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ORIGINAL ARTICLE

Utilization of bromination reactions for the determination of carbamazepine using bromate–bromide mixture as a green brominating agent

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Abstract One titrimetric and two spectrophotometric procedures have been developed for the assay of carbamazepine (CBZ) in bulk drug, formulations and spiked human urine. The methods are based on the bromination of CBZ by the bromine generated *in situ* by the action of the acid on the bromate–bromide mixture. The twin advantages of avoiding liquid bromine and analysis in a cost-effective manner are realized. In titrimetry, the drug was treated with a known excess of bromate–bromide mixture in hydrochloric acid medium followed by the determination of unreacted bromine iodometrically. Spectrophotometry involves the addition of a measured excess of bromate–bromide reagent in acid medium to CBZ, and after the reaction is ensured to be complete, the residual bromine was determined by reacting with a fixed amount of either methyl orange and measuring the absorbance at 510 nm (method A) or indigo carmine and measuring the absorbance at 610 nm (method B). Titrimetric procedure is applicable over the range of 1.00–7.50 mg CBZ, and the calculations are based on a 1:1 reaction stoichiometry (CBZ:$KBrO_3$). In spectrophotometric methods, Beer's law is valid within concentration ranges of 0.25–1.50 and 0.50–6.00 μg ml^{-1} CBZ for methods A and B, respectively. The proposed methods were successfully applied to the determination of CBZ in tablets and syrup, in addition to spiked human urine by the spectrophotometric methods, with mean recoveries of 95.50–104.0% and the results were statistically compared with those of an official method by applying Student's *t*-test and *F*-test.

1. Introduction

Carbamazepine (CBZ), chemically known as 5H-dibenz-[b,f]-azepine-5-carboxamide (Merck Index, 2006), is an anticonvulsant and mood stabilizing drug used primarily in the treatment of epilepsy and bipolar disorder, as well as trigeminal neuralgia. The drug is official in the British Pharmacopoeia (1973) which describes a UV-spectrophotometric method for its assay in tablets. Since its introduction into clinical medicine in the mid-1960s, literature on the methods for the determination of CBZ in biological

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materials is vast (> 120 published articles). In contrast, a limited number of techniques have been reported for the assay of CBZ in pharmaceutical dosage forms and include HPLC (Panchagnula et al., 1998; Tatar Ulu, 2006; Demirkaya and Kadioglu, 2005, 2008; Yuan et al., 2003), LC (Predrag et al., 2009; Walker, 1988), GC (Kadioglu and Demirkaya, 2007; Liu et al., 1991), flow injection-spectrophotometry (Çomoğlu et al., 2006), FI-spectrofluorimetry (Huang et al., 2002), chemiluminescence (CL) (Lee et al., 2003), FI-CL (Xiong et al., 2009), electrolysis-fluorescence (Pan and Yao, 1998), polarography (Pachecka and Giovanoli, 1982), UV-spectrophotometry (Tatar Ulu, 2006; Demirkaya and Kadioglu, 2008) and visible spectrophotometry (Rao and Murty, 1982; Agrawal et al., 1989). All these methods are reviewed in Tables 1 and 2.

In spite of the suitability of the proposed methods, many require expensive instruments or materials such as chromatographic, flow injection and chemiluminescence techniques. Besides, chromatographic methods (Panchagnula et al., 1998; Tatar Ulu, 2006; Yuan et al., 2003; Predrag et al., 2009; Walker, 1988; Kadioglu and Demirkaya, 2007; Liu et al., 1991) need a suitable compound as internal standard, which makes the procedure more complex. Visible spectrophotometry, because of its simplicity and cost effectiveness, sensitivity and selectivity, fair accuracy, precision and easy access in most quality control laboratories, has remained competitive in an area of chromatographic techniques for pharmaceutical analysis.

To the best of our knowledge, no titrimetric method has ever been reported and there are only two reports on the use of visible spectrophotometry for the determination of CBZ in pharmaceuticals. The first report (Rao and Murty, 1982) is based on the oxidation of CBZ with sodium metaperiodate in acidic medium after heating for 1 h, extraction of the chromogen into *n*-butanol before measuring the absorbance at 410 nm. The second method (Agrawal et al., 1989) is based on the reaction of amide group in CBZ with hydroxylammonium chloride–NaOH under hot conditions, followed by reaction with ferric chloride in HCl medium and measuring the absorbance at 510 nm. The visible spectrophotometric methods currently available (Rao and Murty, 1982; Agrawal et al., 1989) involve extraction or heating step and their sensitivity is poor.

The scientific references found in the CAS and SCI database, relating to green analytical chemistry or environmental-friendly analytical methods have been growing significantly in recent years (Armenta et al., 2008). The recent development of new analytical methods with good characteristics such as selectivity and sensitivity is not sufficient; modern analytical methods need to be green (Sharma et al., 2003; Vidotti et al., 2004). Hence, the purpose of this study was to develop three new methods for the determination of CBZ based on bromination of CBZ by a green brominating agent (i.e. bromine-generated *in situ*). The methods employ titrimetric and spectrophotometric techniques, and use bromate–bromide mixture, methyl orange (MO) and indigo carmine (IC) as reagents. The proposed methods have the advantage of accuracy and precision besides being free from interference from common tablet excipients.

2. Experimental

2.1. Apparatus

All the absorbance spectral measurements were made using a Systronics model 106 digital spectrophotometer equipped with 1 cm matched quartz cells.

2.2. Materials and reagents

Pharmaceutical grade carbamazepine (CBZ) was received from Jubilant Organosys Ltd., Mysore, India, as a gift and used as received. All pharmaceutical preparations were obtained from commercial sources in the local market. All reagents and chemicals used were of analytical reagent grade and distilled water was used throughout the study.

A standard stock solution of bromate–bromide mixture equivalent to 5 mM $KBrO_3$ and 10-fold molar excess of KBr was prepared by dissolving accurately weighed 0.209 g of potassium bromate (s.d. fine-chem Ltd., Mumbai, India) and 1.488 g of potassium bromide (Merck, Mumbai, India) in water and diluting to volume in a 250 ml calibrated flask, and used in titrimetric method. Another stock standard solution of $KBrO_3$–KBr equivalent to 200 μg ml^{-1} $KBrO_3$

Table 1 Chromatographic methods reported for the determination of CBZ in pharmaceuticals.

Technique	Chromatographic conditions			LOD (μg ml^{-1})	Rang (μg ml^{-1})	References
	Mobile phase	Flow rate (ml min^{-1})	Detection			
HPLC	0.01 M potassium phosphate buffer of pH 7/acetonitrile/methanol (11:5:3)	1.0	At 214 nm	0.100		Panchagnula et al. (1998)
HPLC	Acetonitrile:water (75:25, v/v)	1.0	At 285 nm	0.055	0.2–2.0	Tatar Ulu (2006)
HPLC	Acetonitrile–Milli-Q grade water (30:70, v/v)	1.0	UV at 220 nm	0.05	0.25–25	Demirkaya and Kadioglu (2005)
HPLC	(28:72, v/v) acetonitrile:0.02 M sodium phosphate buffer (pH 7.8)	1.0	UV at 230 nm	0.018	5.0–25.0	Yuan et al. (2003)
HPLC–DAD	Acetonitrile–Milli-Q grade water (30:70, v/v)	1.0	At 220 nm	0.05	0.25–25	Demirkaya and Kadioglu (2008)
LC	(50:50, v/v) methanol–10 mM ammonium acetate buffer, pH adjusted to 2.21 with glacial acetic acid	1.5	UV at 260 nm	0.0125	100–500	Predrag et al. (2009)
LC	THF–methanol–water (8:37:55)	1.0	At 254 nm		0.2–1.7	Walker (1988)
GC			FID		2–30	Kadioglu and Demirkaya (2007)
GC	Carrier gas is nitrogen	20	FID			Liu et al. (1991)