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ScienceDirect
Journal of Pharmaceutical and Biomedical Analysis 46 (2008) 181–186
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Short communication

Development and application of a validated HPLC method for the analysis of dissolution samples of gabapentin drug products☆

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Received 10 April 2007; received in revised form 19 July 2007; accepted 28 August 2007
Available online 1 September 2007

Abstract

A simple isocratic reversed-phase HPLC method was developed and validated for the analysis of dissolution samples of gabapentin tablets and capsules. Separation of gabapentin from its major degradation impurity, 3,3-pentamethylene-4-butyrolactam was achieved on a Phenomenex Luna Cyano column using a methanol–acetonitrile–20 mM KH_2PO_4 (pH 2.2) (5:5:90, v/v/v) mobile phase. The compounds were eluted isocratically at a flow rate of 1.25 mL/min. Both compounds were analyzed with UV detection at 210 nm. The method was validated according to USP Category I requirements for gabapentin. The validation characteristics included accuracy, precision, linearity, range, specificity and limit of quantitation. Robustness testing was also conducted to evaluate the effect of minor changes to the chromatographic system and to establish appropriate system suitability parameters. Validation acceptance criteria were met in all cases. This method was used successfully for the quality assessment of five gabapentin drug products.
Published by Elsevier B.V.

Keywords: Gabapentin; HPLC; Impurity; Lactam; Drug products; Dissolution

1. Introduction

Gabapentin [1-(aminomethyl)cyclohexaneacetic acid; structure I] is a γ-aminobutyric acid (GABA) analog used for treatment of partial seizures in adults and children [1]. It has also been shown to be effective for neuropathic pain [2]. Gabapentin increases GABA levels in the brain clinically [3]. However, its mechanism of action is still not clear. It had been suggested that gabapentin may bind to an undefined receptor or binding site in the brain [4]. More recently it has been proposed that gabapentin inhibits calcium influx by inhibiting calcium channels in presynaptic terminals [5]. Gabapentin is rapidly absorbed following oral dosing. The T_{max} is approximately 2–3 h and the plasma half-life is between 5 and 7 h [1]. Gabapentin, whose protein binding is <3%, is eliminated by renal excretion without significant metabolism [1].

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 [lactam, structure II].

I II

Various analytical methods for therapeutic monitoring have been reported in the literature for the quantitative determination of gabapentin in human plasma or serum [7–15]. Methods for the analysis of gabapentin in pharmaceutical formulations are quite limited and typically involve a derivatization step [16–19]. The

☆ 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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0731-7085/$ – see front matter. Published by Elsevier B.V.
doi:10.1016/j.jpba.2007.08.023

authors had earlier reported a novel method for the determination of gabapentin and its major degradation impurity in tablets and capsules which did not require derivatization [20].

To the best of our knowledge there is only one reference for the analysis of gabapentin dissolution samples. No details for this HPLC method are given except for detector wavelength [21]. Hence, an attempt has been made to develop a simple, efficient and selective method for the analysis of the dissolution samples of gabapentin tablets and capsules. The method requires no extraction or derivatization steps. HPLC instrumentation with UV detection, which is readily available in most analytical and pharmaceutical laboratories, was used. A total analysis run time of less than 10 min was achieved. The method was used successfully to evaluate the dissolution profiles of five marketed gabapentin drug products.

2. Experimental

2.1. Materials

Gabapentin and 3,3-pentamethylene-4-butyrolactam (lactam) certified reference standards were purchased from the United States Pharmacopeia (Rockville, MD, USA). Gabapentin drug substance was purchased from Interchem Corporation (Paramus, NJ, USA). Nylon syringe filters were purchased from Millipore Corp. (Bedford, MA, USA). HPLC grade monobasic potassium phosphate (KH_2PO_4), ACS grade phosphoric acid and ACS grade hydrochloric acid (HCl) were purchased from Fisher Scientific (Fairlawn, NJ, USA). HPLC grade acetonitrile and methanol were purchased from Burdick and Jackson (Muskegon, MI, USA). HPLC ready deionized 18 MΩ water was obtained, in-house, from a Milli-Q Gradient A-10 water purification system, Millipore Corp., (Bedford, MA).

2.2. Dissolution

A calibrated dissolution apparatus (USP II) was used with paddles at 50 rpm and bath temperature maintained at 37 ± 1 °C. Nine hundred millilitre freshly prepared and degassed 0.06N HCl solution was used as the dissolution medium.

Six tablets/capsules were evaluated for each drug product tested. Dissolution samples were collected at 5, 10, 20 and 30 min for the capsule drug products and at 10, 20, 30 and 45 min for the tablet drug products [22]. At each time point, a 5 mL sample was removed from each vessel using an auto-sampler and filtered through a nylon filter (0.45 μm, 25 mm) into labeled glass tubes and analyzed by HPLC.

The amount of gabapentin in the test samples was calculated, as percentage dissolved, from the measured peak area for the test samples and compared it with the peak area for the standard gabapentin solution using the following equation:

$$\text{Dissolved}\,(\%) = \frac{900}{\text{Drug Load}} \times \frac{\text{Peak Area (sample)}}{\text{Peak Area (standard)}} \times \text{Concentration (standard)} \times 100$$

where drug load is 600 or 800 for the tablets and 300 for the capsules.

2.3. Instrumentation and chromatographic conditions

The HPLC system consisted of a Hewlett Packard 1050 series (Agilent Technologies, Wilmington, DE, USA) 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). Separation was achieved on a Phenomenex Luna cyano column 250 mm × 4.6 mm, 5 μm fitted with a 4.0 mm × 3.0 mm, Phenomenex cyano security guard cartridge (Phenomenex, Torrance, CA, USA). The elution was isocratic at 1.25 mL/min with a mobile phase of methanol–acetonitrile–20mM KH_2PO_4 (pH 2.2) (5:5:90, v/v/v). The column temperature was maintained at 26 °C. The injection volume was 40 μL with UV detection at 210 nm.

2.4. Preparation of standard solutions

2.4.1. Preparation of gabapentin calibration standards

Gabapentin stock solution I of 5 mg/mL was prepared in water using the USP gabapentin reference standard. Calibration standard solutions at eight levels were prepared daily by diluting the stock solution I to concentrations of 0.05, 0.10, 0.15, 0.20, 0.25, 0.35, 0.50 and 0.65 mg/mL.

2.4.2. Preparation of gabapentin quality control standards

Gabapentin stock solution II of 5 mg/mL was prepared in water using the gabapentin reference standard. Quality control (QC) standard solutions were prepared by diluting the stock solution II for the final QC concentrations of 0.06, 0.16, 0.24, 0.44 and 0.64 mg/mL. Gabapentin stock solution III of 5 mg/mL was prepared in water using the gabapentin drug substance.

2.4.3. Preparation of lactam standard

Lactam stock solution I of 1 mg/mL was prepared in water using the USP lactam reference standard.

2.5. Method validation

The method was validated according to the United States Pharmacopeia Category I 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 0.4 mg/mL gabapentin and 4 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 were less than 2% relative standard deviation (R.S.D.) for peak area, greater than 6000 column plates, USP tailing factor less than 2.0 and resolution