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ORIGINAL ARTICLE

Synthesis of Impurities in the Manufacture of Oxcarbazepine and Carbamazepine

P Prathyun[1], Mayukh Baidya[1,*]

[1] *Department of Pharmaceutical Chemistry, Krupanidhi College of Pharmacy, Bangalore, Karnataka, India*

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* *Corresponding author.*
Mayukh Baidya

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ABSTRACT

Oxcarbazepine and carbamazepine are both commonly used anticonvulsant drugs, and the identification and control of impurities are of paramount importance for product safety and efficacy. The aim of this study was to synthesise, isolate, and characterise the major process-related impurities that form during their production. Process-related impurities were synthesised through selective chemical reactions of raw materials, such as 10-methoxyiminostilbene, hydroxylamine hydrochloride, and sodium cyanate, in a controlled environment. Two reaction schemes were used to produce oximinostilbene,10-methoxycarbamazepine, oxcarbazepine, and carbamazepine. Purification was performed via solvent extraction and recrystallisation. Characterisation was performed using Thin Layer Chromatography (TLC), infrared (IR) Spectroscopy, Nuclear Magnetic Resonance (NMR), and Mass Spectrometry (MS). The synthesised process-related impurities were confirmed by physicochemical and spectroscopic methods. Oximinostilbene (73% yield), 10-methoxycarbamazepine (80%), oxcarbazepine (75%), and carbamazepine (46%) yielded clear melting points and Rf values. IR, NMR, and MS analyses confirmed the structural identity and purity of each compound. The present study provides a detailed synthesis and extensive structural elucidation of process-related impurities not only in oxcarbazepine but also in carbamazepine routes to support impurity profiling for regulatory and quality control standards.

Keywords: Oxcarbazepine; Carbamazepine; Impurities; Mass spectra

INTRODUCTION

Impurities in drug compounds are of paramount importance to drug safety, efficacy, and regulation. Impurities, even at trace levels, may affect pharmacokinetics, cause toxicity, and undermine the therapeutic efficacy. Regulatory agencies such as the United States Pharmacopeia (USP) and the International Council for Harmonisation (ICH) enforce rigorous identification, quantitation, and control of impurities in active pharmaceutical ingredients (APIs), especially in highly prescribed medications such as oxcarbazepine and carbamazepine. These drugs, both dibenzazepine derivatives, are extensively utilized as anticonvulsants and mood stabilizers for the management of epilepsy and bipolar disorder.[1]

In the process of manufacturing oxcarbazepine and carbamazepine, structurally analogous impurities, such as oximinostilbene, iminodibenzyl, and 10-methoxy carbamazepine, tend to be formed because of incomplete reactions, side reactions, or degradation.[2,3] The synthesis and proper characterisation of these impurities are needed not only for process optimisation but also for adherence to pharmacopoeial specifications and regulatory compliance. Some studies have also highlighted the necessity of strong analytical methods to detect and describe these impurities employing spectroscopic methods like Infrared (IR), Nuclear Magnetic Resonance (NMR), and Mass Spectrometry.[4]

The aim of the present study was to synthesise known impurities that are likely to be produced in the industrial manufacturing of oxcarbazepine and carbamazepine and to characterise the prepared impurities through IR, NMR, and Mass spectroscopy.

MATERIALS AND METHODS

The methods used for the synthesis and characterisation of impurities include the use of targeted raw materials, predetermined reaction conditions, and analysis methods. The synthesised products were characterised using spectral data and physicochemical parameters.

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Materials used for the synthesis

Raw materials, such as 10-methoxyiminostilbene, sodium cyanate, DL-mandelic acid, dichloromethane, sodium bicarbonate, isopropyl alcohol, concentrated hydrochloric acid, ethyl acetate, oxalic acid dihydrate, methanol, BW 280 carbon, and Hi Flow were used. Every compound had a special function in the chemical reactions undertaken and was weighed according to its molecular weight to ensure stoichiometric proportions.

Scheme of synthesis

Impurities were synthesised according to two reaction schemes. In Scheme 1, 10-methoxyaminostilbene was prepared by reacting 10-methoxystilbene with hydroxylamine hydrochloride and sodium acetate with glacial acetic acid under reflux. The resulting product was oxidised with hydrogen peroxide and formic acid to produce oximinostilbene. The product was further hydrolysed with oxalic acid and urea at 80–100 °C to produce 10-methoxycarbamazepine. The product was then cyclised under acidic conditions to produce oxcarbazepine. In Scheme 2, oximinostilbene reacts with methanolic hydrochloric acid and formaldehyde to yield carbamazepine through methoxylation and cyclisation. The melting points, Rf values (through TLC in n-hexane:ethyl acetate 6:4), and yields were obtained for all the synthesised compounds.

Instrumentation

The synthesised compounds were identified and characterised using Thin Layer Chromatography (TLC), infrared (IR) Spectroscopy, Nuclear Magnetic Resonance (NMR) spectroscopy, and mass spectrometry (MS). TLC was carried out using a hexane/ethyl acetate (6:4 v/v) solvent system on Silica Gel 60 F254 plates. IR spectra were obtained using a SHIMADZU FTIR 8400S spectrometer using the KBr pellet technique. NMR spectra were recorded on a BRUKER AVANCE-300 instrument using tetramethylsilane as an internal reference. Mass spectra were taken from a SHIMADZU GC/MS 210 spectrophotometer.

Synthesis of Oximinostilbene

In a 500 mL four-necked round-bottom flask, 40 g of 10-methoxyiminostilbene was dissolved in 400 mL of dichloromethane. 55.5 g of boric acid and 53.8 g of urea were added. The reaction mixture was then refluxed at 35–45°C. The reaction was monitored using thin-layer chromatography (TLC). After cooling, the reaction mixture was filtered and washed with dichloromethane. The solvent was completely evaporated, and 80 mL of ethanol was added. The mixture was maintained for 1 h before it was filtered, washed with ethanol, and subjected to vacuum drying. The product, oximinostilbene, was obtained as a white crystal.

Synthesis of 10-Methoxycarbamazepine

A 500 mL four-neck flask was loaded with 40 g of 10-methoxyiminostilbene and 1000 mL of dichloromethane. Sodium cyanate (175 g) and DL-mandelic acid (240 g) were then added to the flask. The mixture was stirred and heated to 40–45°C for 6 h. The reaction was monitored using thin-layer chromatography (TLC). The solution was cooled, 1000 mL of distilled water was added, and the solution was then separated into layers. The aqueous layer was then extracted with dichloromethane. The organic layers were combined, washed with sodium bicarbonate solution and distilled water, and dried. Isopropyl alcohol was added, and the solvent was distilled. The residue was cooled, filtered, and dried to obtain 10-methoxycarbamazepine as a white crystalline solid.

Synthesis of Oxcarbazepine

100 g of 10-methoxycarbamazepine was placed in a 500 mL four-necked round-bottom flask. Distilled water (1000 mL) and oxalic acid dihydrate (71 g) were then added. The mixture was then refluxed for 18 h at 95–105°C. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the mixture was cooled, filtered, and dried. The residue was resuspended in water, filtered, and dried. Isopropyl alcohol (800 mL) was added, and the mixture was refluxed for 3 h at 75–85°C. After cooling for 1 h, the mixture was filtered and washed with IPA. The final reflux with water was performed for 3 h and then cooled and filtered. The pure oxcarbazepine product was isolated as a white crystalline solid.

Characterization Techniques

Melting Point Determination:

The melting points were determined in open capillary tubes using a Scientific MP digital instrument. All determinations were uncorrected and used for purity assessment.

Thin Layer Chromatography (TLC):

Thin-layer chromatography was performed to determine the product purity. Typical Rf values verified the identity of the synthesised compounds.

Infrared Spectroscopy (IR):

IR spectra were obtained for all the compounds using the KBr pellet method. Functional group assignments were performed using characteristic absorption bands.

Nuclear Magnetic Resonance (NMR):

Proton and carbon-13 NMR spectra were obtained, and chemical shifts were attributed to individual atoms in the molecule. Tetramethylsilane was used as an internal reference.

Mass Spectrometry (MS):

Mass spectra verified the molecular weights of the target compounds using protonated molecular ions and fragmentation patterns.

RESULTS

The synthesised impurities were identified and characterised successfully using thin-layer chromatography (TLC), infrared (IR) spectroscopy, and NMR spectroscopy. TLC was carried out with an n-hexane/ethyl acetate solvent system at a 6:4 v/v ratio. IR spectra were obtained using a SHIMADZU FTIR 8400S spectrometer by adopting the KBr pellet method, and NMR was performed on a BRUKER AVANCE-300 spectrophotometre.

Oximinostilbene ($C_{14}H_{11}NO$) had a molecular weight of 209.24, with a yield of 73%, a melting point of 197 to 199°C, and Rf value of 0.46. 10-Methoxy carbamazepine ($C_1H_{14}N_2O_2$) demonstrated a molecular weight of 266.29, yield of 80%, a melting point of 186 to 188°C, and an Rf value of 0.38. Oxcarbazepine ($C_{15}H_{12}N_2O_2$) had a molecular weight of 252.26, a yield of 75%, a melting point of 218 to 224°C, and an Rf value of 0.40. Carbamazepine ($C_{15}H_{12}N_2O$) yield was 46%, with a molecular weight of 236.27, a melting point of 189 to 192°C, and an Rf value of 0.48 (Table 1).

IR and NMR analyses further validated the structures and functional groups of the synthesised impurities. The NMR and mass spectra of Oximinostilbene, 10-methoxy carbamazepine, Oxcarbazepine and Carbamazepine are shown in Figures 1, 2, 3 and 4.

DISCUSSION

The synthesised impurities were identified and systematically characterised using TLC, IR spectroscopy, and NMR spectroscopy. The application of a solvent system of n-hexane and ethyl acetate in a ratio of 6:4 v/v for TLC analysis conforms to previous research that shows to the potency of non-polar to moderately polar solvent systems in the separation of structurally related compounds.[5] Rf values in the current study ranged from 0.38 to 0.48, offering sufficient separation and initial identification of impurities. These values enable qualitative identification and further support the robustness of the analytical method. IR and NMR spectroscopic investigations provided further information about the chemical functionalities and structural characteristics of the impurities, confirming their identities and supporting the TLC observations.

Infrared spectroscopy was carried out with the KBr pellet technique on a SHIMADZU FTIR 8400S spectrometer, which confirmed the presence of critical functional groups such as carbonyl (C=O), amine (NH_2), and aromatic rings. Application of IR spectroscopy for verification of particular functional groups among carbamazepine analogs is widely

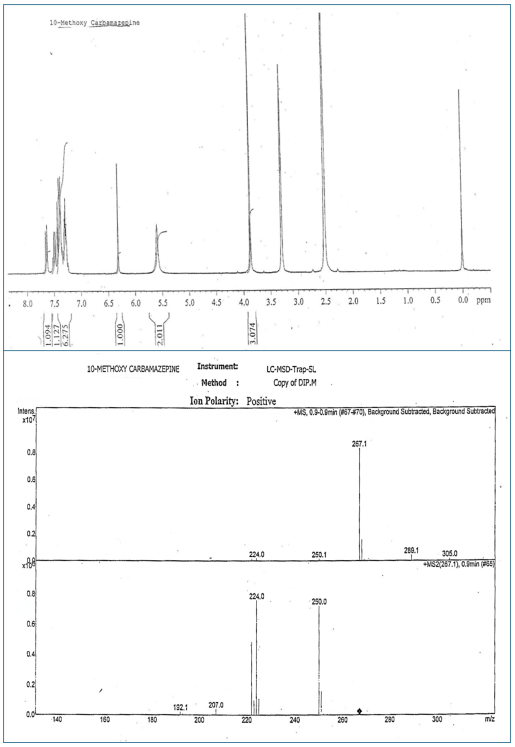

Fig. 1: NMR and Mass spectra of Oximinostilbene (10,11-Dihydro-10-OXO-5H-dibenz[b,f]azepine)

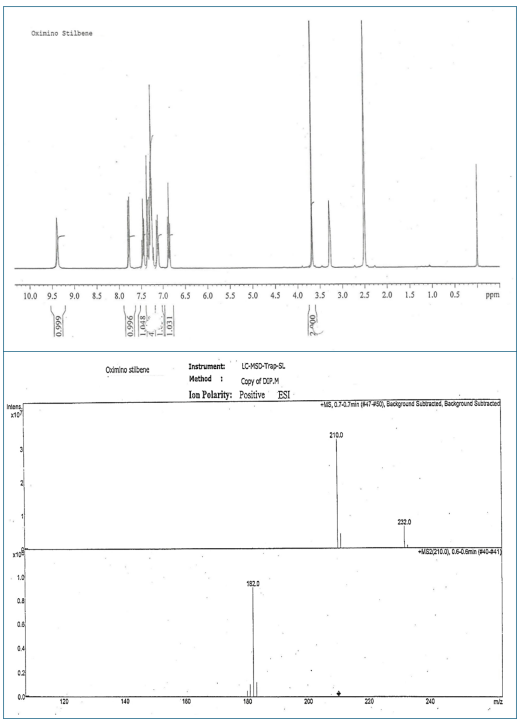

Fig. 2: NMR and Mass spectra of 10-methoxy carbamazepine (10-methoy-5H-dibenzo[b,f]azepine-5-carboxamide)

Table 1: Physical characterization data of synthesized impurities

Sr. No.	Sample	Molecular Formula	Molecular weight	Yield	Melting Point	R_f Value
1	Oximinostilbene	$C_{14}H_{11}NO$	209.24	73%	197-199 °C	0.46
2	10-methoxy carbamazepine	$C_{16}H_{14}N_2O_2$	266.29	80%	186-188°C	0.38
3	Oxcarbazepine	$C_{15}H_{12}N_2O_2$	252.26	75%	218-224 °C	0.40
4	Carbamazepine	$C_{15}H_{12}N_2O$	236.27	46%	189-192 °C	0.48

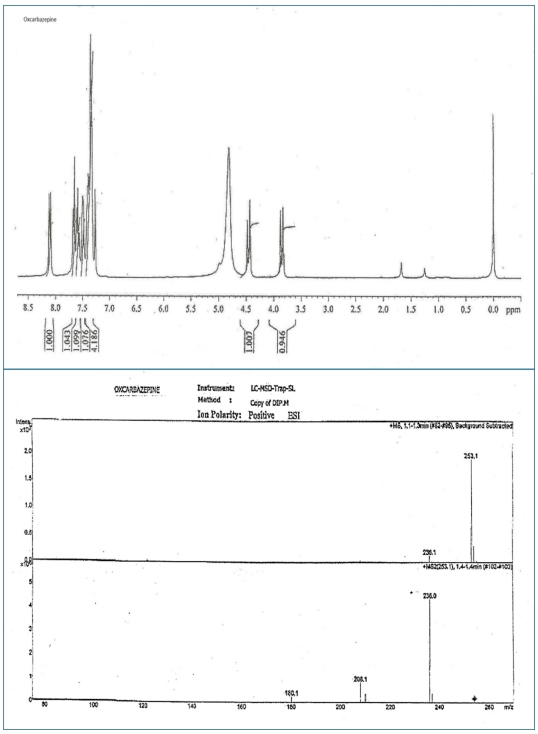

Fig. 3: NMR and Mass spectra of Oxcarbazepine (10,11-dihydro-10-oxo-5H-dibenz (b,f) azepine -5-carboxamide)

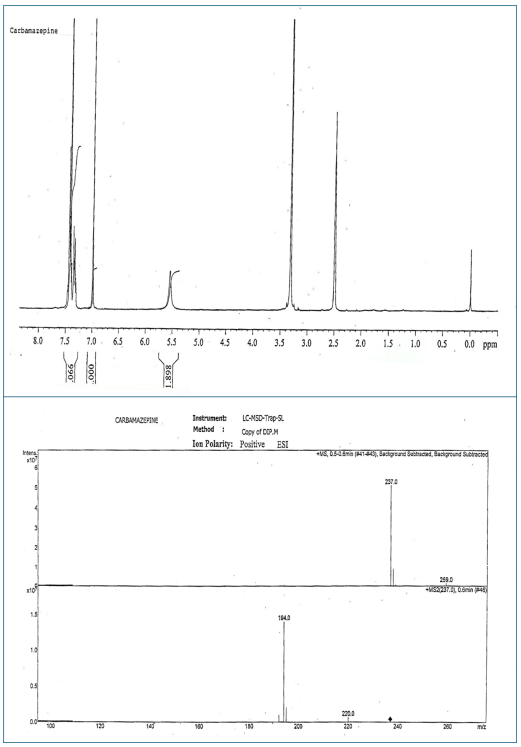

Fig. 4: NMR and Mass spectra of Carbamazepine (5H-dibenzo[b,f]azepine-5- carboxamide)

reported in previous literature.[4]

NMR spectroscopy of BRUKER AVANCE-300 provided detailed insights into the chemical environments of hydrogen and carbon atom chemicals in the synthesised impurities. The chemical shifts and splitting patterns matched those of the proposed structures, which were oximinostilbene, 10-methoxy carbamazepine, oxcarbazepine, and carbamazepine. NMR spectroscopy proved to be a reliable analytical tool for structural elucidation of the synthesised impurities.

The melting points and yields of the prepared compounds confirmed their purity and synthetic efficacy. The melting points ranges correspond closely with those reported in previous pharmacopoeial and synthetic chemistry texts, and this supports the reproducibility of the synthetic procedures used.[1] For example, oxcarbazepine's melting point (218 to 224°C) concurs with published values, verifying its identity as well as structural integrity.[6]

A 2011 study utilised liquid chromatography-tandem mass spectrometry (LC-MS/MS) to identify and analyse unknown impurities present in the active pharmaceutical ingredients of carbamazepine. The impurity was identified as tetrabenzo[b,f,b'f']azepino[4',5':4,5]thieno[2,3-d]azepine-3,9-dicarboxamide, indicating the complexity of the impurity profiles in the carbamazepine synthesis.[7] Another study used a reversed-phase high-performance liquid chromatography (RP-HPLC) method to quantify carbamazepine and the known impurities iminostilbene and iminodibenzyl in tablet drug products. The procedure exhibited specificity, linearity, and accuracy; thus, it is applicable for routine quality control.[8] The United States Pharmacopeia (USP)has established definite limits for related compounds in carbamazepine, such as iminostilbene and iminodibenzyl. These guidelines were intended to ensure the purity and safety of

carbamazepine products.[8]

Oxcarbazepine is structurally related to carbamazepine and, consequently, shares some common impurities such as iminostilbene and carbamazepine. Analytical procedures were formulated to estimate oxcarbazepine, carbamazepine, and these impurities simultaneously, so as to cover entire quality control.[3] The current study shows the significance of identifying and controlling impurities in the production process of carbamazepine and oxcarbazepine to ensure drug efficacy and patient safety.

CONCLUSION

In conclusion, the synthesised impurities, oximinostilbene, 10-methoxy carbamazepine, oxcarbazepine, and carbamazepine, were successfully characterised and identified by TLC, IR, and NMR, confirming their structural purity and integrity. The analytical results, such as the Rf values, melting points, and spectral findings, demonstrated the reliability of the employed synthesis and characterisation processes. The present study highlights the importance of impurity profiling to ensure the quality and safety of pharmaceutical products.

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