Review Article: A Review of HPLC Methods Developed for Quantitative Analysis of Carbamazepine in Plasma Samples

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ABSTRACT

The present review aims to examine the use of carbamazepine (CBZ) in plasma based on various techniques, such as high-performance liquid chromatography (HPLC) and chromatographic analysis. The review considered in this research is narrative, which is based on previous studies. The effects of CBZ in treating seizures and epilepsy are investigated comprehensively. Accordingly, the related studies regarding the effects of CBZ in plasma based on HPLC were investigated in detail. Due to the findings given in the previous studies, it was revealed that the effects of CBZ are positive and negative for people's health. Due to the obtained results, micellar electro-kinetic chromatography (MEKC) is used for specifying CBZ. Furthermore, the benefits of single reference HPLC are well documented in the literature for therapeutic drug monitoring (TDM) of phenytoin (PHT) and CBZ in plasma. Notably, the use of metal analysis was useful for indicating the positive effect of CBZ in the epilepsy treatment. The combination of chlorpromazine (CPZ) with other drugs can prevent its adverse effects and make it more popular in medicine. The prevention of seizure progression and epilepsy using the CBZ and its counterparts is still a controversial issue that should be tackled in the future.

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Content

1. Introduction

The development of drugs such as Carbamazepine (CBZ) has been significant in recent years [1]. The structure of CBZ (5H-Dibenz[b.f]azepine-5-carboxamide) employed for treating bipolar disease is highlighted in **Figure 1** [2,3]. Even though geriatric patients and elderlies have significantly complained regarding the use of CBZ, it is still considered as an anti-cholinergic agent [4]. CBZ is fundamentally effective in controlling various types of seizures. CPZ and CBZ, whose structure is depicted in **Figure 1**, are employed as internal standards. Besides, CBZ refers to the acidic and non-polar aromatic ester. The chemical structure of CBZ contains a carbamoyl moiety at the fifth position, as displayed in **Figure 1** [5].

CBZ can be further used as a drug used to treat epilepsy or nerve pain caused by diabetes (peripheral neuropathy) [5]. The use of CBZ is also effective in alleviating a painful facial condition called trigeminal neuralgia. Since about one-third of the patients with focal epilepsy have no response to a maximum dose of CBZ, additional anti-epileptic drugs are required to control the seizures [6]. However, this combination therapy might lead to drug interactions [7]. The combination of CBZ with other anti-epileptic drugs like valproic acid or phenytoin has received much attention in the literature. For example, the synergic effect of the combined treatment of exercise and CBZ in epileptic rats was examined by Barzroodi Pour in 2021 [8]. Due to the obtained results, the CBZ efficacy was enhanced using the exercise, and the anti-epileptic dose decreased. In another research, Peng *et al.* specified the efficacy and clinical factors associated with the pharmacodynamics of single or integration treatments of valproic acid (VPA), carbamazepine (CBZ), and oxcarbazepine (OXC) [9]. The authors obtained OR 1.030 [1.024-1.037], p<0 0.0001; OR 1.250 [1.146-1.63], p<0.0001 for the serum concentrations of VPA and CBZ, respectively. In 2019, Velghe *et al.* extended and verified a fully automated dried blood spot-based technique to quantify anti-epileptic drugs [10]. Notably, the binding of carbamazepine to human plasma proteins has been widely considered in the literature. The *in vitro* studies at 37 °C demonstrated the linear relationship between the concentration of unbound drug and total drug considering the range of total concentration of 5 to 50 mg/ml [11]. In 2018, Sofie and Velghe extended and validated the liquid chromatography-tandem mass spectrometry (LC-MS/MS) technique for specifying and quantifying four anti-epileptic drugs (carbamazepine, valproic acid, phenobarbital, and phenytoin) and one active metabolite (carbamazepine-10,11-epoxide) in specimens collected through Volumetric absorptive microsampling (VAMS) [12]. In some related studies, CBZ is regarded as an iminostilbine derivative which is fundamentally associated with tricyclic antidepressants. The effective control of seizure is achieved using plasma with concentrations between 17 to 50 umol/L.

There are many techniques used in the related studies for the CBZ analysis, such as high-performance liquid chromatography (HPLC). In 2006, a sensitive method based on HPLC with ultraviolet (UV) detection was extended for the CBZ and carbamazepine-10,11-epoxide (CBZ-E) in human plasma [13].

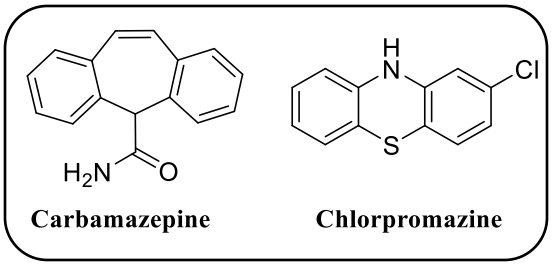

Figure 1. The structure of CBZ and CPZ [5]

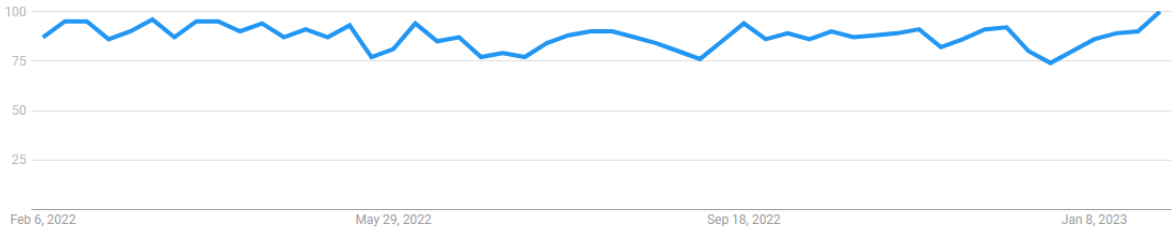

Figure 2. The growing interest in CBZ issue in the literature [15-19]

The obtained results indicated that the proposed method has the highest sensitivity, precision, and accuracy, with the remarkable application for the oral administration of a single 200 mg CBZ CR tablet. In another research, Matalon *et al.* [14]. Over time, an extensive literature has developed on CBZ analysis, as shown in **Figure 2** [15-19]. The information outlined in **Figure 2** highlights the growth of interest in the research related to CBZ, especially in the previous two years.

The current review examines the carbamazepine analysis in plasma using various techniques like HPLC and chromatographic analysis. The CBZ analysis is outlined in the second section. Thereafter, the concept of high-performance liquid chromatography (HPLC) is illustrated in the third section. The fourth section gives some information regarding the CBZ analysis in plasma. The various technique of CBZ analyses is also illustrated in the fifth section. Finally, the findings and suggestions for future studies are drawn in the sixth section.

2. Carbamazepine

Carbamazepine is one of the most commonly used drugs from the group of anti-epileptic drugs, sold under the brand name Tegretol [20]. This substance is used for treating schizophrenia along with other drugs and as a second-line agent in bipolar disorder. Carbamazepine seems to work, as well as phenytoin and valproate, for focal and generalized seizures. It is not effective for the treatment of absence seizures or myoclonic seizures [21]. As mentioned mainly in the literature, the use of CBZ is highly recommended for tackling seizure disorders and neuropathic pain [22]. In this section, more information regarding the utilization of this drug is given.

2.1. CBZ consumption

A seizure is a nervous attack caused by a disturbance in the electrical activity of the brain, and carbamazepine is used by reducing the abnormal electrical current of brain cells alone or together with other anti-epileptic drugs to reduce seizure attacks. In the United States, medical uses approved by the FDA include epilepsy (including partial seizures, tonic-clonic seizures, and mixed seizures), trigeminal neuralgia, and manic episodes and mixed episodes of depression and mania in bipolar disorder [23].

The common side effects of carbamazepine consist of Nausea, fever, vomiting, dizziness, confusion, headache, ataxia, restlessness (in the elderly), visual disturbances (especially diplopia associated with peak plasma drug), constipation or diarrhea, anorexia, mild erythematous rash, leukopenia, and other disorders. Furthermore, the skin disorder is important (Steven Johnson's skin syndrome) if you notice skin itching, spotting, or red spots on your skin while taking the medicine. The effects of the production of red blood cells, white blood cells, and platelets are remarkable. Rarely, major effects of aplastic anemia and agranulocytosis are reported, and usually, minor changes, such as a decrease in the number of white blood cells or platelets, are present, but these cases do not lead to more serious problems. Increased risk of suicide,

increased risk of hyponatremia if a person suddenly stops taking the drug, there is risk of seizures, and risks to the fetus in pregnant women, especially congenital abnormalities such as Spina bifida and developmental disorders [24]. Notably, the daily dose of CBZ is between 200-1200 mg, generating drug plasma levels of about 4-12 mg/L. The analytical techniques are mainly applied to specifying the metabolites and concentration of CBZ in the environment and biological specimens considering HPLC [25].

2.2. Sample preparation

There are many methods used in the related studies for sample preparation of CBZ. For example, in 2017, Zhang *et al.* employed the solution technique in the ethanol-water solvent mixture and polyvinyl pyrrolidone (PVP) solution for preparing the CBZ cocrystal [26]. The cocrystal conformers selected in the study were nicotinamide (NIC) and saccharin (SAC). The authors used Fourier Transform Infrared Spectroscopy (FTIR) to specify the cocrystal screening products and achieved important results. In another research, the amino-functionalized metal-organic framework was employed as a sorbent for specifying CBZ in the specimens of urine and water [27]. In the following, the Zr-MOF-NH_2 was applied as an adsorbent in pipette-tip solid phase extraction (PT-SPE) of CBZ. As in innovation, Mohiuddin *et al.* synthesized a porous molecularly imprinted polymer (PMIP) as a solid-phase extraction absorbent that helped in the sample preparation of CBZ [25]. Before quantitation, the authors used HPLC in different sample statuses like river water, pharmaceuticals, and drinking water. Besides, Behbahani *et al.* employed an amine-modified hierarchical lotus leaf-like mesoporous silica sorbent and HPLC-UV analysis for determining and measuring lamotrigine and CBZ in the water and biological media.

2.3. Direct injection

Carbamazepine injection was employed to treat individuals with certain forms of seizures (epilepsy) as an alternative to oral carbamazepine. Carbamazepine acts in the cerebral cortex and neurological system to regulate seizures. This medication works as an anticonvulsant.

This medication should be only administered through or according to the direct supervision of a healthcare professional. Following direct injection in LC, a semipermeable surface (SPS) silica column was used in another research to determine CBZ and its active 10,11-epoxide metabolite (EPO) in plasma [28]. The hydrophobic inner phase of the SPS packing material was an ODS ligand, and the hydrophilic outer phase was a polyoxyethylene network. When a 5-microliter portion of intact plasma was injected onto the column with a mobile phase of phosphate buffer (pH 7.1, ionic strength 0.1)-acetonitrile (4:1, v/v), the plasma proteins had been size-excluded, but the drug and its metabolite were retained and separated from each other as well as other commonly co-administered drugs like phenobarbital (PB) and phenytoin (DPH). The calibration graphs of CBZ, EPO, and PB (peak area vs. concentration) exhibited linear throughout the therapeutic range of plasma concentration (r more than 0.998) and had low relative standard deviations (RSD less than 3.98%, n = 5). The plasma recoveries were nearly complete (greater than 96.6%). The analysis took 17 minutes. The devised approach was used in research on the time period between plasma concentrations of unaltered CBZ and EPO after intravenous injection of CBZ into rats.

2.4. Protein precipitation

Protein precipitation is a method of separating protein from any excess impurities that may be present [29]. It is a crucial aspect of downstream processing and might be accomplished using various approaches. Precipitation occurs when an alteration in pH or hydrophobicity changes the interactions between the protein and the aqueous environment or when salts or metals bind to protein functional groups, disrupting intramolecular interactions and causing the proteins to denature, aggregate, and fall away from the solution. Precipitation occurs when an alteration in pH or hydrophobicity changes the interactions between the protein and the

aqueous environment or when salts or metals bind to protein functional groups, disrupting intramolecular interactions and causing the proteins to denature, aggregate, and fall away from solution [30].

Protein precipitation is a common technique to create LC/MS specimens for bioanalysis. In another research, plasma samples were typically combined with organic solvents such as acetonitrile and methanol or acidified treatments like diluted trifluoroacetic acid and perchloric acid, in amounts ranging from 3-5 times their volume before acids might be employed for protein precipitation; analysts must be aware of the compound's stability at low pH. The mixtures are centrifuged at 3000 rpm or filtered to obtain a clear supernatant or filtrate solution. The supernatant or filtrate could be immediately injected into an LC/MS system or dried and re-constituted in an HPLC mobile phase to obtain the final concentrated samples. If the evaporation and re-constitution procedures were skipped, diluted samples were obtained, and the assay's limit of quantitation (LOQ) may be compromised. Furthermore, when using a rapid gradient, supernatant and filtrate solutions containing large percentages of organic solvent may not be accepted for direct injection [31].

PPT is a sample extraction technique that is widely used in bioanalysis. This procedure is reasonably easy and allows for rapid sample cleanup, particularly in whole blood, plasma, and serum. The operation depends on the inclusion of an organic solvent, acid, or salt in the sample. When an organic solvent is added to a sample, such as plasma, it reduces the dielectric constant in the specimen, including the proteins, such as plasma, whole blood, or serum. This causes water to be displaced from the hydrophobic portion of the protein surface, which disrupts hydrophobic connections among the proteins in the sample, leading proteins to separate from the liquid [32].

2.5. CBZ analysis

As mentioned earlier, CBZ alleviates abnormal electrical activity in the brain [33]. Besides, CBZ contributes to treating epilepsy and nerve pain. CBZ is one of the most widely used drugs in the group of anti-epileptic ones. Convulsions occur due to the disruption of the electrical current in the cells of a part of the brain. A seizure is a nervous attack caused by a disturbance in the electrical activity of the brain, and carbamazepine is used to reduce the abnormal electrical current of brain cells alone or simultaneously, along with other anti-epileptic drugs to reduce seizure attacks [34]. Carbamazepine is also prescribed to treat chronic pain caused by nerve damage, such as burning and severe facial nerve pain. In addition, carbamazepine can have a therapeutic effect in some conditions of neurological and mental diseases, such as bipolar disease, since it can control some pains or mood disorders.

Since several companies manufacture this drug, the effect of the drug produced by different companies may be various for the patient. Thus, the methods proposed to take this drug differ according to the manufacturing company and the drug's brand name [35]. For example, slow-release tablets must be swallowed whole and should not be crushed or cut in half. Some brands are better to take after food, and some should be taken before food. The patients need to pay attention to the following recommendation to avoid potential risks:

- It is better to avoid changing the brand or the company producing the drug every time to get a new prescription and inform the doctor if necessary.
- At the beginning of treatment with this medicine, the uncomfortable thoughts may increase more than before. The patient should know that these thoughts are caused by the use of this drug and the start of its effectiveness, and they will disappear over time.
- Due to the side effects caused by this medicine for the fetus, if the patient intends to become pregnant or suspects pregnancy, she needs to inform her doctor to change the medicine and use the appropriate method to prevent pregnancy while taking this medicine.
- At the beginning of the treatment of epilepsy with carbamazepine, the number or type of seizures may change slightly but do not worry because this problem will be solved over time.

Therefore, observe the necessary precautions and be in contact with your doctor.

- Drinking alcohol during treatment with this drug can increase the possibility of side effects caused by this drug.
- Driving is not suitable for patients with epilepsy, but if no seizures have occurred within a year, the patient can start driving again with the doctor's opinion and with caution. Besides, they should be aware of the time of taking the drugs and the drowsiness caused by them.

In the review of 2014, pharmaceutically active compounds (PhACs) were presented as a new environmental issue due to their continuous input and persistence in the aquatic ecosystem [36]. The related studies emphasized the highest frequency of CBZ leading to aquatic systems through wastewater treatment plants (WWTPs), among other sources. Zhang *et al.* examined the relationship between the polymorphisms rs3812718 and rs2298771 of the theSCN1A gene and obtained remarkable results [37]. The authors demonstrated that Asian patients with epilepsy and the SCN1A rs2298771 polymorphism are likely to resist CBZ. In another research, Roy *et al.* solved the problem of CBZ degradation using a hybrid advanced oxidation system of hydrodynamic cavitation (HC) aided UV/persulfate with composite $ZnO/ZnFe_2O_4$ particles. The authors analyzed the thermodynamic and kinetic behaviors of reactions of CBZ with and $SO_4^{\cdot-}$ And $\cdot OH$ considering according to the density functional theory (DFT) at B3LYP/6-31 g(d) level. In a major advance of 2022, the efficacy of CBZ and retention rate (RR) were evaluated in randomized, controlled trials (RCTs) in epilepsy [38]. The analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The anti-seizure medications (ASMs) were compared using random-effects meta-analyses. The outcomes of this research indicate the effect of the RCTs design examining ASM and possibly challenge the extensive utilization of CBZ as a comparator. In 2022, the use of self-assembled monolayers (SAMs) with various groups was considered for a gold quartz monitor crystal [39]. The authors emphasized the key role of SAMs in the selectivity of polymorphism during the crystallization of carbamazepine. **Table 1** summarizes the related studies based on the CBZ effect and its accuracy.

As can be seen from **Table 1**, the effects of CBZ are positive and negative for people's health. For example, Nishiyama *et al.* indicated the use of CBZ might disrupt thyroid function. The following examines the relationship between the use of CBZ and HPLC.

2.6. CBZ analysis in plasma

Overall, CBZ is not chemically related to other anticonvulsant drugs, and the mechanism of its effect is not specified [45,46]. This drug limits the development of seizures by reducing multiple synaptic responses. Many experts consider CBZ a good choice to start anticonvulsant treatment, especially in women and children. This drug is increasingly preferred over phenobarbital for use in children since it has less effect on alertness and behavioral patterns. In treating seizure disorders, CBZ can be used alone or with other anticonvulsant drugs [47]. CBZ acts specifically to relieve trigeminal nerve pain by reducing synaptic transmission. Carbamazepine binds to plasma proteins up to 75%. CBZ is effective against partial generalized tonic-clonic seizures. The drug blocks sodium channels in therapeutic concentrations. CBZ is very effective in some patients with trigeminal neuralgia and is also useful in some patients with mania. Although CBZ is entirely absorbed, its absorption rate varies greatly in different patients. The maximum blood level is the drug that usually appears 6-8 hours after its administration [48]. Taking the slow absorption of the drug after food leads to greater tolerance of the total daily intake. The drug has a high ability to induce liver enzymes. The most common side effects related to the CBZ dose are diplopia and ataxia, which can be solved by

Table 1. The extensive use of CBZ for alleviating the various disorders in the literature

No.	References	Purposes	Dose of CBZ	Results
1	[40]	Examining the effects of anti-seizure drugs on the properties of recurrent seizures (SRSs)	10 mg/kg, 30 mg/kg, and 100 mg/kg	A rise in the dose of CBZ (10-100 mg/kg) prevents the frequency of convulsive and nonconvulsive seizures.
2	[41]	Examining the impact of adverse carbamazepine therapy in patients with focal seizures and impaired awareness on the electrocardiogram (ECG)	The various dosages for 36 cases	The lack of influence of carbamazepine on ECG time intervals
3	[42]	Investigating the efficacy and safety of once-daily eslicarbazepine acetate compared to the twice-daily (BID) controlled-release carbamazepine monotherapy in patients with epilepsy	Three dose levels including 800 mg/carbamazepine-CR 200 mg BID, 1200 mg/carbamazepine-CR 200 mg BID, and 1600 mg/carbamazepine-CR 200 mg BID	The treatment of seizure was found in 70.8% and 74% of patients with eslicarbazepine acetate and carbamazepine-CR with the dose of average risk difference = −3.07, 95%, and CI = −9.04 to 2.89
4	[43]	Examining the effect of CBZ in reducing circulating 25-hydroxyvitamin D (250HD)	The average and control dose of 21.8 ng/mL and four ng/mL	The acceptable performance of CBZ in reducing the 250HD level
5	[44]	Examining the effect of CBZ and levetiracetam (LEV) on the lipid and thyroid hormone levels of children with epilepsy	baseline: 1.15 ± 0.06 ng/dl, 1 month: 1.00 ± 0.16 ng/dl, 6 months: 0.98 ± 0.14 ng/dl	LEV is not dangerous for thyroid function, but CBZ monotherapy leads to thyroid dysfunction.

Table 2. The previous studies related to the CBZ analysis in plasma

No.	References	Purpose	Method
1	[50]	Determination of carbamazepine	Using g-C3N4@CuS nanocomposite and thermal polymerization of melamine
2	[51]	Quantifying carbamazepine in human plasma	The strategy of the high-performance liquid chromatography-tandem mass spectrometry (HPLC/MS^3)
3	[52]	Use a new monolithic column incorporated with Schiff base network-1 (SNW-1) for in-tube solid phase microextraction (SPME) of anti-epileptic drugs	SPME-HPLC method
4	[53]	Determination of Favipiravir using CBZ as an internal standard in spiked human plasma	Simple and reproducible reverse-phase liquid chromatography (RP-HPLC)
5	[54]	Simultaneous separation and concentration of neutral analytes	Micellar electro-kinetic chromatography
6	[55]	Electrophoresis determination of carbamazepine	Finger-prick dried blood spot (DBS) collection based on the blood level monitoring

reconsidering the order and daily distribution of prescribed doses [49]. Pollution and hyponatremia, and water intoxication occur, which may be dose-dependent. The most common idiosyncratic reaction is a red skin rash. Concomitant use with calcium channel blockers increases the concentration of carbamazepine significantly. Its simultaneous use with MAO inhibitors causes a crisis of high blood pressure because carbamazepine induces the CYP3A4 enzyme and interferes with drugs excreted through this pathway, such as macrolide antibiotics (erythromycin, azithromycin, etc.) and against azole fungi (ketoconazole, itraconazole, fluconazole, etc.) and antihistamines like loratadine and antipsychotics (clozapine, olanzapine, etc.). **Table 2** presents the studies conducted on CBZ analysis in plasma.

3. HPLC Analysis of CBZ

HPLC analysis, or High-Performance Liquid Chromatography, is a significant method in chemistry used to separate, identify, and measure small amounts of substances. HPLC consists of two stationary and mobile phases [56]. The stationary phase may be solid or liquid, and the mobile phase may be liquid. HPLC has undoubtedly been the fastest-growing of all analytical separation methods, with annual sales in the billion-dollar range. The reasons for this explosive growth are the sensitivity of the method, its rapid adaptability to perform accurate quantitative measurements, its suitability for the separation of non-volatile or thermally unstable species, and most importantly, its wide application to materials that are in the field of industry [57]. Various sciences and society are of primary importance. The advantage of chromatography over column distillation is that it is easy to achieve. Although a distillation column may take several days to reach its maximum efficiency, a chromatographic separation can be completed in minutes or hours. Another prominent advantage of chromatography methods is that they are quiet. This means that the probability of separating materials by these methods is lower than by other methods. Likewise, in these methods, only a slight amount of the mixture is required for analysis. Hence, analytical methods related to chromatographic separation can be performed on a micro and semi-micro scale. In the beginning, simpler methods such as paper and thin-layer chromatography are tried. If they are able to separate directly with these methods, the separation should be done by them. HPLC can be the answer when simple methods lack the necessary efficiency. HPLC is used for substances that are of primary importance in industry, various fields of science, and society. The major examples are amino acids, proteins, nucleic acids, hydrocarbons, carbon hydrates, drugs, terpenoids, insecticides, antibiotics, steroids, organic or metallic species, and a group of various mineral substances [58]. The different parts of the HPLC device include solvent tanks, pump, injector, column, detector, controller, and degasser.

Numerous studies have investigated CPZ and HPLC devices [5,59]. In 2021, Mansour *et al.* extended and verified a novel green and straightforward liquid chromatographic system for quantifying the new drug brivaracetam with piracetam and carbamazepine [60]. Employing an RP C-18 column, three compounds were assayed, considering a mobile phase made from a (70:30v/v) mixture of 1% triethylamine in water and acetonitrile. In 2019, RP-HPLC was the significant chromatographic condition that included about 90% of the separations [58]. HPLC has immense popularity which is relatively straightforward and inexpensive. Nowadays, more than 6000 RP-HPLC columns exist for customers with striking differences in selectivity and production quality. In 2013, Ezzeldin *et al.* proposed a straightforward technique for specifying CBZ based on HPLC with ultraviolet absorbance detection (UV) [61]. The technique consisted of two stages: protein precipitation and liquid-liquid extraction. The use of an analytical Thermo C8 (250 x 4.6 mm), 5 µm column with mobile phase including acetonitrile: isopropyl alcohol: phosphate buffer pH: 3 (36:15:49) was considered for separation. The peak-area ratio was plotted against the concentration of carbamazepine in plasma. The authors verified the linearity of the calibration curves from 0.1-8 µg/ml, and the

Table 3. A summary of previous studies regarding the CBZ analysis based on HPLC

No.	References	Purpose	Drug / Usage	HPLC	Analytical results
1	[63]	Examining therapeutic drug monitoring (TDM) of phenytoin (PHT) and carbamazepine (CBZ) in plasma	LOQ values of 1.56 µg/mL and 0.40 µg/mL for TDM and CBZ	A single reference high-performance liquid chromatographic (SR-HPLC)	The correlation coefficient and the slope of the intercept were 0.964 and 0.992647 for PHT and 0.969 and 1.072089 for CBZ.
2	[64]	Quantifying carbamazepine, carbamazepine-10,11-epoxide, S-licarbazepine, lacosamide and levetiracetam in human saliva	0.2–6 mg L^{-1}	HPLC coupled with diode-array detection (DAD).	$p < 0.05$ for carbamazepine ($r^2 = 0.6887$; r = 0.8299)
3	[65]	Specifying zonisamide (ZNS) in human plasma	Mobile phase composed of acetonitrile/water (35 : 65, v/v)	HPLC diode array detection method	The linearity achieved for ZNS (r2 = 0.9960) between 0.2-80 µg mL^{-1} was acceptable in plasma.
4	[66]	Examining the absorption rate of bisphenol, A (BPA), and CBZ in an aqueous solution	The values of 346.07 mg/g and 55.13 mg/g for BPA and CBZ	Partially reduced graphene oxide by HPLC.	The obtained results were acceptable.

corresponding regression equation was r= 0.998. In addition, Shi *et al.* investigated the utilization of the therapeutic drug monitoring of CBZ for clinical application [62]. The study aimed to reach therapeutic concentration and minimize the risk of concentration-dependent toxicity. The authors used an ultrafast analytical assay for quantifying CBZ in human plasma. The obtained results were extended and verified according to the direct analysis in real-time tandem mass spectrometry (DART-MS/MS). More related studies are also listed in **Table 3**.

4. Detection Method of HPLC

4.1. Ultra violet (UV)

Notwithstanding the increasing popularity of the modular mass spectrometric detector, UV detectors remain unquestionably the most commonly utilized form of the detector with HPLC systems, and this will continue for many years. Some biological compounds are capable of absorbing electromagnetic energy in the form of UV and visible light photons. The wavelength range often employed in UV detection for HPLC is 200-400nm, which encompasses either UV or the lower part of the visible spectrum. It should be emphasized that, as specified by equation 1, the shorter the wavelength, the greater the energy of the photons of light [67].

To absorb light energy, electrons inside the atoms need to be promoted from a ground state to an excited state, and the specific energy transition will be dictated through the energy that is accessible levels, defined by the type of atoms and bonding within the molecule, and the energy of the incumbent radiation, stated by the wavelength of chosen light.

In a study in 2009, HPLC with UV detection was used to analyze urine for endogenous thiols and thiol drug levels [68]. The other methods for detecting and measuring thiols in urine have not yet been described. An overview of metabolism was provided, as well as the roles of the major biological thiols in physiological and pathological processes and their reference concentrations in urine. Urine sample preparation techniques were addressed in detail, including thiol-disulfide reduction, chemical derivatization, and reversed-phase HPLC separation stages. Some clinical information regarding the methods used for determining the endogenous thiols cysteine, cysteinyl glycine, homocysteine, N-acetylcysteine, thioglycolic acid, and thiol drugs cysteamine, tiopronin, d-penicillamine, captopril, mesna, methimazole, propylthiouracil, and thioguanine has been reviewed.

4.2. Fluorescence

HPLC fluorescence (FL) detectors are distinguished from other types of HPLC detectors by their high sensitivity and specificity. FL detectors use light emission from excited atoms in an analysis to extract information from a solution collected from an HPLC column. The piperazine assessment, which residues in whole eggs, albumen, and yolk, was accomplished using high-performance liquid chromatography-fluorescence detection (HPLC-FLD) and pre-column derivatization with dansyl chloride [69]. The analytes were purified using solid phase extraction (SPE) after the egg samples were treated with accelerated solvent extraction (ASE). The mobile phase for gradient elution was acetonitrile/ultrapure water. The linear dynamic range for whole eggs was 6.80 to 200.0 g/kg, albumen was 7.50 to 200.0 g/kg, and the yolk was 6.50 to 200.0 g/kg, with coefficients of determination (R^2) better than or equal to 0.9992. When the concentrations were equivalent to the limit of quantification, 0.5 times the highest residue limit, equal to the highest residue limit, and twice the maximum residue limits, the mean recoveries of piperazine from egg samples ranged from 72.86 to 89.26%. The corresponding standard deviations ranged from 1.73 to 4.99%. Piperazine detection limits in eggs ranged from 1.92 to 2.50 g/kg, and quantification limits ranged from 6.50 to 7.50 g/kg. The approach meets the requirements of the European Union, the People's Republic of China's Ministry of Agriculture, and the United States Food and Drug Administration (FDA) for determining veterinary drug residues. This validated HPLC-FLD method successfully determined piperazine residues in 50 eggs obtained from local supermarkets.

4.3. Mass spectrometer

Ultra-high-performance liquid chromatography high-resolution mass spectrometry (UHPLC-HRMS) versions are currently the greatest instruments for addressing the difficulties of metabolite complexity and a lack of complete coverage [56]. UHPLC enabled the detection and identifying a wide spectrum of metabolites by combining flexible and efficient separation with high-sensitivity detection by HRMS. The authors address current prevalent methodologies for UHPLC-HRMS-based metabolomics, with an emphasis on increasing metabolite coverage. The type of information provided in a mass spectrum is mostly determined by the ionization process that can be divided into hard and soft techniques. The former is distinguished by the substantial quantity of energy transmitted to the molecules, resulting in fragment-rich spectra that aid in structural elucidation. Soft ionization methods, on the other hand, provide fragment-poor spectra that are frequently dominated by molecular weight information [70,71].

5. Conclusion and future work

In the medical field, the CBZ utilization is recommended alone or in combination with other drugs better to control specific kinds of seizures in people with epilepsy. The use of CBZ has also been observed for treating trigeminal neuralgia, which leads to facial nerve pain. As reported in the literature, CBZ acts as an anticonvulsant or anti-epileptic drug and can be beneficial for relieving nerve pain. Using CBZ, the distribution of seizure activity reduces in

the brain, and the balance of the nerve activity is kept normal. The practitioners attempt to monitor the CBZ doses in the limited therapeutic range to avoid any adverse consequences. The previous studies reported the occurrence of seizures, mania, or pain in the case of taking excessive CBZ, which eventually brings toxic side effects for the high levels of dose. Hence, the present review examined the therapeutic effects of CBZ on various diseases with a certain dose. Accordingly, about 200 papers were extracted from valid resources, including Google Scholar and Science Direct. Furthermore, related studies regarding the effects of CBZ in plasma based on HPLC were investigated comprehensively. Due to the findings given in the previous studies, it was revealed that the effects of CBZ are positive and negative for people's health. For instance, thyroid function can be disrupted by the use of CBZ. There are many methods for specifying CBZ, among which MEKC is significantly straightforward and sensitive, as indicated in the current review. Also, the benefits of single reference HPLC were proved for therapeutic drug monitoring (TDM) of phenytoin (PHT) and CBZ in plasma. Despite such interest, many future gaps and shortcomings must be considered. Actually, the CPZ combination with other drugs can prevent its adverse effects and make it more popular in medicine. The prevention of seizure progression and epilepsy using the CBZ and its counterparts is still a controversial issue that should be tackled in the future. Moreover, the other techniques of CBZ analysis were reviewed in this research, and it was revealed that metal analysis was helpful in indicating the positive effect of CBZ in treating epilepsy. HPLC–UV was beneficial for extracting the CBZ from the human plasma specimens. The recommendation that can be considered as novel topics is as follows:

- The use of nanoparticles or nanomaterials can be widely employed for CBZ determination.
- The use of computer-aided techniques such as machine learning (ML) and deep learning (DL) can contribute to raising the accuracy of predicting the CPZ capabilities in treating the seizure.
- The combination therapies based on the various drugs and CPZ need more consideration to prevent adverse effects.
- The quantitative and qualitative detection of carbamazepine concentration in human plasma requires improvement that can be obtained by LC-MS^3 or other materials.

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Conflict of interest

The authors do not have any conflicting financial interests or personal ties that may have influenced the work disclosed in this study.

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