

## A Review of Analytical Methods on Carbamazepine an Antiepileptic Drug

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**ABSTRACT:** Carbamazepine is used to control and treat bipolar 1 disorder's acute manic and mixed episodes, trigeminal neuralgia, and epilepsy. Generalized tonic seizures (grand mal), mixed seizure patterns, and partial seizures with complicated symptomatology (psychomotor, temporal lobe) are the only indications for epilepsy. Trigeminal neuralgia or tic douloureux are first-line conditions for which carbamazepine is FDA-recommended. In individuals with acute manic or mixed episodes of bipolar 1 mania, a comprehensive evaluation demonstrates the effectiveness of carbamazepine extended release. Carbamazepine is contraindicated in patients with bone marrow depression and hypersensitivity to this drug or tricyclic compounds such as amitriptyline. Dizziness, sleepiness, ataxia, nausea, and vomiting are some of the most typical adverse effects of carbamazepine. With the ability to penetrate the placenta and pass through breast milk in nursing infants, carbamazepine necessitates a choice between stopping the medication in the mother or stopping nursing. Different analytical techniques developed and validated as per ICH guidelines for the determination of carbamazepine, including High performance liquid chromatography (HPLC), Ultra performance liquid chromatography (UPLC), mass spectrometric, Liquid chromatography-Mass spectroscopy (LC-MS), and UV-Spectrophotometry has been explained in this article as it is important to analyze the drug content and % purity in bulk and Pharmaceutical formulations for quality control purpose.

**KEYWORDS:** Seizure, UV-Spectrophotometric methods, HPLC, UPLC, ICH.

### INTRODUCTION

Carbamazepine, is chemically 5H dibenzo (b, f) azepine-5-carboxamide (fig. 1) an antiepileptic medication used for treating psychomotor and grand mal epilepsy. It is regarded as one of the most important medications for treating trigeminal neuralgia-related pain<sup>[1-2]</sup>. It is iminostilbene derivative with a carbamoyl group in the fifth position; this moiety is necessary for the compound's powerful antiseizure action<sup>[3-4]</sup>. It is a white or nearly white, crystalline powder that is sparingly soluble in acetone and alcohol and essentially insoluble in ether. It is easily soluble in methylene chloride and practically insoluble in water. Carbamazepine is recognized by IP, USP, BP, and other organizations<sup>[5]</sup>. Different analytical techniques developed and validated as per ICH guidelines for the determination of carbamazepine, including High performance liquid chromatography (HPLC), Ultra performance liquid chromatography (UPLC), mass spectrometric, Liquid chromatography-Mass spectroscopy (LC-MS), and UV-Spectrophotometry has been presented in this article for researchers.

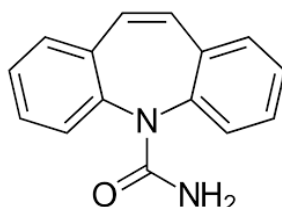


Fig. 1- Chemical structure of Carbamazepine.

### UV-SPECTROSCOPIC METHODS

Several UV spectroscopic methods have been used to determine the presence of carbamazepine alone or in combination with other medication are as follows.



**KHARDE et al,<sup>[10]</sup> 2020:** A UV spectroscopic method for measuring carbamazepine was created and verified. Carbamazepine was discovered to have a maximum wavelength of 246 nm. When the drug's concentration was between 2 and 12  $\mu\text{g}/\text{mL}$ , it follows Beer's Law, with a regression coefficient of 0.9992 at 284 nm. The total recovery was found to range from 99.06 to 99.60%, demonstrating that the technique was free from interference from contaminants and other excipients included in the formulation. The method's precision and reproducibility were indicated by the low value of % RSD. The % RSD for intra-day and inter-day precision was determined to be 0.56 to 1.82 & 0.36 to 0.59 correspondingly, which is  $< 2\%$ , proving that the procedure is precise. The analysis findings have been confirmed in accordance with the ICH guidelines. Both tablet dosage form and bulk dose form of carbamazepine can be routinely analyzed using the established approach.

**MANOJ P et al,<sup>[11]</sup> 2015:** By sonicating 50 mg of carbamazepine (CBZ) in 30 ml of methanol for 10 minutes, the standard stock solution was created. Methanol was then used to increase the volume to 50 mL. A variety of concentrations ranging from 8 to 18  $\mu\text{g}/\text{ml}$  were prepared by diluting various aliquots from the standard stock solution (1000  $\mu\text{g}/\text{ml}$ ) with distilled water separately. In the 400–200 nm range, pure water was used as a blank and the standard CBZ solution (10  $\mu\text{g}/\text{mL}$ ) as a test sample. Figure 2 shows that the solution's maximum wavelength is 284 nm. Using distilled water as a blank, the absorbance of each solution was measured at 284 nm. By graphing absorbance versus CBZ concentration ( $\mu\text{g}/\text{mL}$ ), the calibration curve was created.

**NITYANAND ZADBUKE et al,<sup>[12]</sup> 2015:** To create and validate a spectrophotometric method for the quantitative determination of carbamazepine in a pharmaceutical formulation that is easy to use, accurate, quick, precise, reproducible, and affordable. The new UV spectrophotometric approach uses methanol as a solvent to assess absorption at maximum wavelength 284 nm for the quantitative quantification of carbamazepine. The carbamazepine stock solution was created, and then an appropriate dilution in distilled water was created to create the standard curve. The carbamazepine standard solution has absorption maxima at 284 nm. In the concentration range of 2–14  $\mu\text{g}/\text{mL}$ , the drug followed Beer's law, with a regression coefficient of 0.9997 at 284 nm. The overall recovery rate was 99.99%, indicating that the procedure was free from influence from the other excipients and contaminants utilized during formulation. The method reproducibility were indicated by the low percentage RSD value. The percentage RSD for intra-day and inter-day precision was determined to be 0.1568 and 0.1746, respectively, which is  $< 2\%$ , proving the precision of the approach. According to ICH (International Conference on Harmonization) standards, the analyses' findings have been validated. Both tablet dosage form and bulk dose form of carbamazepine can be routinely analyzed using the established approach.

**SURINI et al,<sup>[13]</sup>2019:** By employing polyvinyl alcohol as a stabilizer during the solvent evaporation process, carbamazepine was enclosed in ethyl cellulose microparticles. CBZ was first dissolved in methanol, and then it was diluted with distilled water. To validate and guarantee the efficacy of this method, the CBZ medication, excipients, and microparticles underwent tests for specificity, solution stability, linearity, precision, and accuracy. In the targeted wavelength range of 286 nm, the results showed no excipient interference. With an  $R^2$  value of 0.9992, it showed linearity between 2 and 12  $\mu\text{g}/\text{mL}$ . 24 hours of CBZ solution stability. Precision and accuracy fell within acceptable bounds ( $100 \pm 2\%$ ). Every result met the requirements of the ICH-Q2 standard.

**A PADMA et al,<sup>[14]</sup>2019:** Distilled water was used as the solvent because carbamazepine in it produced a single identifiable peak with strong absorbance in the UV spectrum that could be seen. For the bulk medication, 284nm was discovered to be the wavelength of maximum absorbance (max). In the 2-12  $\mu\text{g}/\text{mL}$  range, carbamazepine displayed excellent linearity. 0.999 was found to be the correlation coefficient.

## HPLC METHODS

**Dural et al,<sup>[15]</sup>2019:** This HPLC approach, which was created and verified for CBZ quantify analysis, was easy, quick, and reliable. The method's precision and accuracy test results, which were RSD% 4.2 and RE% values between (-5.6) and 3.6, respectively, demonstrated good repeatability. Simple, quick sample extraction produced reliable recovery values between 82.4% and 105.7%. This method was perfect for quantifying carbamazepine in human plasma due to the ease of sample preparation, quick analysis time (6 min), and excellent sensitivity.

**Essam Ezzeldin et al,<sup>[16]</sup>2013:** High performance liquid chromatography (HPLC) with ultraviolet absorbance detection (UV) was used to create an easy method for determining the presence of carbamazepine. Protein precipitation and liquid-liquid



extraction are the two phases in the procedure. As the internal standard (is), diclofenac sodium was employed. An analytical thermo C8 (250 x 4.6 mm), 5 m column with a mobile phase made up of acetonitrile, isopropyl alcohol, and phosphate buffer pH: 3 (36:15:49) was used for the separation. There was a 1.2 mL/min flow rate. The eluent was observed at 220 nm with a sensitivity setting of 0.05 absorbance units. For concentrations ranging from 0.1 to 8.0 g mL<sup>-1</sup>, linear detection response was achieved. The limit of quantitation was 0.1 g mL<sup>-1</sup>. The suggested HPLC approach is straightforward, quick, and extremely sensitive, and it may be trustworthy for pharmacokinetic investigations in people. The method was successfully verified for the determination of carbamazepine.

**K. JOHNSTON AND G.H. LESTER et al,<sup>[17]</sup>1979:** The determination of plasma carbamazepine levels. In order to extract the protein, acetonitrile containing the internal standard N-acetyltryptophan ethyl ester was added. Reverse-phase high-pressure liquid chromatography was used for separation, with an acetonitrile : water mobile phase. and 280 nm UV absorption is used for detection. Rt was less than 7 min. According to preliminary findings, the within-batch and between-batch coefficients of variance were both under 2%. with a 97% average recovery. The approach is unaffected by other popular anticonvulsant medications.

## OTHER ANALYTICAL METHODS

**Marta De-Diego et al,<sup>[18]</sup>2022:**Anticonvulsant medication carbamazepine is primarily used to treat epilepsy. For the purpose of determining the presence of CBZ in saliva, a quick and easy liquid chromatographic technique with UV detection was created and validated. With an RP-18 column containing acetonitrile and water with triethylamine at pH 7,3 as the mobile phase in isocratic elution mode, chromatographic separation was accomplished at a flow rate of 1 mL/min. Bromazepam at a concentration of 1.5 g/mL was utilized as the IS for the 230 nm detection. The show lasted five minutes. Over a range of 0.5 - 5.5µg/mL, the reported technique was linear. The intraday and interday precision, expressed as the RSD, i.e., 0.69 and 0.72 respectively. The extraction recoveries were between 100.67 and 100.69%, and the assay showed sufficient selectivity and specificity. The LOQ is below the therapeutic level, indicating that the procedure is sensitive enough. The findings demonstrated that the suggested method was successful in quantifying CBZ in saliva.

**DEMIRKAYA, KADIOGLU et al,<sup>[19]</sup>2005:** In addition to being used as an anticonvulsant, carbamazepine (CBZ) also has antiepileptic, antidepressive, antianalgesic and antimanic properties. In the current work, a reversed-phase (RP)-HPLC technique for the quantitative determination of CBZ in pure forms and in pharmaceutical preparations was devised. The International Conference on Harmonization Guidelines were followed while studying parameters like linearity, precision, accuracy, specificity, stability, limit of detection, and limit of quantitation. Testing was done on multiple analytical columns that had different stationary phases. Bondolone C18 column (150 x 3.9 mm, 5 m) was used to obtain good separation. A mobile phase of acetonitrile-Milli-Q grade water (30:70 v/v) injected at a flow rate of 1 ml/min was used for RP-HPLC. The peak detection was done at 220 nm, and the injection volume was 10µl. The range of 0.25 to 25 g ml<sup>-1</sup> obeyed linearity. CBZ in pharmaceutical formulations was successfully measured using the described approach. This technique is appropriate for routine analysis of pharmaceuticals made for sale. The proposed method was validated for various parameters such as linearity and range, accuracy, sensitivity and specificity according to ICH Q2 (R1) guideline and USP guidelines.<sup>[20-21]</sup>

## CONCLUSION

In this review article, several analytical techniques, including High performance liquid chromatography, Ultra performance liquid chromatography, Mass spectroscopy, liquid chromatography-Mass spectroscopy, and UV Spectrophotometric methods, have been discussed for the estimation of carbamazepine.

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