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A REVIEW ON CHROMATOGRAPHIC AND SPECTROPHOTOMETRIC ESTIMATION OF ESCITALOPRAM OXALATE AND ESZOPICLONE IN BULK AND IN DIFFERENT DOSAGE FORMS

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ABSTRACT

Nowadays antidepressant drugs like selective serotonin reuptake inhibitors (SSRIs) represent the first choice in the treatment of moderate to severe depressive illness, various phobias, and personality disorders and non-benzodiazepine have a demonstrated efficacy in treating sleep disorders. This review includes most of the published analytical methods for estimation of Escitalopram oxalate and eszopiclone based on high-performance liquid chromatography coupled with UV, fluorescence and mass spectrometry detectors, capillary electrophoresis and gas chromatography with mass spectrometry detectors among others. Thus, this paper will help in the selection and development of proper analytical methodologies for estimation of SSRIs and non-benzodiazepine to achieve satisfactory results.

KEYWORDS: Selective Serotonin Reuptake Inhibitors (SSRIS), Non – benzodiazepine, High-Performance Liquid Chromatography (HPLC), Gas Chromatography (GC).

INTRODUCTION

Selective serotonin re-uptake inhibitors or serotonin-specific reuptake inhibitors (SSRIs) are a class of compounds typically used as antidepressants in the treatment of major depressive disorder and anxiety disorders.

Escitalopram oxalate is an orally administered selective serotonin reuptake inhibitor (SSRI). Escitalopram utilized as a part of treatment of major depressive disorder and generalized Anxiety Disorder Escitalopram is the pure S-enantiomer (single isomer) of the racemic bicyclic phthalane derivative citalopram. Escitalopram oxalate is designated S-(+)-1-[3-(dimethyl-amino) propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile oxalate.

The mechanism of antidepressant action of Escitalopram, the S-enantiomer of racemic citalopram, is presumed to be linked to potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT).

Escitalopram oxalate are believed to increase the extracellular level of the neurotransmitter serotonin by limiting its reabsorption into the presynaptic cell, increasing the level of serotonin in the synaptic cleft available to bind to the postsynaptic receptor. They have varying degrees of selectivity for the other monoamine transporters, with pure SSRIs having only weak affinity for the norepinephrine and dopamine transporters.

Use of Escitalopram oxalate is, the main indication for SSRIs is major depressive disorder (also called "major depression", "clinical depression" and often simply "depression"). It is prescribed for anxiety disorders, such as social anxiety disorder, panic disorders, obsessive–compulsive disorder (OCD), eating disorders, chronic pain and occasionally, for posttraumatic stress disorder (PTSD). It is also frequently used to treat depersonalization disorder, although generally with poor results.

Escitalopram oxalate have the power to markedly improve mood, outlook, and behavior in people with depression.

The no benzodiazepines are positive allosteric modulators of the GABA-A receptor. Like the benzodiazepines, they exert their effects by binding to and activating the benzodiazepine site of the receptor complex. Many of these compounds are subtype selective providing novel anxiolytics with little to no hypnotic and amnesiac effects and novel hypnotics with little or no anxiolytic effects.

Eszopiclone is a no benzodiazepine hypnotic agent that is a pyrrolopyrazine derivative of the cyclopyrrolone

class. The chemical name of eszopiclone is (+)-(5S)-6-(5-chloropyridin-2-yl)-7-oxo-6, 7-dihydro-5H-pyrrolo [3, 4-b] pyrazin-5-yl 4-methylpiperazine-1-carboxylate. Its molecular weight is 388.81, and its empirical formula is $C_{17}H_{17}ClN_6O_3$. Eszopiclone has a single chiral center with an (S)-configuration.

The precise mechanism of action of eszopiclone as a hypnotic is unknown, but its effect is believed to result from its interaction with GABA-receptor complexes at binding domains located close to or allosterically coupled to benzodiazepine receptors.

Side effect of eszopiclone Memory loss, mental/mood/behavior changes (such as new/worsening depression, abnormal thoughts, thoughts of suicide, hallucinations, confusion, agitation, aggressive behavior, and anxiety).

Allergic reaction, including: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.

This paper gives an overview of various analytical methods for estimation of Escitalopram oxalate and eszopiclone. Different methods have been developed for determination of Escitalopram oxalate and eszopiclone like UV-Spectroscopy, liquid Chromatography, HPTLC and LC-MS.

Reported methods are categorized depending on the following considerations

1. Escitalopram oxalate and eszopiclone analyzed by UV-Spectroscopy methods and Chromatographic method.
2. Analysis of Escitalopram oxalate and eszopiclone from combination formulation with other drug by UV-Spectroscopy methods and Chromatographic method

Analysis of Escitalopram oxalate individual and combination with other drug by spectrophotometric and chromatographic method

Escitalopram oxalate is official in Indian pharmacopoeia.

TABLE 1.1: OFFICIAL METHODS FOR ESTIMATION OF ESCITALOPRAM OXALATE

Sr. No.	DRUG	METHOD	DESCRIPTION	Ref. No.
1	Escitalopram oxalate (IP 2014)	**Liquid chromatography**	**Detection Wavelength:** 240 nm **Mobile Phase:** n-hexane, Ethanol, Trifluoroacetic Acid (50:50 v/v) **Stationary Phase:** Stainless Steel Column 25 cm × 3.6 mm packed with Octadecylsilane **Flow Rate**: 0.4 ml/min	[7]

TABLE 1.2 REPORTED METHOD OF ESCITALOPRAM OXALATE

Sr. No.	DRUG	METHOD	DESCRIPTION	Ref. No.
1	Escitalopram in Tablet Dosage Forms	**Colorimetric Method**	**Wavelength:**417 nm **Linearity Range:**2-10 µg/ml **Correlation Coefficient (R^2):** 0.9996 **LOD:** 0.00345 µg/ml **LOQ:** 0.01045 µg/ml **%Recovery:** 98-102%	[8]
2	Escitalopram in Tablet Dosage Forms	**RP-HPLC Method**	**Detection Wavelength:**226 nm **Mobile Phase:** Methanol: disodium hydrogen phosphate: acetonitrile (28:44:28v/v) **Stationary phase:** BDS C8, 5- column (250x4.6mm) **Linearity Range:** 0.25-1.5 mg/ml **Retention Time:** 8.45 min **Flow Rate:** 1.5 ml/min **%Recovery:** 99.05% **LOD:** 0.023 µg/ml **LOQ:** 0.072 µg/ml	[9]
3	Escitalopram in Tablet Dosage Forms	**UV Spectrophotometric Method**	**Zero Order Derivative** **Wavelength:**238 nm **Solvent:** Methanol : Water (8:2v/v) **Linearity Range:** 2-20 µg/ml **Correlation Coefficient (R^2):** 0.9999 **LOD:**0.160 µg/ml	[10]

			LOQ:0.534 µg/ml **%Recovery:**99.98%	
4	Escitalopram in Tablet Dosage Forms	**HPLC Method**	**Detection Wavelength:**238 nm **Mobile Phase:** Acetonitrile : Methanol :5mM ammonium acetate buffer pH :3 (30:20:50 v/v/v) **Stationary phase:** Kromosil 5µ column (250×4.6 mm) **Linearity Range :**5.09-15.27µg/ml **Correlation Coefficient (R^2):** 0.9997 **Retention Time:** 5.36 min **Flow Rate:** 1.0 ml/min **%Recovery:** 101.86%	[11]
5	Escitalopram oxalate in Pharmaceutical dosage Forms	**HPLC**	**Detection Wavelength:**238 nm **Mobile Phase:** buffer : Acetonitrile : Methanol (670:280:50 v/v/v) **Stationary phase:** Inertsil ODS-2 (250 x 4.6 mm, 5µm) **Linearity Range :**50-200µg/ml **Correlation Coefficient (R^2):** 0.9974 **Retention Time:** 14 min **Flow Rate:** 1.0 ml/min **%Recovery:** 99.40% **LOD:** 1.54 **LOQ:**4.67	[12]
6	Escitalopram oxalate in Tablet Dosage Forms	**Spectrophotometric Method**	**Wavelength:**507 nm **Solvent:** Methanol **Linearity Range:** 2-14 µg/ml **%Recovery :** 100.5% **Correlation Coefficient (R^2):** 0.9983 **LOD:** 0.5µg/ml **LOQ:** 2 µg/ml	[13]
7	Escitalopram oxalate and clonazepam in combined dosage form	**UV Spectrometry Method**	**First Order Derivative Wavelength** Escitalopram oxalate : 238 nm Clonazepam: 273 nm **Solvent:** Methanol **Linearity Range:** Escitalopram oxalate : 5-100 µg/ml Clonazepam : 5-50 µg/ml **%Recovery :** Escitalopram oxalate : 99.07 Clonazepam :98.56	[14]
8	Escitalopram oxalate and Etizolam in combined dosage form	**RP-HPLC Method**	**Detection Wavelength:**254 nm **Mobile Phase:** Acetonitrile:0.005 M Hexane Sulfonic Acid pH 3.0 (40 : 60 /v/v) **Stationary phase:** Kromasil 100 C18, 5µ(150×4.6 mm) **Linearity Range:** Escitalopram :20 - 160µg/ml Etizolam : 2 – 16 µg/ml **Correlation coefficient:** Escitalopram **:**0.9994 Etizolam **:**0.9993 **%Recovery :** Escitaopram**:**98.14-101.72% Etizolam **:**98.83-101.12 % **Retention Time:** Escitalopram: 3.66 min Etizolam: 8.07 min	[15]

			Flow Rate: 1 ml/min	
9	Escitalopram oxalate and Flupentixol Dihydrochloride in combined dosage form	**First derivative spectroscopy**	**Detection Wavelength:** Escitalopram : 237 nm Flupentixol dihydrochoride:226 nm **Solvent :** Methanol **Linearity range :** Escitalopram **:** 20 – 120 µg/ml Flupentixol dihydrocholride **:** 1- 6 µg/ml **Correlation coefficient :** Escitalopram **:** 0.9995 Flupentixol dihydrocholride **:** 0.9991 **LOD :** Escitalopram **: 0.82 µg/ml** Flupentixol dihydrochloride **: 0.04 µg/ml** **LOQ:** Escitalopram **: 2.5 µg/ml** Flupentixol dihydrochloride **: 0.15 µg/ml**	[16]
10	Escitalopram oxalate and clonazepam in combined dosage form	**UV Spectrometry Method**	**Wavelength** Escitalopram oxalate : 238 nm Clonazepam: 222 nm **Solvent:** Methanol **Linearity Range:** Escitalopram oxalate : 10 - 24 µg/ml Clonazepam : 2 - 14 µg/ml **LOD**: Escitalopram oxalate : 0.44 µg/ml Clonazepam : 0.53 µg/ml **LOQ** : Escitalopram oxalate : 1.33 µg/ml Clonazepam : 1.61 µg/ml **Correlation coefficient :** Escitalopram oxalate : 0.9992 Clonazepam :0.9992s	[17]
11	Escitalopram oxalate and clonazepam in combined dosage form	**HPLC and UV Detection Method**	**Detection Wavelength:**240 nm **Mobile Phase:** buffer : acetonitrile (50:50 v/v) **Stationary phase:** Hypersil ODS C18 column (250mm X 4.6mm; 5µ) **Linearity Range:** Escitalopram :20 - 120µg/ml Clonazepam : 1 – 6 µg/ml **Correlation coefficient:** Escitalopram **:0.9992** Clonazepam **:0.9991** **LOD :** Escitaopram**:**2.39 Clonazepam **:**0.064 **LOQ**: Escitaopram:7.27 Clonazepam :0.194 **Retention Time:** Escitalopram:2.840± 0.007 min Clonazepam :4.007±0.006 min **Flow rate** : 1ml/min	[18]

12	Escitalopram oxalate and Fenofibrate in combined dosage form.	**RP – HPLC Method**	**Detection Wavelength:**239 nm **Mobile Phase:** buffer : Methanol: Phosphate buffer (pH 6.0) (80:20 v/v) **Stationary phase:** Agilent C18, 250 × 4.6 mm, 5µ particle size column **Linearity Range:** 2- 20 ppm **Correlation coefficient:** Escitalopram :0.995 Fenofibrate :0.996 **LOD :** Escitaopram:50ng/ml Fenofibrate :100ng/ml **LOQ:** Escitaopram:100ng/ml Fenofibrate :200ng/ml **Retention Time:** Escitalopram: 2.7min Fenofibrate: 8.3 min Flow rate : 1ml/min	[19]
13	Escitalopram oxalate and Etizolam in combined dosage form	**Spectrophotometric Method**	**First Method:** **Simultaneous Equation Method:** **Wavelength:** Escitalopram:238.2nm Etizolam: 251.6 nm **LOD :** Escitalopram : 1.13 Etizolam : 0.60 **LOQ:** Escitalopram : 3.42 Etizolam : 1.83s **Second Method:** **Q-Absorbance Ratio:** Isoabsorptive Point: Escitalopram :238.2 nm Etizolam: 248.8 nm **LOD :** Escitalopram :1.13 Etizolam : 0.57 **LOQ:** Escitalopram : 3.42 Etizolam : 1.72 **Third Method:** **Absorbance correction method** Escitalopram : 238.2 nm Etizolam :292.8 nm **LOD** : Escitalopram :1.13 Etizolam :0.57 **LOQ:** Escitalopram :3.42 Etizolam : 1.72 **Solvent:** 0.1 N NaOH **Linearity Range:** Escitalopram: 10- 60 µg/ml Etizolam: 5 - 30 µg/ml **Correlation Coefficient (R^2):** Escitalopram: 0.9989 Etizolam:0.9998	[20]

14	Escitalopram oxalate in tablet dosage form	**Stability indicating HPTLC METHOD**	**Chromatographic Development:** **Detection Wavelength:** 239 nm Stationary phase: TLC aluminum plates precoated with silica gel 60F-254 **Mobile Phase:** toluene: acetone: ethanol: ammonia (5:1:1:0.2 v/v/v/v) **Linearity Range:** 100-1000 ng.spot-1. **Correlation Coefficient (R^2):0.9987** **LOD: 20** ng.spot-1. **LOQ: 50** ng.spot-1. %Recovery: 98.72	[21]
15	Escitalopram in bulk and pharmaceutical dosage form	**Extractive spectrometric method**	**Method- A** **Detection Wavelength:** 415nm **Linearity range** : 2-10µg/ml **Correlation coefficient** : 0.9986 **%RSD** : 1.98 **%Range of error** : 1.656 **Method- B** **Detection wavelength** : 426 nm **Linearity range** : 2-10µg/ml **Correlation coefficient** : 0.9998 **%RSD** : 1.97 **%Range of error**: 1.647	[22]

Eszopiclone is official in United State pharmacopoeia (USP NF 2016).

TABLE 2.1: OFFICIAL METHODS FOR ESTIMATION OF ESZOPICLONE

Sr. No.	DRUG	METHOD	DESCRIPTION	Ref. No.
1	Eszopiclone	**Liquid chromatography**	**Detection Wavelength:** 303 nm **Mobile Phase:** Buffer: Acetonitrile (62:38 v/v) **Stationary Phase:** 4.6-mm 25-cm; 5-µm packing L1 **Flow Rate**: 1.5 ml/min	[23]

TABLE 2.2 REPORTED METHOD OF ESZOPICLONE

Sr. No.	DRUG	METHOD	DESCRIPTION	Ref. No.
1	Eszopiclone in Bulk and Tablet Dosage Forms	**Spectrometric Method**	**Wavelength:**308 nm **Solvent:** Methanol **Linearity Range:**4-24 µg/ml **Correlation Coefficient (R^2):** 0.9995 **LOD:** 0.624 µg/ml **LOQ:** 1.130 µg/ml	[24]
2	Eszopiclone in Bulk and Tablet Dosage Forms	**RP-HPLC Method**	**Detection Wavelength:**305 nm **Mobile Phase:** Methanol : Water (80:20 v/v) **Stationary phase:** Phenomenex Gemini C18 column(250 mm x 4.6.0 mm, 5 µ) **Linearity Range:** 5-30µg/ml **Retention Time:** 5.38 min **Flow Rate:** 1.0 ml/min **%Recovery:**99.90-100.09% **LOD:** 0.310/ml **LOQ:** 0.572µg/ml	[24]
3	Eszopiclone in Bulk and Pharmaceutical Dosage Forms	**UV Spectrophotometric Method**	**Zero Order Derivative Wavelength:**250 nm **Second Order Derivative Wavelength:** 241 nm **Solvent:** Methanol **Linearity Range:** 10-50 µg/ml **Correlation Coefficient (R^2):** 0.999	[25]

4	Eszopiclone in Rabbit Plasma	**RP-HPLC-MS Method**	**Detection Wavelength:** **Mobile Phase:** 15 mM Ammonium format: methanol (15:85 v/v) **Stationary phase:** Ascentis express CN (50X4.6 mm, 2.7 µm column) **Linearity Range:** 0.05 - 210.0 mg/ml **Correlation Coefficient (R^2):** 9850 **Retention Time:** **Flow Rate:** 0.6 mL/min **%Recovery:** 77.46%	[26]
5	Eszopiclone and It's Degradation Products	**HPLC Method**	**Detection Wavelength:**304 nm **Linearity Range:** 4-24 µg /mL **Correlation Coefficient (R^2):** 0.9982 **Mobile Phase:** Methanol: Water(40:60) pH-2.5 **Acid Hydrolysis Stability-Indicating Assay:** (70:30 v/v, pH 7.2) **Stationary phase:** Thermo Hypersil BDS–C18 (250 mm × 4.6 mm, 5.0 µ) **Relative Retention Time (RRT): Acid Hydrolysis Stability-Indicating Assay:** 2.95 min **Alkali Hydrolysis Stability-Indicating Assay:** 2.85 min **Oxidation Stability-Indicating Assay:** 2.85 min **Photochemical stability–Indicating Assay**:2.52 and 2.85 min **Flow Rate:** 1 ml/min **LOD**: 1 µg/ml **LOQ**: 2 µg/ml **%Recovery:** 98.80 -100.47 %	[27]
6	Eszopiclone in Pure Form and Pharmaceutical Dosage Forms	**UPLC Method**	**Wavelength:**305 nm **Mobile Phase:** Sodium phosphate buffer : Acetonitrile (85:25 v/v) **Stationary Phase:** HSS C18, 100 mm x 2.1 mm, column with 1.7µm particles **Linearity Range:** 0.05-20 µg/ml **Correlation Coefficient (R^2):**0.996	[28]
7	Eszopiclone in Pharmaceutical Tablet Forms	**HPLC Method**	**Detection wavelength:** 303 **Mobile Phase** : Phosphate Buffer (3.5 pH) : Acetonitrile (50:50 v/v) **Stationary Phase :** Purospher® Star RP18e,(150 x 4.6 mm; 5µ) **Retention Time :** 4.762 **Flow Rate:** 1.5 ml/min **LOD :** 0.054µg/ml **LOQ:** 0.132µg/ml	[29]
8	Eszopiclone combined with escitalopram oxalate	**UV Spectrophotometric method**	**Detection wavelength:** **Eszopiclone:**304nm **Escitalopram oxalate:**238nm **Linearity range:** **Escitalopram oxalate :** 5-25µg\ml **Eszopiclone:** 3-18µg\ml **LOD:Escitalopram oxalate:** 2.5 **Eszopiclone:**1.5 **LOQ:Escitalopram oxalate:** 5 **Eszopiclone:** 3	[30]

CONCLUSION

This review represents the reported chromatographic methods; developed and validated for determination of Escitalopram oxalate and Eszopiclone. All the reported method was simple, precise and accurate those mostly emphasize separation techniques like liquid and gas chromatography. The analysis is done on individual and several combinations of Escitalopram oxalate and Eszopiclone with other drugs. Comparing various validation parameters of already reported methods, it can be concluded that different analytical methods like spectrophotometric, HPTLC and HPLC can be developed for escitalopram oxalate and eszopiclone showing its simplicity, sensitivity (low LOD and LOQ values) linearity and accuracy. Most of the researchers have used the reversed-phase HPLC and UV absorbance detection because this provided with best available reliability, repeatability, analysis time and sensitivity.

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