Review Degradation Study for Production and Identification of Oxcarbazepine Impurities

Jyoti Bind [1]
[1]Department of Pharmacy, Chhatrapati Shivaji Maharaj University, Panvel 410206

***Abstract*—The present paper describes the development of a stability indicating Thin Layer Chromatography method (TLC) oxcarbazepine in the presence of its impurities and degradation products generated from forced decomposition studies. The drug substance was subjected to stress conditions of hydrolysis, oxidation, photolysis and thermal degradation. The degradation of oxcarbazepine was observed under base hydrolysis. The drug was found to be stable to other stress conditions attempted. Successful separation of the drug from the synthetic impurities and degradation product formed under stress conditions was achieved on a C18 column (4.6-mm × 25-cm; 3-µm packing L1) operated at 50°. The optimal mobile phase was found to be a Solution A: Acetonitrile, tetrahydrofuran, Buffer B, and water (1:2:2:15) and Solution B: Acetonitrile, tetrahydrofuran, Buffer B, and water (6:1:1:2). The flow rate was set at 0.8 mL per minute, and detection was performed at a wavelength of 240 nm.**

The developed HPLC method was validated with respect to linearity, accuracy, precision, specificity and robustness. The developed HPLC method to determine the related substances and assay determination of oxcarbazepine can be used to evaluate the quality of regular production samples. It can be also used to test the stability samples of oxcarbazepine.

***Keywords*— Oxacabazepine; stress studies;c18 coloum; uv detection 240nm**

I. INTRODUCTION

Oxcarbazepine [sold under brand name Trileptal or Oxtellar]. Oxcarbazepine (10, 11-dihydro-10-oxo-5Hdibenzazepine-5-carboxamide) is a 10-keto analogue of carbamazepine. It is an anticonvulsant and mood-stabilizing drug, used primarily in the treatment of epilepsy and also treat anxiety and mood disorders.

It belongs to the Chemical Class: Iminostilbenes

Molecular formula: C15H12N2O2.

Molecular weight: 252.27 g/mol.

Storage: Store in a tightly closed container protected from light in a cool and dry place

Shelf Life: 24 months when stored properly

Poisonous: Non-poisonous under standard usage conditions

Melting Point: 215C - 218C

Colour: White to off-white.

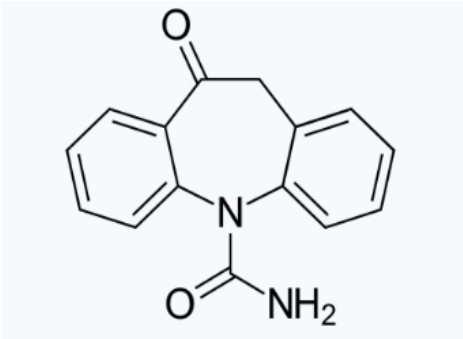
Solubility: Slightly soluble in ethanol practically insoluble in water

Oxcarbazepine is structurally a derivative of carbamazepine, adding an extra oxygen atom on the dibenzoazepine ring. This difference helps reduce the impact on the liver of metabolizing the drug, and prevents the serious forms of anaemia occasionally associated with carbamazepine. Aside from this reduction in side effects, it is assumed to have the same mechanism as carbamazepine - sodium channel inhibition, and is generally used to treat the same conditions. Its mechanism of action involves its action, which block the voltage sensitive Na+ channel, and stabilizes hyper-excited neutral membrane it suppresses repetitive neural firing and diminishes transmission of synaptic impulses. Generally, it is administered orally in the form of tablets or suspension. Drug is 67% protein bound and is widely distributed thought the body.Oxcarbazepine has some common drug reaction such as sedation, dizziness, headache, ataxia, fatigue, nausea, vomiting.

Forced degradation study of any API is process where a pharmaceutical API is exposed to server physicochemical condition. The main aim of forced degradation study is to accelerate the natural degradation of the product, identify its potential degraded impurity, and check the stability of API. Impurities are degraded product, which are formed during forced degradation of API. Any minor presence of impurity can influence the efficacy and safety of drug. Oxcarbazepine structurally resembles to Carbamazepine substitution of ketone group in the place of carbon-carbon double bond in the structure of carbamazepine yields oxcarbazepine. The IUPAC name of oxcarbazepine is 10, 11dihydro-10-oxo-5H-dibenz [b, f] azepine-5-carboxamide.

It has a neutral pH level of around 7 in aqueous solution and is commonly used in the treatment of epilepsy for managing partial and generalized seizures. This pharmaceutical grade product has a melting point of 215C - 218C and is tasteless and odourless. It is non-poisonous under standard usage conditions and has a shelf life of 24 months when stored properly. With a purity of 99.0%, our Oxcarbazepine API is a high-quality active pharmaceutical ingredient that is slightly soluble in ethanol and practically insoluble in water.

STRUCTURE:



II. MATERIAL AND METHODS

Sample of Oxcarbazepine API was supplied or provided by in house department. All solvent used in the process were of HPLC grade.

COMPOUND NAME	MAKE
HCL	SPECTRO CHEM
CAN	FINAR
NAOH	ACYTYLIS
MCBPA	SWATI CHEMICAL
METHANOL	RANKEM
CHLOROFORM	MEMBA CHEM INDIA
ETHYL ACETATE	ADVENT CHEMBIA PVT.LTD
HEXANE	ACETO PHARMA
AMMONIA	ACYTYLIS

CHROMATOGRAPHIC CONDITION:
Chromatography of different impurities was done by using mobile phase ethyl acetate: hexane in ratio of 80:20[v/v]

COLOUMN CHROMATOGRAPHY
SILICA USED IN CHROMATOGRAPHY ARE OF 3 TYPES:
1.) 60:120- Acidic [acidic or less basic compound]
2.) 100:200- Basic [if compound is more basic 60:120 can stuck the column and therefore the 100:200 is used.]
3.) Neutral- Here for column chromatography 60:120 silica was used.

HPLC
• ORGANIC IMPURITIES PROCEDURE:
Buffer A: 0.004 mol/L of monobasic potassium phosphate and 0.063 mol/L of dibasic sodium phosphate

Buffer B: To 1 L of 3.6 g/L edetate disodium in water add 1 L of Buffer *A*.

Diluent: 1.8 g/L of ascorbic acid in water

Solution A: Acetonitrile, tetrahydrofuran, Buffer *B*, and water (1:2:2:15)

Solution B: Acetonitrile, tetrahydrofuran, Buffer *B*, and water (6:1:1:2)

Mobile phase: See table below.

Time (min)	Solution A (%)	Solution B (%)
0	80	20
1	80	20
29	30	70
30	30	70
33	80	20
42	80	20

System suitability solution: 2 µg/mL each of USP Oxcarbazepine Related Compound A RS, USP Oxcarbazepine Related Compound B RS, USP Oxcarbazepine Related Compound D RS and USP Oxcarbazepine Related Compound E RS in a 1:1 mixture of acetonitrile and Diluent
Standard stock solution: 0.1 mg/mL of USP Oxcarbazepine RS in acetonitrile
Standard solution: 2 µg/mL of USP Oxcarbazepine RS in a 1:1 mixture of acetonitrile and Diluent
Sample solution: 1.0 mg/mL of Oxcarbazepine in a 1:1 mixture of acetonitrile and Diluent
CHROMA
TOGRAPHIC SYSTEM
Mode: LC

Detector: UV 240 nm
Column: 4.6-mm × 25-cm; 3-µm packing L1
Column temperature: 50°
Flow rate: 0.8 mL/min
Injection volume: 50 µL
System suitability
Samples: System suitability solution and Standard solution
Suitability requirements
Resolution: NLT 1.0 between oxcarbazepine related compound A and oxcarbazepine related compound B;

NLT 1.2 between oxcarbazepine related compound D and oxcarbazepine related compound E, System suitability solution
Relative standard deviation: NMT 5.0%, Standard solution
Analysis:

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Oxcarbazepine related compound Fa	0.76	0.59	0.2
Oxcarbazepine	1.0	—	—
N-Carbamoyl oxcarbazepine	1.1	0.91	0.05
Oxcarbazepine related compound Ac	1.2	1.1	0.2
Oxcarbazepine related compound Bd	1.3	1.1	0.1
Dibenzazepinodionee	1.7	2.0	0.1
Oxcarbazepine related compound Df	2.3	1.7	0.2
Oxcarbazepine related compound E	2.4	3.3	0.05
Any individual unspecified impurity	—	1.0	0.05
Total impurities	—	—	1.0

Samples Standard solution and Sample solution

Calculate the percentage of each impurity in the portion of Oxcarbazepine taken:

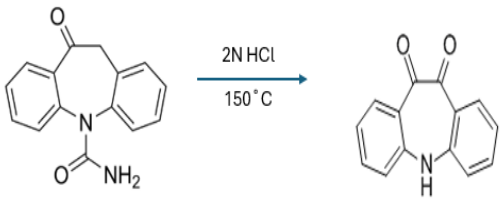
Result = $(r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$
r_U = peak response of each impurity from the Sample solution
r_S = peak response of oxcarbazepine from the Standard solution
C_S = concentration of USP Oxcarbazepine RS in the Standard solution (mg/mL)
C_U = concentration of Oxcarbazepine in the Sample solution (mg/mL)
F = relative response factor
Acceptance criteria: See [NOTE—disregard any peak below 0.03%.]

SYNTHESIS

Forced degradation of oxcarbazepine API was performed and observed in 6 different conditions.

1. Acid Degradation DP-1
2. Base Degradation DP-2
3. Oxidation Degradation DP-3
4. MCBPA Degradation DP-4
5. Thermal Degradation DP-5
6. Photochemical Degradation DP-6

Degradation General Procedure:
1.) Acid Hydrolysis: 2N HCl, 100°C
Procedure: 2N HCl (10 Vol) was added to API at 0 °C and after addition allowed the reaction mixture to stirred at RT for 30 min. The reaction was monitored by TLC and further the reaction mixture was heated to 100 °C and monitored by TLC. The reaction mixture was heated at 100 °C for about 8-10 h and then monitored by TLC and mass analysis.
Work up: The reaction mixture allowed to RT and checked solid precipitates out or not, further cooled reaction mixture to 0 °C°C and basify with aq. ammonia and extracted with Chloroform (10 Vol X 2), combined the Chloroform layer, dried over sodium sulphate and concentrated up to dryness.
Purification: The column purification performed using Ethyl acetate: hexane as solvent system and 60:120 silica mesh. The pure fraction obtained were concentrated up to dryness. The pure product submitted for analysis.



2) Base Hydrolysis: 2N NaOH, 100°C

Procedure: 2N NaOH (10 Vol) was added to API at 0 °C and after addition allowed the reaction mixture to stirred at RT for 30 min. The reaction was monitored by TLC and further the reaction mixture was heated to 100 °C and monitored by TLC. The reaction mixture was heated at 100 0C for about 8-10 h and then monitored by TLC and mass analysis.

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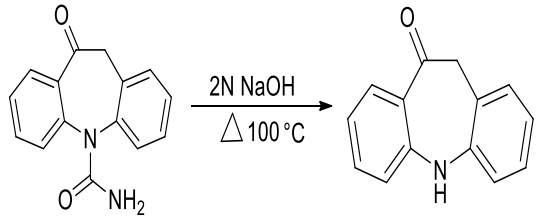

3) Oxidation: 30% H2O2, 100 °C

Procedure: 30% H2O2 (10 Vol) was added to API at 0 °C and after addition allowed the reaction mixture to stirred at RT for 30 min. The reaction was monitored by TLC and further the reaction mixture was heated to 100 °C and monitored by TLC. The reaction mixture was heated at 100 °C for about 8-10 h and then monitored by TLC and mass analysis.

Work up: The reaction mixture allowed to RT and checked solid precipitates out or not, further cooled reaction mixture to 0 °C and basify with aq. ammonia and extracted with Chloroform (10 Vol X 2), combined the Chloroform layer, dried over sodium sulphate and concentrated up to dryness.

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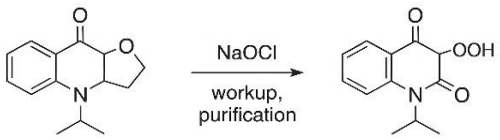
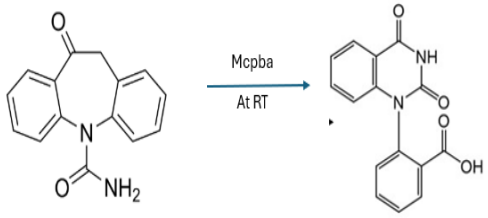


4) Oxidation: mCPBA, ACN, RT

Procedure: To a stirred solution of API in Acetonitrile 10 (vol) mCPBA (1.5 eq.) was added at 0 °C and after addition allowed the reaction mixture to stir at RT for 8 h. The reaction was monitored by TLC and mass analysis.

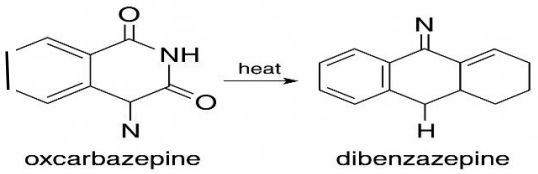
Work up: The reaction mixture allowed to RT and added water (10 Vol) and extracted with Chloroform (10 Vol X 2), combined the Chloroform layer, dried over sodium sulphate and concentrated up to dryness.

Purification: The column purification performed using EA: Hexane as solvent system and 60:120 silica mesh. The pure fraction obtained were concentrated up to dryness. The pure product submitted for analysis.



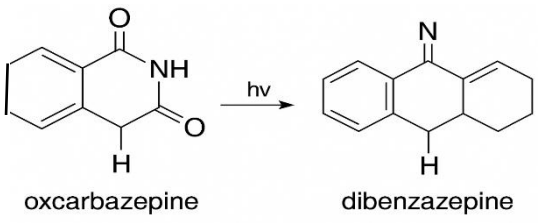
5) Thermal degradation: Water, 100°C

Procedure: Water (10 Vol) was added to API at 0 °C and after addition allowed the reaction mixture to stirred at RT for 30 min. The reaction was monitored by TLC and further the reaction mixture was heated to 100 °C and monitored by TLC. The reaction mixture was heated at 100 °C for about 8-10 h and then monitored by TLC and mass analysis



6) Photochemical degradation: Water, 30% H2O2, RT

Procedure: Water (8 Vol) and 30% H2O2 (2 vol) was added to API at 0 °C and after addition allowed the reaction mixture to stirred at RT under sunlight for about 8-10 h and then monitored by TLC and mass analysis.



III. REVIEW

Oxycarbamazepine shows a good stability under acidic, oxidative, thermal and photolytic conditions, with only minor degradation observed. The drug is loss occur under basic hydrolysis, indicating higher ssceptibiliyi in aklaine medium,\. The stability indicate the LC method clearly resolved the drug peak from its degradation product, supporting its use in forced degradation and shelf life studies. The finding shows that formulation pH and excipients alkalinity should be carefully controlled to maintain product quality.

IV. CONCLUSION

Forced degradation such as condition on Oxcarbazepine API was performed, observed while quantitative and brief study was also done by using HPLC method.

Oxcarbazepine Impurities were synthesized, identified and characterized using mass, HPLC and NMR Values.

The study confirms that oxcarbazepine is stable under hydrolytic conditions but degrades under thermal, oxidative, and photolytic stress, forming impurities such as dibenzoazepine and oxidized derivatives.

These findings are essential for:

- Developing a stability-indicating analytical method,
- Ensuring regulatory compliance,
- Designing robust formulations that minimize impurity formation during manufacturing and storage.

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