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A Comprehensive Review of Analytical Methods for the Analysis of Topiramate and Ionic Impurities in Pharmaceutical Compound: Methods and Applications

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ABSTRACT:
Topiramate is a broad-spectrum antiepileptic drug approved for the management of epilepsy. It has found applications in the treatment of migraine headaches, bipolar disorder, and other neurological disorders. Topiramate's therapeutic success is tied to its unique mechanism of action. This review explores a range of analytical techniques employed to characterize topiramate.Notably, a singular set of chromatographic and detection conditions has not been universally established for the analysis of topiramate and its impurities.HPLC coupled with Mass Spectrometry (MS) is expounded as an advantageous approach, offering heightened specificity, sensitivity, and efficiency in analysis time.Nevertheless, the selection of detection methods and the development of HPLC methodologies for topiramate and its impurities pose significant challenges, contingent upon the investigation's intended purpose, considering factors such as equipment availability, cost, and desired selectivity. For quantifying topiramate exclusively in raw materials and formulations, several methods may prove suitable, with the selection contingent upon desired sensitivity. HPLC coupled with conductivity detection is identified as particularly apt for detecting inorganic impurities, such as sulfate and sulfamate. While MS detection emerges as the optimal choice for simultaneous determination of topiramate and its impurities due to enhanced sensitivity, its feasibility for routine analysis is tempered by the associated high equipment costs.This review underscores the ongoing exploration of alternative approaches for topiramate analysis, emphasizing the necessity for continued research to refine and expand the analytical arsenal for this pharmaceutical compound.

Keywords: Topiramate, Antiepileptic Drug, Analytic Technique, Pharmaceutical Formulation, Quantitative assay,

I. INTRODUCTION:

Topiramate, chemically known as 2,3:4,5-Bis-O-(1-methylethylidene)-beta-D-fructopyranose sulfamate, is a broad-spectrum antiepileptic drug that has gained significant attention for its efficacy in treating various neurological disorders[1]. Initially approved by the U.S. Food and Drug Administration (FDA) for the management of epilepsy, Topiramate has since found applications in the treatment of migraine headaches, and bipolar disorder, and as an adjunctive therapy for weight management[2].

Topiramate, a monosaccharide with a sulfamate substitution, is officially approved for both monotherapy and adjunctive treatment of generalized tonic-clonic seizures, partial onset seizures with or without secondary generalization, and seizures associated with Lennox–Gastaut syndrome [3]. Additionally, it holds approval for migraine prevention[4]. Beyond its approved indications, the off-label use of topiramate has expanded, demonstrating efficacy in various conditions. Research indicates its effectiveness in managing bipolar disorder [5]and post-traumatic stress disorder[6]. Furthermore, topiramate exhibits potential applications in treating obesity[7] and alcohol dependence[8]. Ongoing investigations explore its utility in bulimia nervosa[9], obsessive-compulsive disorder[10], idiopathic intracranial hypertension[11], neuropathic pain[12], infantile spasm[13], and as an aid for smoking cessation[14].

The therapeutic success of topiramate is closely tied to its unique mechanism of action, involving the modulation of ion channels and neurotransmitter systems[15].

As the pharmaceutical industry continues to recognize the importance of this versatile drug, there is an increasing need for a comprehensive understanding of its analytical aspects, spanning

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from the assessment of the drug substance to the evaluation of impurities in pharmaceutical formulations[16]. The effectiveness of topiramate in treating these conditions necessitates a rigorous and accurate analytical assessment of the drug, highlighting the importance of developing robust methods for its quantification [17].

Spectrophotometry, a versatile analytical technique based on the interaction of electromagnetic radiation with matter, has become a cornerstone in analyzing pharmaceutical compounds, including topiramate [18]. Spectrophotometric methods' simplicity, cost-effectiveness, and widespread applicability make them attractive for routine analysis and quality control in pharmaceutical research and manufacturing [19].

UV-visible absorption spectroscopy, one of the most commonly employed techniques, relies on the absorption of light by chemical compounds, offering a straightforward approach to the quantitative determination of topiramate in pharmaceutical formulations[20]. Infrared spectroscopy, on the other hand, exploits the characteristic vibrational modes of molecular bonds, providing valuable insights into the structural elucidation of topiramate and facilitating its quantitative analysis[21].

Fluorescence spectroscopy, with its high sensitivity and selectivity, has gained prominence in the analysis of topiramate due to the compound's intrinsic fluorescence properties[22]. This method not only allows for the quantification of topiramate but also enables the detection of impurities and degradation products, enhancing the overall analytical capabilities[23].

Among the various analytical techniques available, reverse-phase high-performance Liquid Chromatography (RP-HPLC) has emerged as a pivotal method for the quantitative determination and characterization of topiramate [24]. rpHPLC offers distinct advantages, including high sensitivity, selectivity, and efficiency, making it an indispensable tool in pharmaceutical analysis [25].

Additionally, the application of rpHPLC in the determination of impurities, metabolites, and related substances in topiramate formulations will be thoroughly examined [20]. The review will highlight the specificity and robustness of rpHPLC methods in ensuring the accurate quantification of topiramate, even in complex matrices.

This review intends to explore a range of analytical methods utilized in investigating topiramate. It covers methodologies for assessing the drug substance, identifying and quantifying impurities, and analyzing different pharmaceutical formulations. A thorough critical examination of these analytical techniques is crucial to guarantee high quality, safety, and efficacy standards in medications containing topiramate.

In the course of this review, we will extensively examine each spectrophotometric method, exploring their underlying principles, and applications, as well as the advantages and limitations associated with their use in the analysis of topiramate. Additionally, we will place special emphasis on recent advancements and innovative approaches within spectrophotometric techniques employed for determining topiramate. This detailed exploration aims to provide readers with a comprehensive understanding of the dynamic and evolving landscape within the critical field of pharmaceutical analysis.

In this thorough investigation, we will explore a range of analytical techniques employed to characterize topiramate. These methods encompass spectroscopic techniques, chromatographic methodologies, and emerging technologies. Moreover, we will specifically address the challenges linked to detecting and quantifying impurities. Additionally, we will delve into the advancements made in the analysis of pharmaceutical formulations containing topiramate-based products.

By integrating insights from various analytical methodologies, this review seeks to enhance the overall comprehension of topiramate. It aims to furnish researchers, scientists, and pharmaceutical professionals with a valuable resource to uphold the quality and dependability of pharmaceuticals containing topiramate. Through this exploration, the intention is to encourage ongoing progress in analytical sciences, ultimately contributing to the advancement of safer and more effective medications for individuals who depend on topiramate for their medical requirements.

II. DRUG PROFILE OF TOPIRAMATE:

IUPAC Name: 2,3:4,5-Bis-O-(1-methyl ethylidene)-Beta-D-fructopyranose sulfamate
Common names: Topiramate, topiramic acid, topiramatum, topamax
Chemical Formula: $C_{12}H_{21}NO_8S$
Pka: 8.6
Molecular Weight: 339.36 g/mol
Solubility: Soluble in water (9.8 mg/ml).
Melting Point: 123-125 ºC

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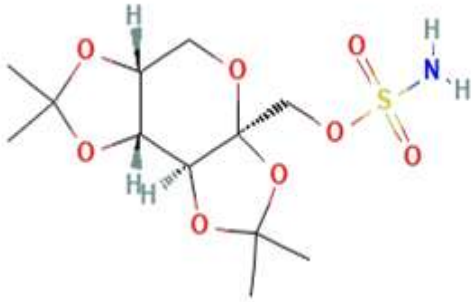
pH: 6.3 (saturated solution) [26].



Topiramate is acompound derived from hexose, specifically 2,3:4,5-di-O-isopropylidene-beta-D-fructopyranose, where the hydroxyl group has been transformed into the corresponding sulfamate ester [27]**.**

It functions by inhibiting voltage-dependent sodium channels and is employed as an antiepileptic medication for the prophylaxis of migraines [28]. Its role extends to serving as both an anticonvulsant and a blocker of sodium channels. It is a cyclic ketal, a sulfamate ester, and a ketohexose derivative[29].

Mechanism of Action: Topiramate's mechanism of action (MOA) resembles a versatile orchestra performer, harmoniously uniting diverse mechanisms to achieve its therapeutic effects in various medical conditions. Instead of relying on a single mechanism, it plays manifold roles:

The calming influence of GABA: Topiramate acts like a conductor amplifying the signals of the brain's natural inhibitory neurotransmitter, gamma-aminobutyric acid (GABA)[30]. By boosting GABA's activity, it dampens down excessive neuronal firing, contributing to its anti-seizure and migraine-preventive properties[2].

Beyond boosting GABA, topiramate takes on the role of a modulator, fine-tuning ion channels that control the flow of charged particles into and out of neurons[31]. This dampens the excitatory buzz of glutamate, another prominent neurotransmitter, further calming neuronal activity and contributing to its therapeutic effects[32].Topiramate also directly silences some glutamate receptors, key players in excitatory signaling. By acting as an antagonist, it directly reduces the impact of glutamate, adding another layer of control to neuronal excitability[33].

This intricate interplay between enhancing inhibition, modulating ion channels, and antagonizing glutamate receptors paints a compelling picture of how Topiramate's multifaceted MOA contributes to its diverse therapeutic applications. This exploration allows us to appreciate the complex symphony it conducts within the brain, ultimately leading to improved clinical outcomes for various medical conditions.

Pharmacokinetic Profile: Topiramate, a sulfamate-substituted monosaccharide, has garnered significant attention in the field of pharmacotherapy due to its diverse therapeutic applications. A crucial aspect of understanding the clinical efficacy and safety of topiramate lies in unraveling its pharmacokinetic profile. Topiramate demonstrates favorable oral bioavailability, with rapid absorption observed after oral administration. While food does affect the rate and extent of absorption, topiramate can be administered irrespective of meals [34]. The distribution of topiramate within the body is widespread, and it readily crosses the blood-brain barrier. The drug exhibits a relatively low binding affinity to plasma proteins, allowing for a higher volume of distribution[35]. It undergoes minimal metabolism, with the majority of the administered dose excreted unchanged. The hepatic cytochrome P450 enzymes play a limited role in its metabolism. A detailed examination of the metabolic pathways and the impact of hepatic impairment on topiramate metabolism will be presented[36]. Renal excretion serves as the primary route of elimination for topiramate, with approximately 70-80% of the administered dose excreted unchanged in the urine[2].

III. DRUG STABILITY, DEGRADATION PRODUCT, AND IMPURITIES:

As we know topiramate is a sulfamate-substituted monosaccharide, has gained prominence as a therapeutic agent for various neurological disorders [37]. To ensure the quality, safety, and efficacy of pharmaceutical formulations containing topiramate, an in-depth understanding of its stability, potential degradation pathways, and impurity profile is imperative [17].

The stability of topiramate is a critical parameter in pharmaceutical formulations. Factors such as temperature, humidity, light exposure, and the presence of other excipients can influence the stability of the drug [38]. The factors that influence the stability of topiramate can be influenced by various external factors, and understanding these is essential for formulating strategies to preserve its chemical integrity. Temperature, humidity, light

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exposure, and the presence of other excipients in pharmaceutical formulations are critical determinants [39]. To assess and monitor the stability of topiramate, stability-indicating methods play a pivotal role.These methods are designed to detect and quantify degradation products and impurities that may arise during storage or exposure to unfavorable conditions.Various analytical techniques, such as high-performance liquid chromatography (HPLC), gas chromatography (GC), and spectroscopy, are employed for this purpose [40], [41], [42].

Understanding the potential degradation pathways of topiramate is essential for formulating strategies to mitigate degradation and enhance product stability. This knowledge is indispensable for ensuring the sustained efficacy, safety, and quality of topiramate-containing pharmaceutical formulations throughout their shelf life. By identifying the potential routes of degradation, pharmaceutical scientists can implement targeted measures to protect the integrity of the drug, ultimately enhancing its stability and preserving its therapeutic benefits.

Topiramate, a medication susceptible to degradation, readily breaks down when exposed to heat, humidity, or light, or interacts with other chemicals. The primary topiramate is degraded by following pathways including hydrolysis, oxidation, and photodegradation[43]. Knowing these pathways is key to predicting how topiramate might degrade over time.Hydrolysis represents a significant degradation route for topiramate, particularly under conditions of increased humidity [17].Exploration of the hydrolytic cleavage of ester and amide bonds in topiramate leads to the formation of specific degradation products[44]. Conversely, another method for the degradation of topiramate is oxidation, which is triggered by exposure to air or other oxidative agents and contributes to the formation of degradation products with altered chemical profiles [45]. On the other hand, an alternative approach to emphasize the susceptibility of topiramate to degradation involves photodegradation. Exposure to light, particularly UV radiation, can induce photodegradation in topiramate, resulting in the generation of specific degradation products[46].

The presence of impurities in pharmaceutical formulations can impact the safety and efficacy of the drug. The impurity profile of topiramate, including process-related impurities, degradation-related impurities, and potential contaminants.Researchers extensively discuss the detailed exploration of analytical techniques utilized in impurity profiling, including chromatography and spectroscopy [17].

IV. HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY:

HPLC is a widely utilized chromatographic technique based on the separation of compounds within a liquid mobile phase through a stationary phase[47]. This article delves into the core principles of HPLC, highlighting the critical interplay between the mobile and stationary phases in achieving optimal separation of topiramate from its potential impurities.

Developing an HPLC method tailored to the unique characteristics of topiramate is crucial for accurate and reliable analysis. The article will delve into the considerations involved in method development, including a selection of columns, mobile phases, and detection systems. Factors influencing peak resolution, sensitivity, and selectivity will be discussed, providing insights into optimizing HPLC conditions for topiramate quantification.

V. TYPES OF HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY:

Sr. No.	Type	Principle	Stationary Phase	Application	Reference
1.	Normal Phase Chromatography (NPC):	Separation based on the polarity of compounds	Polar stationary phase (silica) and nonpolar mobile phase (organic solvents).	Suitable for separating nonpolar compounds, isomers, and compounds that are insoluble in water.	[48], [49]
2.	Reverse Phase Chromatography (RPC)	Separation based on hydrophobicity	Nonpolar stationary phase (hydrophobic) and	Commonly used for separating polar	[50], [51]

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			polar mobile phase (aqueous or water-miscible)	compounds, separation, and characterization of proteins/peptides.	
3.	Ion-Exchange Chromatography (IEC)	Separation is based on ionic interactions between charged compounds and the charged stationary phase.	Positively or negatively charged resin.	Useful for separating ions and charged molecules.	[52], [53]
4.	Size-Exclusion Chromatography (SEC) or Gel Filtration Chromatography	Separation based on size and molecular weight.	Porous gel beads	Effective for separating biomolecules and polymers based on size, and viruses, enzymes, proteins, antibodies, nucleic acids, and hormones are all able to be separated and purified.	[54], [55], [56]
5.	Affinity Chromatography	Separation based on specific interactions between a biological molecule and a ligand attached to the stationary phase	Ligand-bound resin	Highly selective for isolating specific biomolecules	[57], [58]
6.	Hydrophilic Interaction Chromatography (HILIC)	Separation based on hydrophilic interactions	Hydrophilic stationary phase	Suitable for polar compounds and highly water-soluble analytes	[59], [60]
7.	Chiral Chromatography	Separation based on the interaction of enantiomers with a chiral stationary phase	Chiral selector	Used in drug discovery and confirmation of enantiomeric drug purity, food science, and environmental analysis	[61]
8.	Reversed-Phase Ion-Pair Chromatography (RP-IPC)	Combines reverse phase and ion-exchange	Nonpolar stationary phase with the addition of ion-pairing reagents	Useful for separating charged compounds in	[62], [63]

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		mechanisms.		reverse-phase conditions	
9.	Two-Dimensional Liquid Chromatography (2D-LC)	Combines two different separation mechanisms in a series	Two different phases in each dimension	Provides enhanced separation capabilities for complex samples	[64], [65]

VI. OFFICIAL ANALYTICAL METHOD OF TOPIRAMATE:

The US Pharmacopeia provides multiple HPLC methods for the determination of topiramate and its impurities in raw materials, tablets, and capsules [66].

1.1 Sensitive Capillary Gas Chromatography-Mass Spectrometry (GC-MS) Method for Analysis of Topiramate:

A Sensitive Capillary Gas Chromatography-Mass Spectrometry (GC-MS) method represents a powerful analytical approach for the precise and selective analysis of volatile and semi-volatile compounds in complex samples[67]. This method combines the separation capabilities of capillary gas chromatography with the high sensitivity and specificity of mass spectrometry, offering a robust platform for the detection and quantification of trace-level analytes[68].

As we are very well-known topiramate is an antiepileptic medication used for epilepsy and migraine prophylaxis. A GC-MS assay was developed to detect topiramate plasma concentrations after rectal or oral administration.The assay utilized solid phase extraction and quantification by GC-MS analysis. Standard curves were split into two ranges to improve accuracy. The accuracy of the standards ranged from 94.6 to 107.3, and the precision ranged from 1.0 to 5.3 for both curves at all concentrations[41].

Contrastingly, the researcher adopts an approach aimed at placing increased emphasis on the discussion regarding the analysis of residual organic solvents (methanol, ethanol, and toluene) in topiramate drug substance, which is a potent anticonvulsant drug under clinical evaluation. The drug is recrystallized from ethanol denatured by either methanol or toluene, and each residual solvent is controlled at 0.1 (w/w) level.

A capillary GC method is described for the analysis. This method utilizes a DB-WAX column and the injector temperature is set at 120°C to prevent degradation of the thermally labile compound. The oven temperature is programmed from 55°C to 160°C at a rate of 30°C min^{-1}.

The sample solvent used is dimethylformamide pretreated with molecular sieves to remove trace amounts of alcohol that may interfere with the assay. The method is validated to be specific, linear, precise, sensitive, rugged, and shows excellent recovery[69].

1.2 Capillary Electrophoresis (CE):

Capillary Electrophoresis is a technique based on the differential migration of charged analytes in an electric field [70], [71]. The researcher adopts an approach aimed atthe exploration of topiramate by capillary electrophoresis conversed about the development and validation of a bioanalytical method for analyzing the antiepileptic drug topiramate in plasma samples by using capillary electrophoresis with capacitively-coupled contactless conductivity detection (CE-C4D). This method exploits a simple background of electrolyte, hydrodynamic inoculations, and a moderate separation voltage to attaincomparatively short analysis times.The sample pre-treatment comprises liquid-liquid extraction using methyl terc-butyl ether as the solvent and plasma samples. This method was corroborated according to the guidelines from the European Medicine Agency and revealed linearity in the plasmatic concentration range of 1 to 30 mg/mL, which covers the clinically relevant interval. This method was successfully applied to analyze plasma samples and identified 80 under-medicated patients in the patient pool[72].

On the contrary, the researcher takes an approach focused on accentuating the discourse surrounding the development and validation of a rapid capillary zone electrophoresis method with indirect UV detection for determining topiramate in plasma [73]. The method utilizes a background electrolyte consisting of 10 mM sulfamethoxazole as a chromophore in a phosphate buffer (25 mM, pH 12.0), with gabapentin serving as the internal standard. The analysis is completed in under 5 minutes at a voltage of 15 kV, and indirect UV detection is carried out at 256 nm. Topiramate is extracted from plasma using a solid-phase extraction procedure on C18 cartridges. This

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method demonstrates a linear response across the concentration range of 2-60 mg of topiramate per mL of plasma, with a limit of detection (LOD) of 0.8 mg mL-1 and a limit of quantitation (LOQ) of 2.0 mg mL-1. Precision, expressed as relative standard deviation, consistently remains below 7.3%, and extraction yields consistently exceed 92%. The method is effectively applied to analyze plasma samples from epileptic patients undergoing topiramate therapy, demonstrating satisfactory precision and selectivity[74], [75].

1.3 Liquid Chromatography-Mass Spectrometry (LC-MS):

Liquid Chromatography-Mass Spectrometry (LC-MS) is a powerful analytical technique that combines liquid chromatography and mass spectrometry[76]. It provides sensitivity, selectivity, and versatility, making it valuable in pharmaceuticals, environmental monitoring, proteomics, and metabolomics. LC-MS is widely used for drug development, environmental analysis, and studying complex biological systems[77]. Ongoing innovations address challenges, ensuring LC-MS remains a forefront technology in analytical chemistry.

The researcher has found that the LC-MS technique was to develop and validate an LC-MS method for quantifying topiramate and its main metabolites in human plasma samples. This method used liquid-liquid extraction with a mixture of ethyl acetate and diethyl ether as the extraction solvent. The chromatographic separation was achieved using a 1290 Infinity UHPLC coupled to a 6460 Triple Quad Mass Spectrometer. This method employed gradient elution with water and methanol as the mobile phase with a Kinetex C18 column was used for chromatographic separation, and a stable isotope-labeledTopiramate (TPM) was used as an internal standard. This method was selective, accurate, precise, and linear over the concentration ranges of 0.10-20 mg/mL for TPM, 0.01-2.0 mg/mL for 2,3-des isopropylidene TPM, and 0.001-0.200 mg/mL for 4,5-des isopropylidene TPM, 10-OH TPM, and 9-OH TPM. The researcher has revealed that this method was successfully developed and used to quantify all analytes in plasma samples of patients with epilepsy[78].

On the contrary, the researcher takes an approach focused on accentuating the discourse surrounding the development and validation of an LC-MS method for the detection to determining topiramate in plasma[79].The researcher has outlined a swift and validated technique for analyzing topiramate in human plasma, employing liquid chromatography coupled with tandem mass spectrometry (LC-MS). This process entails a straightforward liquid extraction of topiramate and prednisone (used as an internal standard) using acetonitrile, followed by separation through HPLC with a Capcell Pak C18 column. Detection is performed on an API 2000 MS system using multiple reactions monitoring mode. This method boasts a total run time of 2.5 minutes and demonstrates robust linearity across a working range of 20-5000 ng/mL in human plasma[80].

1.4 Fourier Transform Infrared (FT-IR) Spectroscopy:

Fourier Transform Infrared (FT-IR) spectroscopy is a powerful analytical technique widely employed in pharmaceutical research[81]. By analyzing the characteristic absorption of infrared radiation by molecular vibrations, FT-IR provides valuable insights into the composition and structure of compounds. In the case of topiramate, FT-IR facilitates rapid, non-destructive analysis, offering a unique fingerprint of its molecular features. This versatile method enables both qualitative and quantitative assessments, making it indispensable in pharmaceutical quality control and formulation studies.

The researcher has investigated the vibrational and thermal properties of crystalline topiramate, a powerful anticonvulsant drug. This study aims to utilize the techniques such as FT-IR. The researchers can tentatively assign most of the normal vibrational modes of the crystal through their analysis. The thermal analysis revealed that the material does not undergo any structural phase transition and decomposes in a two-step exothermic process. This study provides valuable insights into the properties of topiramate, which can contribute to a better understanding of its behavior and potential applications[82].

1.5 Nuclear Magnetic Resonance (NMR) Spectroscopy:

Nuclear Magnetic Resonance (NMR) is a sophisticated analytical technique widely used in chemistry and biochemistry [83]. It exploits the magnetic properties of certain atomic nuclei, providing detailed information about molecular structure, composition, and dynamics. NMR spectroscopy is particularly effective in elucidating the arrangement of atoms within organic molecules, helping researchers understand

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molecular interactions, identify compounds, and study biological processes[84]. It is a non-destructive and versatile tool with applications in diverse fields, including chemistry, biology, and materials science [85].

Topiramate is a well-knownantiepileptic drug, that has been synthesized and identified using 1H NMR, 13C NMR, 1H-1H COSY, HMQC, and HMBC spectra[86]. NMR spectral data is commonly used in combination with computational methods for the determination of the conformation of biologically active molecules like Topiramate.

The researchers have focused on the sulfamate methyl ($CH_2OSO_2NH_2$) fragment of fructopyranose in Topiramate to determine its conformation details in solution. Researchers used experimental and theoretical methods to correlate the dependencies of 1J and 2J involving 1H and 13C on the C1-C2 (o) and C1-O1 (th) torsion angles in the glycosidic part of Topiramate. New Karplus equations were proposed to assist in the structural interpretation of these couplings. The analyses of experimental coupling constants for protons on the pyranose ring of Topiramate indicate a twistboat structure for Topiramate in solution[87].

On the contrary, the researcher takes an approach focused on accentuating the discourse surrounding the development and validation of the NMR spectroscopy method for a novel quantitative NMR spectrometry method was developed to determine topiramate in a tablet formulation using a 400 MHz NMR instrument [88]. DMSO-d6 was selected as the NMR solvent for this method. The signals of the methyl proton of topiramate appeared as four independent singlet peaks with baseline separation, and the peak at 1.47 ppm was selected for quantification. The internal standard used in this method was 3,5-dimethylpyrazole (DMP), with its singlet peak at 5.74 ppm. The linearity of the method was observed between 0.05 and 0.85 mg mL^{-1}, with an R2 value of 0.9992. The limits of detection (LOD) and quantification (LOQ) for topiramate were determined to be 0.04 and 0.16 mg mL^{-1}, respectively [89].

1.6 UV-Visible Spectrophotometry:

UV-visible spectroscopy is a valuable analytical technique applied to study the interaction of topiramate with light in the ultraviolet and visible regions. This method provides information about the electronic transitions within the molecule, aiding in the characterization of topiramate and its behavior under different conditions [90]. UV-visible spectroscopy is commonly used to assess the concentration of topiramate in solutions, investigate its stability, and explore any interactions with other substances. This technique plays a crucial role in pharmaceutical analysis, contributing to the understanding of the optical properties and chemical behavior of topiramate.

Topiramate dose forms in pharmaceutical studies are estimated using straightforward, accurate spectroscopic techniques. By weighing 100 mg of topiramate in 100 ml of methanol and adding methanol to fill the volumetric flask, the standard stock solution for topiramate was established. The stock was made using methanol at 1000µg/ml. The diluted sample was scanned at a wavelength of 235 nm. It was discovered that the correlation coefficient was 0.999 it will be stated analogously. The range of the regression equation is found to be Y=0.998X + 0.0259. The resilience, robustness, range, linearity, accuracy, LOD, and LOQ of the spectroscopic method should all be validated. It was discovered that the limits of detection and quantitation for topiramate were, respectively, 0.015 and 0.028 parts per million. The recovery research includes what is referred to as a recovery percentage. The technique that was found has a lot of potential for Topiramate determination in pharmaceutical dosage forms [91].

VII. HPLC METHODS FOR THE ANALYSIS OF TOPIRAMATE AND ITS DEGRADATION PRODUCTS:

1.7 Exploring Topiramate Analysis through High-Performance Liquid Chromatography with Fluorescence Detection:

The primary emphasis was on analyzing topiramate within biological matrices, a topic that will be elaborated upon in subsequent discussions.

Nevertheless, the researcher has unveiled an applied knowledge of group techniques to ascertain the drug substance content through a specific method. In this instance, fluorescence detection was employed exclusively to compare results obtained through the HPLC-MS method [92].

1.8 Optimizing Sensitivity: High-Performance Liquid Chromatography Coupled with Chemiluminescent Nitrogen Detector for Enhanced Analytical Precision:

The researcher takes an approach focused on accentuating the discourse surrounding the development and validationof an HPLC method utilizinga chemiluminescent nitrogen

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detector(CLND) to assess a liquid oral solution of topiramate. The authors contended that the RI detection method proved unsuitable for evaluating such a solution due to the presence of a significant amount of water-soluble excipients co-eluting with topiramate. Initially, the authors explored the viability of capillary GC with flame ionization detection (FID); however, they deemed this technique unpromising due to observed thermal instability in topiramate. Another avenue considered was a reverse-phase HPLC method with light scattering detection, but it proved suitable only for analyzing the drug substance and failed to detect low levels of degradation products[93]. The CLND method focused on monitoring Impurity 2 as the sole impurity due to its nitrogen content. Additionally, the authors acknowledged that topiramate might have different degradation products in solution formulations compared to solid dosage forms. Method development primarily concentrated on optimizing detector parameters, resulting in final conditions: pyrolysis furnace at 1,050°C, dryer membrane at 85°C, and flow rates for oxygen, argon, makeup, and ozone set at 250, 150, 50, and 25 cm3/min, respectively[20].

1.9 Enhanced Detection: Exploring High-Performance Liquid Chromatography Coupled to Evaporative Light Scattering Detection (HPLC-ELSD)

Advancements in Topiramate Analysis: Dual Analytical Methods Utilizing Evaporative Light Scattering Detection (ELSD). The researchers proposed and validated a method for analyzing raw materials, tablets, and capsules of topiramate. During the ELSD method development, they noted that the ELSD impactor position (on/off), flow rate, and drift tube temperature significantly influenced method sensitivity. Inadequate carrier gas flow rates resulted in droplet formation inside the detector, leading to a noisy signal, while excessively high flow rates reduced droplet numbers and signal intensity. Drift tube temperature extremes affected solvent evaporation, impacting signal quality. The authors identified optimal conditions: impactor position off, flow rate 2.8 L/min, and drift temperature 100°C. The method demonstrated linearity within the range of 400–2,000 µg/mL. A comparison with an HPLC-RI method recommended by the drug supplier revealed the advantages of the ELSD method, including avoiding instrument balance time, temperature sensitivity, and baseline instability associated with RI. Additionally, the ELSD method exhibited a superior linear range (400–2,000 µg/mL) compared to the RI method (1,000–10,000 µg/mL). The authors achieved the same drug content as the RI method[94].

On the contrary, the researcher takes an approach focused on accentuating the discourse surrounding the development and validation of a short paper on the determination of the drug substance topiramate using ELSD. The authors evaluated five different compositions of mobile phases considering the solvents acetonitrile, methanol, water, and ammonium acetate. The method was linear over the range of 500–3,000 µg/mL. The main advantage of their method was the fast run time of 8 min, in which the topiramate retention time was 4 min. The authors did not present applications of the ELSD method to topiramate formulations [17].

1.10 Exploring the Potential of HPLC-Coupled Electrospray Ionization Mass Spectrometry in Analytical Chemistry:

Four distinct methodologies have been developed for the analysis of topiramate drug substance, its formulations, and/or impurities, employing mass spectrometry (MS) detection [92], [95], [96], [97].

The investigator created a method combining ion exchange chromatography with electrospray ionization mass spectrometry (ESI-MS) to identify anionic species in tablet samples of topiramate.The researcher described that when the topiramate tablet was analyzed on an anion exchange column, many unknown peaks originating from the formulation excipients were detected. In addition, acetic acid was used as an ion suppressor agent for the sodium species, to reduce baseline drift and to allow detection of the ions at low levels. Without the ion suppressoragent, the main peak witnessed was the sodium adduct [M+Na] +, m/z 362, whereas using the sodium hydroxide gradient elution with the ion suppressor, the predominant peak of topiramate was from the ammonium adduct [M+NH4] +, m/z 357. The authors argued that besides the higher sensitivity obtained using [M+NH4] +, it also fragments more easily than [M+Na] + when they applied collision-induced dissociation. The researcher observed some retention for topiramate using the ion exchange column, but it produced tailing and broad peaks. They suggested some reverse-phase interaction between the drug and the polymeric matrix stationary phase (containing polystyrene, divinyl benzene, and acrylate polymer) due to the

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fact that topiramate would be ionized at pH ~10 of the mobile phase. Although the authors had indicated that their method could be used for the identification of several inorganic species in topiramate tablets, no data were provided concerning the analysis of sulfamate. The authors only reported that it was necessary to use sodium in gradient elution to separate sulfamate from the formulation's excipients[96].

On the other hand, the method developed by scientist Biro et al. by using MS detection is the most complete analytical techniqueaccessible so far to analyze topiramate and its impurities. Using the chromatographic conditions and the m/z, it was possible to separate and detect the drug substance and four impurities in pharmaceutical formulations. The authors applied the method to a forced degradation study, in which the drug was submitted to stressful conditions such as acidic, basic, and neutral hydrolysis, oxidation, heat, and photostability, as presented in Official analytical methods for topiramate. Reasonable values of the limit of quantitation and limit of detection were obtained for the four impurities evaluated [95].

Two additional analytical approaches utilizing mass spectrometry (MS) detection were implemented to assess topiramate under negative ionization conditions. Koba et al. conducted a comparative analysis of their MS results for the quantification of topiramate against another method devised by the same research group, which utilized high-performance thin liquid chromatography (HPTLC). The calibration curve exhibited reliability within the concentration range of 0.25–10.0 µg/mL, with topiramate eluting at 1.3 minutes. The authors emphasized that the developed method is well-suited for routine quality control of the drug. However, it is important to note that this particular method is specifically designed for determining the content of the drug substance [21], [97].

Conversely, another researcher has developed anHPLC-MS method to support their topiramate derivatization technique. The MS method aimed to optimize the derivatization conditions by detection of unreacted topiramate, m/z 339, and topiramate derivatized with 9-fluoroenylmethyl chloroformate (FMOC-Cl), m/z 560. The authors evaluated the effect of the reaction parameters time, temperature, pH, and concentration of buffer/organic phase on the derivatization technique. The mass obtained after the derivatization represents the FMOC adduct of topiramate after the loss of HCl. The main conclusion of the authors was that this derivatization technique is reversible, mainly in the presence of the amino acid glycine, and commonly used to remove the excess FMOC.

1.11 High-Performance Liquid Chromatography Utilizing UV Detection: An Analytical Approach for Compound Analysis:

Topiramate dosage forms in pharmaceutical studies are assessed using straightforward, accurate spectroscopic techniques. By weighing 100 mg of topiramate in 100 ml of methanol and adding methanol to fill the volumetric flask, the standard stock solution for topiramate was established. The stock was made using methanol at 1000µg/ml. The diluted sample was scanned at a wavelength of 235 nm. It was discovered that the correlation coefficient was 0.999 it will be stated analogously. The range of the regression equation is found to be Y=0.998X + 0.0259. The resilience, robustness, range, linearity, accuracy, LOD, and LOQ of the spectroscopic method should all be validated. It was discovered that the limits of detection and quantitation for topiramate were, respectively, 0.015 and 0.028 ppm. The recovery research includes what is referred to as a recovery percentage. The technique that was found has a lot of potential for Topiramate Determination in Pharmaceutical Dosage Forms[98].

1.12 Optimizing Separation: Exploring Reversed-Phase High-Performance Liquid Chromatography

Topiramate has been estimated using a straightforward, accurate, dependable, quick, and repeatable reversed-phase high-performance liquid chromatography (RP-HPLC) technique that has been verified for topiramate.With a mobile phase made of methanol, chromatography was performed using a Youngling (S.K) Gradient System UV Detector on a C18 (4.6X250 mm) column.The mobile was subjected to a pH adjustment of 0.05 percent orthophosphoric acid (pH-3).A UV detector operating at 263 nm was used for the detection.The TPM was retained for 4.35 minutes.Topiramate's linearity range is 10-50 µg/ml.The correlation coefficient of Topiramate was found to be 0.999.The established technique for concurrent measurement of topiramate in pharmaceutical dose forms was found to be fast, accurate, selective, and precise [24].

VIII. DISCUSSION:

This comprehensive review delineates diverse analytical methodologies devised for the determination of topiramate in pharmaceutical formulations. Predominantly,High-performance liquid chromatography(HPLC) emerges as the most prevalent separation technique, deemed highly suitable for routine quality control analyses. This review also delves into alternative methods, encompassing Capillary Electrophoresis (CE), Gas Chromatography (GC), and various non-chromatographic techniques. Within the US Pharmacopeia, distinct chromatographic and detection conditions are stipulated for topiramate and its associated compounds. Notably, a singular set of chromatographic and detection conditions has not been universally established for the analysis of topiramate and its impurities.

HPLC coupled with Mass Spectrometry (MS) is expounded as an advantageous approach, offering heightened specificity, sensitivity, and efficiency in analysis time. Nevertheless, the selection of detection methods and the development of HPLC methodologies for topiramate and its impurities pose significant challenges, contingent upon the analysis's intended purpose, considering factors such as equipment availability, cost, and desired selectivity. For quantifying topiramate exclusively in raw materials and formulations, several methods may prove suitable, with the selection contingent upon desired sensitivity. HPLC coupled with conductivity detection is identified as particularly apt for detecting inorganic impurities, such as sulfate and sulfamate. While MS detection emerges as the optimal choice for simultaneous determination of topiramate and its impurities due to enhanced sensitivity, its feasibility for routine analysis is tempered by the associated high equipment costs.

This review underscores the ongoing exploration of alternative approaches for topiramate analysis, emphasizing the necessity for continued research to refine and expand the analytical arsenal for this pharmaceutical compound.

REFERENCE:

[1] N. Y. Khalil, H. K. AlRabiah, S. S. Al Rashoud, A. Bari, and T. A. Wani, "Topiramate: Comprehensive profile," Profiles Drug Subst Excip Relat Methodol, vol. 44, pp. 333–378, 2019, doi: 10.1016/bs.podrm.2018.11.005.

[2] K. A. Fariba and A. Saadabadi, "Topiramate," in StatPearls, Treasure Island (FL): StatPearls Publishing, 2024. Accessed: Feb. 04, 2024. [Online]. Available: http://www.ncbi.nlm.nih.gov/books/NBK554530/

[3] R. Guerrini and L. Parmeggiani, "Topiramate and its clinical applications in epilepsy," Expert Opin Pharmacother, vol. 7, no. 6, pp. 811–823, Apr. 2006, doi: 10.1517/14656566.7.6.811.

[4] N. M. Ramadan and T. M. Buchanan, "New and future migraine therapy," Pharmacol Ther, vol. 112, no. 1, pp. 199–212, Oct. 2006, doi: 10.1016/j.pharmthera.2005.04.010.

[5] K. Vasudev, K. Macritchie, J. Geddes, S. Watson, and A. Young, "Topiramate for acute affective episodes in bipolar disorder," Cochrane Database Syst Rev, no. 1, p. CD003384, Jan. 2006, doi: 10.1002/14651858.CD003384.pub2.

[6] H. A. Berlin, "Antiepileptic drugs for the treatment of post-traumatic stress disorder," Curr Psychiatry Rep, vol. 9, no. 4, pp. 291–300, Aug. 2007, doi: 10.1007/s11920-007-0035-5.

[7] C. T. Supuran, A. Di Fiore, and G. De Simone, "Carbonic anhydrase inhibitors as emerging drugs for the treatment of obesity," Expert Opin Emerg Drugs, vol. 13, no. 2, pp. 383–392, Jun. 2008, doi: 10.1517/14728214.13.2.383.

[8] D. A. Baltieri, F. R. Daró, P. L. Ribeiro, and A. G. de Andrade, "Comparing topiramate with naltrexone in the treatment of alcohol dependence," Addiction, vol. 103, no. 12, pp. 2035–2044, Dec. 2008, doi: 10.1111/j.1360-0443.2008.02355.x.

[9] S. L. McElroy, A. I. Guerdjikova, B. Martens, P. E. Keck, H. G. Pope, and J. I. Hudson, "Role of antiepileptic drugs in the management of eating disorders," CNS Drugs, vol. 23, no. 2, pp. 139–156, 2009, doi: 10.2165/00023210-200923020-00004.

[10] E. Hollander and B. Dell'Osso, "Topiramate plus paroxetine in treatment-resistant obsessive-compulsive disorder," Int Clin Psychopharmacol, vol. 21, no. 3, pp. 189–191, May 2006, doi: 10.1097/01.yic.0000199453.54799.cc.

[11] N. Celebisoy, F. Gökçay, H. Sirin, and O. Akyürekli, "Treatment of idiopathic intracranial hypertension: topiramate vs acetazolamide, an open-label study," Acta Neurol Scand, vol. 116, no. 5, pp. 322–327,

Nov. 2007, doi: 10.1111/j.1600-0404.2007.00905.x.

[12] E. A. Bendaly, C. A. Jordan, S. S. Staehler, and D. A. Rushing, "Topiramate in the treatment of neuropathic pain in patients with cancer," Support Cancer Ther, vol. 4, no. 4, pp. 241–246, Sep. 2007, doi: 10.3816/SCT.2007.n.021.

[13] L.-P. Zou et al., "Evaluation of open-label topiramate as primary or adjunctive therapy in infantile spasms," Clin Neuropharmacol, vol. 31, no. 2, pp. 86–92, 2008, doi: 10.1097/WNF.0b013e3180986d43.

[14] J. García Campayo et al., "Effectiveness of topiramate for tobacco dependence in patients with depression; a randomised, controlled trial," BMC Fam Pract, vol. 9, p. 28, May 2008, doi: 10.1186/1471-2296-9-28.

[15] N. Lotfy, H. Elsawah, and M. Hassan, "Topiramate for smoking cessation: Systematic review and meta-analysis," Tob Prev Cessat, vol. 6, p. 14, Feb. 2020, doi: 10.18332/tpc/115167.

[16] R. M. Maggio, N. L. Calvo, S. E. Vignaduzzo, and T. S. Kaufman, "Pharmaceutical impurities and degradation products: Uses and applications of NMR techniques," Journal of Pharmaceutical and Biomedical Analysis, vol. 101, pp. 102–122, Dec. 2014, doi: 10.1016/j.jpba.2014.04.016.

[17] E. C. Pinto, M. D. Dolzan, L. M. Cabral, D. W. Armstrong, and V. P. de Sousa, "Topiramate: A Review of Analytical Approaches for the Drug Substance, Its Impurities and Pharmaceutical Formulations," J Chromatogr Sci, vol. 54, no. 2, pp. 280–290, Feb. 2016, doi: 10.1093/chromsci/bmv120.

[18] Y. B. Patel, M. Dalwadi, and D. U. M. Upadhyay, "Develpoment & Validation of Spectroscopy," vol. 5, no. 2.

[19] H. M. Marzouk, E. A. Ibrahim, M. A. Hegazy, and S. S. Saad, "Eco-friendly resolution of spectrally overlapping signals of a combined triple-action over-the-counter pharmaceutical formulation for symptomatic management of COVID-19 pandemic: application to content uniformity testing," BMC Chem, vol. 16, no. 1, p. 73, Oct. 2022, doi: 10.1186/s13065-022-00868-0.

[20] M. Styslo-Zalasik and W. Li, "Determination of topiramate and its degradation product in liquid oral solutions by high performance liquid chromatography with a chemiluminescent nitrogen detector," Journal of Pharmaceutical and Biomedical Analysis, vol. 37, no. 3, pp. 529–534, Mar. 2005, doi: 10.1016/j.jpba.2004.11.010.

[21] M. H. Alqarni et al., "A Greener Stability-Indicating High-Performance Thin-Layer Chromatography Approach for the Estimation of Topiramate," Materials (Basel), vol. 15, no. 5, p. 1731, Feb. 2022, doi: 10.3390/ma15051731.

[22] M. A. Mohamed, A. S. Fayed, M. A. Hegazy, N. N. Salama, and E. E. Abbas, "Fully optimized new sensitive electrochemical sensing platform for the selective determination of antiepileptic drug ezogabine," Microchemical Journal, vol. 144, pp. 130–138, Jan. 2019, doi: 10.1016/j.microc.2018.08.062.

[23] S. Huang, H. Wang, Y. Xu, X. Zhao, J. Teng, and Y. Zhang, "The protective action of topiramate on dopaminergic neurons," Med Sci Monit, vol. 16, no. 9, pp. BR307-312, Sep. 2010.

[24] M. B. Kshirsagar, M. P. Mahajan, and S. D. Sawant, "Method Development and Validation by RP-HPLC for Estimation of Topiramate in Bulk and Pharmaceutical Dosage form," International Journal of ChemTech Research, 2017.

[25] G. Renuka, "RP-HPLC Method Development and Validation For Estimation of Topiramate in Bulk and Tablet Dosage Form," vol. 8, no. 4, 2023.

[26] "Topiramate | C12H21NO8S | CID 5284627 - PubChem." Accessed: Feb. 04, 2024. [Online]. Available: https://pubchem.ncbi.nlm.nih.gov/compound/Topiramate

[27] "topiramate (CHEBI:63631)." Accessed: Feb. 04, 2024. [Online]. Available: https://www.ebi.ac.uk/chebi/chebiOntology.do?chebiId=CHEBI:63631

[28] R. Shahien and K. Beiruti, "Preventive Agents for Migraine: Focus on the Antiepileptic Drugs," J Cent Nerv Syst Dis, vol. 4, pp. 37–49, Feb. 2012, doi: 10.4137/JCNSD.S9049.

[29] D. Zierath, S. Mizuno, and M. Barker-Haliski, "Frontline Sodium Channel-Blocking Antiseizure Medicine Use Promotes Future Onset of Drug-Resistant Chronic Seizures," International Journal of

Molecular Sciences, vol. 24, no. 5, Art. no. 5, Jan. 2023, doi: 10.3390/ijms24054848.

[30] N. A. J. Puts and R. A. E. Edden, "In vivo magnetic resonance spectroscopy of GABA: A methodological review," Progress in Nuclear Magnetic Resonance Spectroscopy, vol. 60, pp. 29–41, Jan. 2012, doi: 10.1016/j.pnmrs.2011.06.001.

[31] R. Kuzniecky et al., "Modulation of cerebral GABA by topiramate, lamotrigine, and gabapentin in healthy adults," Neurology, vol. 58, no. 3, pp. 368–372, Feb. 2002, doi: 10.1212/wnl.58.3.368.

[32] T.-S. Chen, T.-H. Huang, M.-C. Lai, and C.-W. Huang, "The Role of Glutamate Receptors in Epilepsy," Biomedicines, vol. 11, no. 3, p. 783, Mar. 2023, doi: 10.3390/biomedicines11030783.

[33] M. Barker-Haliski and H. S. White, "Glutamatergic Mechanisms Associated with Seizures and Epilepsy," Cold Spring Harb Perspect Med, vol. 5, no. 8, p. a022863, Aug. 2015, doi: 10.1101/cshperspect.a022863.

[34] G. C. Minton, A. D. Miller, P. B. Bookstaver, and B. L. Love, "Topiramate: Safety and Efficacy of its Use in the Prevention and Treatment of Migraine," J Cent Nerv Syst Dis, vol. 3, pp. 155–168, Jun. 2011, doi: 10.4137/JCNSD.S4365.

[35] P. N. Patsalos, "The clinical pharmacology profile of the new antiepileptic drug perampanel: A novel noncompetitive AMPA receptor antagonist," Epilepsia, vol. 56, no. 1, pp. 12–27, 2015, doi: 10.1111/epi.12865.

[36] S. C. Nallani et al., "Dose-dependent induction of cytochrome P450 (CYP) 3A4 and activation of pregnane X receptor by topiramate," Epilepsia, vol. 44, no. 12, pp. 1521–1528, Dec. 2003, doi: 10.1111/j.0013-9580.2003.06203.x.

[37] H. D. Langtry, J. C. Gillis, and R. Davis, "Topiramate. A review of its pharmacodynamic and pharmacokinetic properties and clinical efficacy in the management of epilepsy," Drugs, vol. 54, no. 5, pp. 752–773, Nov. 1997, doi: 10.2165/00003495-199754050-00009.

[38] A. Salawi, "Pharmaceutical Coating and Its Different Approaches, a Review," Polymers (Basel), vol. 14, no. 16, p. 3318, Aug. 2022, doi: 10.3390/polym14163318.

[39] "EP1572159A1 - Stable topiramate formulations - Google Patents." Accessed: Feb. 04, 2024. [Online]. Available: https://patents.google.com/patent/EP1572159A1/en

[40] P. I. Napolitano-Tabares, I. Negrín-Santamaría, A. Gutiérrez-Serpa, and V. Pino, "Recent efforts to increase greenness in chromatography," Current Opinion in Green and Sustainable Chemistry, vol. 32, p. 100536, Dec. 2021, doi: 10.1016/j.cogsc.2021.100536.

[41] J. M. Conway, A. K. Birnbaum, S. E. Marino, J. C. Cloyd, and R. P. Remmel, "A Sensitive Capillary GC-MS Method for Analysis of Topiramate from Plasma Obtained from Single Dose Studies," Biomed Chromatogr, vol. 26, no. 9, pp. 1071–1076, Sep. 2012, doi: 10.1002/bmc.1749.

[42] A. Bolner, V. De Riva, E. Galloni, and F. Perini, "Therapeutic drug monitoring of topiramate with a new HPLC method, SPE extraction and high sensitivity pre-column fluorescent derivatization," Clin Lab, vol. 60, no. 6, pp. 919–923, 2014, doi: 10.7754/clin.lab.2013.130641.

[43] I. M. D. Gonzaga, C. V. S. Almeida, and L. H. Mascaro, "A Critical Review of Photo-Based Advanced Oxidation Processes to Pharmaceutical Degradation," Catalysts, vol. 13, no. 2, Art. no. 2, Feb. 2023, doi: 10.3390/catal13020221.

[44] B. M. Brandsen, A. R. Hesser, M. A. Castner, M. Chandra, and S. K. Silverman, "DNA-Catalyzed Hydrolysis of Esters and Aromatic Amides," J Am Chem Soc, vol. 135, no. 43, pp. 16014–16017, Oct. 2013, doi: 10.1021/ja4077233.

[45] "Drug Degradation - an overview | ScienceDirect Topics." Accessed: Feb. 04, 2024. [Online]. Available: https://www.sciencedirect.com/topics/immunology-and-microbiology/drug-degradation

[46] I. Golonka, S. Wilk, and W. Musiał, "The Influence of UV Radiation on the Degradation of Pharmaceutical Formulations Containing Quercetin," Molecules, vol. 25, no. 22, p. 5454, Nov. 2020, doi: 10.3390/molecules25225454.

[47] O. Coskun, "Separation techniques: Chromatography," North Clin Istanb, vol. 3, no. 2, pp. 156–160, Nov. 2016, doi: 10.14744/nci.2016.32757.

[48] "Normal-Phase Chromatography - an overview | ScienceDirect Topics." Accessed:

Feb. 04, 2024. [Online]. Available: https://www.sciencedirect.com/topics/chemistry/normal-phase-chromatography

[49] N. Editor, "Exploring the Distinctions and Applications of Normal Phase Chromatography and Reverse Phase Chromatography – Welch Materials." Accessed: Feb. 04, 2024. [Online]. Available: https://www.welch-us.com/the-differences-and-application-ranges-of-normal-phase-chromatography-and-reverse-phase-chromatography/

[50] D. Otter, "PROTEIN | Determination and Characterization," in Encyclopedia of Food Sciences and Nutrition (Second Edition), B. Caballero, Ed., Oxford: Academic Press, 2003, pp. 4824–4830. doi: 10.1016/B0-12-227055-X/00980-9.

[51] "Reversed-Phase Chromatography - an overview | ScienceDirect Topics." Accessed: Feb. 04, 2024. [Online]. Available: https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/reversed-phase-chromatography

[52] "Ion Chromatography - an overview | ScienceDirect Topics." Accessed: Feb. 04, 2024. [Online]. Available: https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/ion-chromatography

[53] "Ion-Exchange Chromatography and Its Applications | IntechOpen." Accessed: Feb. 04, 2024. [Online]. Available: https://www.intechopen.com/chapters/44033

[54] "What are the applications of size-exclusion chromatography? | AAT Bioquest." Accessed: Feb. 04, 2024. [Online]. Available: https://www.aatbio.com/resources/faq-frequently-asked-questions/what-are-the-applications-of-size-exclusion-chromatography

[55] Y. Sun, Q.-H. Shi, L. Zhang, G.-F. Zhao, and F.-F. Liu, "2.47 - Adsorption and Chromatography," in Comprehensive Biotechnology (Second Edition), M. Moo-Young, Ed., Burlington: Academic Press, 2011, pp. 665–679. doi: 10.1016/B978-0-08-088504-9.00123-9.

[56] "Size-Exclusion Chromatography - an overview | ScienceDirect Topics." Accessed: Feb. 04, 2024. [Online]. Available: https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/size-exclusion-chromatography

[57] D. S. Hage et al., "PHARMACEUTICAL AND BIOMEDICAL APPLICATIONS OF AFFINITY CHROMATOGRAPHY: RECENT TRENDS AND DEVELOPMENTS," J Pharm Biomed Anal, vol. 69, pp. 93–105, Oct. 2012, doi: 10.1016/j.jpba.2012.01.004.

[58] E. L. Rodriguez et al., "Affinity Chromatography: A Review of Trends and Developments over the Past 50 Years," J Chromatogr B Analyt Technol Biomed Life Sci, vol. 1157, p. 122332, Nov. 2020, doi: 10.1016/j.jchromb.2020.122332.

[59] "Hydrophilic Interaction Chromatography - an overview | ScienceDirect Topics." Accessed: Feb. 04, 2024. [Online]. Available: https://www.sciencedirect.com/topics/medicine-and-dentistry/hydrophilic-interaction-chromatography

[60] B. Buszewski and S. Noga, "Hydrophilic interaction liquid chromatography (HILIC)—a powerful separation technique," Anal Bioanal Chem, vol. 402, no. 1, pp. 231–247, 2012, doi: 10.1007/s00216-011-5308-5.

[61] "Chiral Chromatography - an overview | ScienceDirect Topics." Accessed: Feb. 04, 2024. [Online]. Available: https://www.sciencedirect.com/topics/chemistry/chiral-chromatography

[62] "Ion Pair Chromatography – How IPC Works, Strengths, Limitations and Applications | Technology Networks." Accessed: Feb. 04, 2024. [Online]. Available: https://www.technologynetworks.com/analysis/articles/ion-pair-chromatography-how-ipc-works-strengths-limitations-and-applications-358440

[63] "[Application of reversed-phase ion-pair chromatography for universal estimation of octanol-water partition coefficients of acid, basic and amphoteric drugs] - PubMed." Accessed: Feb. 04, 2024. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/20055179/

[64] A. Rathore, J. Auclair, S. Bhattacharya, and D. Sarin, "Two-Dimensional Liquid Chromatography (2D-LC): Analysis of Size-Based Heterogeneities in Monoclonal

Antibody–Based Biotherapeutic Products," vol. 40, pp. 27–31, Jan. 2022.

[65] D. R. Stoll and P. W. Carr, "Two-Dimensional Liquid Chromatography: A State of the Art Tutorial," Anal. Chem., vol. 89, no. 1, pp. 519–531, Jan. 2017, doi: 10.1021/acs.analchem.6b03506.

[66] "Topiramate Capsules." doi: 10.31003/USPNF_M84312_02_01.

[67] B. Gruber, F. David, and P. Sandra, "Capillary gas chromatography-mass spectrometry: Current trends and perspectives," TrAC Trends in Analytical Chemistry, vol. 124, p. 115475, Mar. 2020, doi: 10.1016/j.trac.2019.04.007.

[68] "Capillary Gas Chromatography-Mass Spectrometry - an overview | ScienceDirect Topics." Accessed: Feb. 04, 2024. [Online]. Available: https://www.sciencedirect.com/topics/chemistry/capillary-gas-chromatography-mass-spectrometry

[69] A. P. Micheel, C. Y. Ko, and C. R. Evans, "Assay of residual organic solvents in topiramate drug substance by capillary gas chromatography," Journal of Pharmaceutical and Biomedical Analysis, vol. 11, no. 11, pp. 1233–1238, Jan. 1993, doi: 10.1016/0731-7085(93)80109-E.

[70] A. Makahleh, B. Saad, and M. F. Bari, "3 - Synthetic phenolics as antioxidants for food preservation," in Handbook of Antioxidants for Food Preservation, F. Shahidi, Ed., in Woodhead Publishing Series in Food Science, Technology and Nutrition. , Woodhead Publishing, 2015, pp. 51–78. doi: 10.1016/B978-1-78242-089-7.00003-8.

[71] "Capillary Electrophoresis - an overview | ScienceDirect Topics." Accessed: Feb. 04, 2024. [Online]. Available: https://www.sciencedirect.com/topics/food-science/capillary-electrophoresis

[72] A. A. Ishikawa et al., "Determination of topiramate by capillary electrophoresis with capacitively-coupled contactless conductivity detection: A powerful tool for therapeutic monitoring in epileptic patients," ELECTROPHORESIS, vol. 39, no. 20, pp. 2598–2604, 2018, doi: 10.1002/elps.201800046.

[73] R. Mandrioli, A. Musenga, E. Kenndler, M. De Donno, M. Amore, and M. A. Raggi, "Determination of topiramate in human plasma by capillary electrophoresis with indirect UV detection," J Pharm Biomed Anal, vol. 53, no. 5, pp. 1319–1323, Dec. 2010, doi: 10.1016/j.jpba.2010.03.007.

[74] M. Atif, S. H. Khalid, G. L. Onn Kit, S. a. S. Sulaiman, M. Asif, and A. Chandersekaran, "Development and validation of RP-HPLC-UV method for the determination of Glipizide in human plasma," J Young Pharm, vol. 5, no. 1, pp. 26–29, Mar. 2013, doi: 10.1016/j.jyp.2013.01.005.

[75] E. Souri, H. Jalalizadeh, and A. Shafiee, "Optimization of an HPLC method for determination of gabapentin in dosage forms through derivatization with 1-fluoro-2,4-dinitrobenzene," Chem Pharm Bull (Tokyo), vol. 55, no. 10, pp. 1427–1430, Oct. 2007, doi: 10.1248/cpb.55.1427.

[76] S. Tilvi, M. S. Majik, and K. S. Singh, "Chapter 8 - Mass Spectrometry for Determination of Bioactive Compounds," in Comprehensive Analytical Chemistry, vol. 65, T. Rocha-Santos and A. C. Duarte, Eds., in Analysis of Marine Samples in Search of Bioactive Compounds, vol. 65. , Elsevier, 2014, pp. 193–218. doi: 10.1016/B978-0-444-63359-0.00008-2.

[77] J. F. Xiao, B. Zhou, and H. W. Ressom, "Metabolite identification and quantitation in LC-MS/MS-based metabolomics," Trends Analyt Chem, vol. 32, pp. 1–14, Feb. 2012, doi: 10.1016/j.trac.2011.08.009.

[78] D. Milosheska and R. Roškar, "A novel LC–MS/MS method for the simultaneous quantification of topiramate and its main metabolites in human plasma," Journal of Pharmaceutical and Biomedical Analysis, vol. 138, pp. 180–188, May 2017, doi: 10.1016/j.jpba.2017.02.003.

[79] J.-H. Park et al., "Determination of plasma topiramate concentration using LC-MS/MS for pharmacokinetic and bioequivalence studies in healthy Korean volunteers," Biomedical Chromatography, vol. 22, no. 8, pp. 822–829, 2008, doi: 10.1002/bmc.995.

[80] "Determination of topiramate in human plasma using liquid chromatography tandem mass spectrometry - PubMed." Accessed: Feb. 05, 2024. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/23841344/

[81] "Fourier Transform Infrared Spectroscopy - an overview | ScienceDirect Topics." Accessed: Feb. 05, 2024. [Online]. Available: https://www.sciencedirect.com/topics/agricu

ltural-and-biological-sciences/fourier-transform-infrared-spectroscopy

[82] D. M. Sena Jr. et al., "Vibrational and thermal properties of crystalline topiramate," J. Braz. Chem. Soc., vol. 19, pp. 1607–1613, 2008, doi: 10.1590/S0103-50532008000800022.

[83] "Nuclear Magnetic Resonance Spectroscopy - an overview | ScienceDirect Topics." Accessed: Feb. 05, 2024. [Online]. Available: https://www.sciencedirect.com/topics/materials-science/nuclear-magnetic-resonance-spectroscopy

[84] A. J. Simpson, D. J. McNally, and M. J. Simpson, "NMR spectroscopy in environmental research: From molecular interactions to global processes," Progress in Nuclear Magnetic Resonance Spectroscopy, vol. 58, no. 3, pp. 97–175, May 2011, doi: 10.1016/j.pnmrs.2010.09.001.

[85] B. Schneider, "Nuclear magnetic resonance spectroscopy in biosynthetic studies," Progress in Nuclear Magnetic Resonance Spectroscopy, vol. 51, no. 3, pp. 155–198, Nov. 2007, doi: 10.1016/j.pnmrs.2007.02.006.

[86] M. Ghiasi, S. Taheri, and M. Tafazzoli, "Dynamic stereochemistry of rutin (vitamin P) in solution: theoretical approaches and experimental validation," Carbohydrate Research, vol. 345, no. 12, pp. 1760–1766, Aug. 2010, doi: 10.1016/j.carres.2010.05.013.

[87] M. Ghiasi, A. A. Oskouie, and H. Saeidian, "Dynamic stereochemistry of Topiramate (anticonvulsant drug) in solution: theoretical approaches and experimental validation," Carbohydrate Research, vol. 348, pp. 47–54, Feb. 2012, doi: 10.1016/j.carres.2011.11.010.

[88] S. Sun et al., "The Application of Quantitative 1H-NMR for the Determination of Orlistat in Tablets," Molecules, vol. 22, no. 9, p. 1517, Sep. 2017, doi: 10.3390/molecules22091517.

[89] L. Qin, X. Wang, and D. Lu, "Quantitative determination and validation of topiramate and its tablet formulation by 1H-NMR spectroscopy," Anal. Methods, vol. 11, no. 5, pp. 661–668, Jan. 2019, doi: 10.1039/C8AY02316F.

[90] "UV-Vis Spectroscopy: Principle, Strengths and Limitations and Applications | Technology Networks." Accessed: Feb. 05, 2024. [Online]. Available: https://www.technologynetworks.com/analysis/articles/uv-vis-spectroscopy-principle-strengths-and-limitations-and-applications-349865

[91] A. A. Hamad, "Utility of a fluorescent probing strategy for designing a distinctive chemically mutagenized reaction for the determination of an antiepileptic agent; topiramate," Talanta Open, vol. 7, p. 100179, Aug. 2023, doi: 10.1016/j.talo.2022.100179.

[92] B. Mohammadi, E. Tammari, S. Fakhri, and G. Bahrami, "Applicability of LC-MS/MS to optimize derivatization of topiramate with FMOC-Cl using reacted/intact drug ratio," J Chromatogr B Analyt Technol Biomed Life Sci, vol. 928, pp. 32–36, Jun. 2013, doi: 10.1016/j.jchromb.2013.02.041.

[93] E. C. Pinto, M. da S. Gonçalves, L. M. Cabral, D. W. Armstrong, and V. P. de Sousa, "Development and validation of a stability-indicating HPLC method for topiramate using a mixed-mode column and charged aerosol detector," J Sep Sci, vol. 41, no. 8, pp. 1716–1725, Apr. 2018, doi: 10.1002/jssc.201701340.

[94] Z. Xiaohonggaohaimengxinfang and X. An, "HPLC-ELSD determination of topiramate and its preparations," Chinese Journal of Pharmaceutical Analysis, 2006, Accessed: Feb. 05, 2024. [Online]. Available: https://www.semanticscholar.org/paper/HPLC-ELSD-determination-of-topiramate-and-its-Xiaohonggaohaimengxinfang-An/76d175ee322a2953e364416d306e03a1edfa29bd

[95] G. Bahrami, S. Mirzaeei, B. Mohammadi, and A. Kiani, "High performance liquid chromatographic determination of topiramate in human serum using UV detection," J Chromatogr B Analyt Technol Biomed Life Sci, vol. 822, no. 1–2, pp. 322–325, Aug. 2005, doi: 10.1016/j.jchromb.2005.05.032.

[96] X. Xiang, C. Y. Ko, and H. Y. Guh, "Ion-exchange chromatography/electrospray mass spectrometry for the identification of organic and inorganic species in topiramate tablets," Anal Chem, vol. 68, no. 21, pp. 3726–3731, Nov. 1996, doi: 10.1021/ac960425x.

[97] "Application of HPTLC and LC-MS Methods for Determination of Topiramate in

Pharmaceutical Formulations | Bentham Science." Accessed: Feb. 05, 2024. [Online]. Available: https://www.eurekaselect.com/article/18847

[98] S. S. Yenare, D. M. S. Tare, P. S. Navasupe, A. B. Bangar, and S. S. Bole, "UV SPECTROSCOPIC METHOD FOR ESTIMATION OF TOPIRAMATE BULK AND PHARMACEUTICAL DOSAGE FORMS," World Journal of Pharmaceutical Research, vol. 8, no. 8.