQL
B-capsule	300	99.9	BQL
C-tablet	600	98.4	0.16%
D-tablet	600	99.5	0.49%

3.3. Analysis of the marketed products

The validated method was used in the analysis of four gabapentin drug products. These included drug products from three different manufacturers, as two different dosage forms (capsules and tablets), and two different dose strengths (300 and 600 mg). Representative chromatograms are shown in Fig. 2. Results for gabapentin potency and concentration of lactam in each product are summarized in Table 10. All products had a potency of >98%. The amount of lactam was <0.2% in drug product A, B, and C but was 0.49% in drug product D. It is important to note that capsule drug products A and B with the lower dose strength of 300 mg of gabapentin drug substance had lactam levels below the quantitative limit (BQL) of 0.08% while the tablet drug products C and D with the 600 mg dose strength had significantly higher lactam levels.

4. Conclusion

A simple and efficient reverse-phase HPLC method was found to be accurate, precise, and linear across the analytical range. The method was specific for the determination of gabapentin and its primary degradation impurity in pharmaceutical formulations. The method may be used to assess the quality of various gabapentin dosage forms by assaying for potency and accurately monitoring the lactam degradation impurity.

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