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REVIEW ON ANALYTICAL METHOD OF DOXOFYLLINE AND ERDOSTEINE

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ABSTRACT

Bronchiectasis is a long term condition where the airways of the lungs become abnormally widened leading to a buildup of excess mucus that can make the lungs more vulnerable to infection. Combination of a bronchodilator and an anti-inflammatory is used for treating bronchiectasis. Doxofylline is a important constituent in a successful treatment for bronchiectasis since it safely creates bronchodilation and anti-inflammatory effects in one drug. Effective clearance of mucus from the airways is one of the most important, perhaps crucial, treatment modalities that can be instituted in patients with bronchiectasis so erdosteine is mucolytic approved for treating COPD. The combination of Doxofylline and Erdosteine will provide synergistic treatments for bronchiectasis. Many analytical methods are developed for Doxofylline and Erdosteine. Doxofylline is official in IP and other methods like UV, HPLC, RP-HPLC, Stability indicating RP-HPLC, LC-MS/MS are also developed. Erdosteine is not official in any pharmacopeia but UV, HPLC, RP-HPLC, HPTLC, Stability indicating RP-HPLC, LC-MS/MS developed for Erdosteine. In combination for both drugs no method is developed till now.

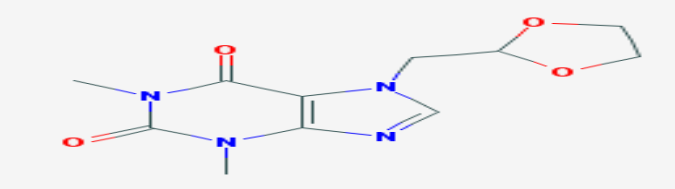
KEYWORDS: Doxofylline, Erdosteine, bronchiectasis, analytical methods.

INTRODUCTION

Doxofylline is a methylxanthine derivative with the presence of a dioxolane group in position 7. Doxofylline does not affect calcium influx and does not antagonize the actions of calcium channel blockers which could explain reduced cardiac adverse reactions associated with the drug Molecular formula of Doxofylline is $C_{11}H_{14}N_4O_4$ and its molecular weight is 266.25

g/mol. Doxofylline is freely soluble in water and acetone .The pKa value of Doxofylline is 9.87.

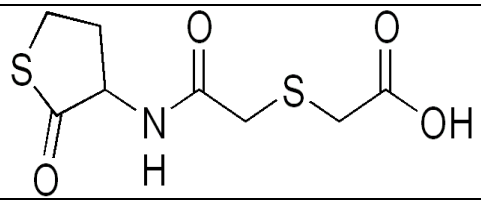
Table 1: Drug Profile of Doxofylline.

Drug Name	Doxofylline
Chemical formula	$C_{11}H_{14}N_4O_4$
Category	Anti asthmatic agent, Bronchodilator
IUPAC	7-[(1,3-dioxolan-2-yl)methyl]-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione
CAS NUMBER	69975-86-6
CDSCO approval	2006
Chemical structure	
Molecular weight	266.25 g/mol
Appearance	White Solid
PKa	9.87
Solubility	Soluble in trichloro methane, soluble in water and acetone
Storage	Keep container tightly closed. Keep container in a cool, well-ventilated area.
Pharmacokinetic	Absorption: It is orally absorbed to an extent of 62.2%.
	Protein binding: Bound to plasma protein to an extent of 48%.
	Metabolism: Doxofylline is extensively metabolized in liver to an extent of 80-90% by demethylation and oxidation.
	Excretion: Less than 4% of an injected dose of Doxofylline is excreted unaltered in the urine.
	Half life: Elimination half life (t½) is around 6-7 hours.
Mechanism of action	Doxofylline inhibits phosphodiesterase IV activities which is responsible for its bronchodilating effects. It has comparatively better safety profile over theophylline for treatment of asthma and chronic obstructive pulmonary ailment due to reduced affinities approaching adenosine A1 and A2 receptors
Contraindication	Despite of the decreased affinities of Doxofylline towards adenosine A1 and A2 receptors, still it is contraindicated to geriatrics, patients suffering from kidney dysfunction, cardiac patients, and patients having liver malfunction
Dose	200-400 mg twice or thrice in a day.
Dosage form	syrup, suspension, tablets
Melting point	141-144°C
Route	oral
Combination with other drugs	Sertraline, Ambroxol, Montelukast sodium, Salbutamol sulphate, Terbutaline Sulphate, Levocetirizine Dihydrochloride,

ERDOSTEINE

Erdosteine {2-({[(2-oxothiolan-3-yl) carbamoyl] methyl} sulfinyl) acetic acid} is a mucolytic. It is a thiol derivative used for treatment of chronic obstructive bronchitis. Erdosteine holds two blocked sulfhydryl groups which are released after first pass metabolism. There are three active metabolites containing mucolytic and free radical scavenging activity. Erdosteine regulates mucus production and viscosity and enhances mucociliary transport and improves expectoration. Molecular formula of Erdosteine is $C_8H_{11}NO_4S_2$ and its molecular weight is 249.299 g/mol. Erdosteine is Soluble in acetonitrile and dimethyl sulfoxide, Slightly soluble in water, methanol. The pKa value of erdosteine is 3.79.

Table 2: Drug Profile of Erdosteine.

Drug name	**Erdosteine**
Chemical formula	$C_8H_{11}NO_4S_2$
Category	Mucolytic agent
IUPAC Name	2-({[(2-oxothiolan-3-yl) carbamoyl] methyl} sulfinyl) acetic acid
CAS number	84611-23-4
Structure	
Molecular weight	249.299 g/mol
Melting point	145-147 ºC(
pKa	3.79 (strongest acidic)
	-3.7 (strongest basic)
Solubility	Soluble in acetonitrile and dimethyl sulfoxide,
	Slightly soluble in water, methanol
Pharmacokinetics	Absorption: Erdosteine is well absorbed orally.
	Metabolism: undergoes first pass metabolism.
	Excretion: urinary elimination
	Half life elimination: 1 to 3 hrs
	Protein binding: 65 %
Mechanism of action	Erdosteine, is an orally administered mucolytic agent. It is classified as a thiol derivative and produced for the management of symptoms caused by chronic obstructive bronchitis. Erdosteine contains sulfhydryl groups which are released after hepatic first-pass metabolism in the liver. Its active metabolites (3 in number) exert both mucolytic activity and scavenging activity against free radicals. Erdosteine acts to regulate the production of mucus in the airway and regulates its viscosity while enhancing mucociliary transport. This leads to an increase in expectoration. Erdosteine shows inhibition

	against the effects of free radicals from cigarette smoke. Clinical studies in patients with chronic obstructive lung disease (COPD) have shown that this drug is generally safe and well tolerated.
Contraindication	Allergy
Side effect	Flushing, Increased Sweating, Nausea, Vertigo, Vomiting
Dose	150 mg/ 300mg twice daily
Dosage form	Capsule
LOG P	-0.43
Melting point	145-147°C
Route	orally
Combination with other drugs	**Cefixime Trihydrate**

OFFICIAL METHOD FOR ESTIMATION OF DOXOFYLLINE

Doxofylline (IP 2018) –HPLC Mobile phase: phosphate buffer (pH 4.5): acetonitrile (80:20v/v) using Column: C_{18} (25 cm × 4.6 mm, 5µ), Detection wavelength 274 nm, Flow rate 1.0 ml/min.

REPORTED METHOD FOR ESTIMATION OF DOXOFYLLINE

1. Development and validation of spectroscopic method for estimation of anti-asthmatic drug Doxofylline in bulk and Pharmaceutical formulation: UV Spectroscopy Detection wavelength: 272 nm, Correlation-co-efficient (R2): 0.9997, LOD: 0.09623µg/ml, LOQ: 2.9161µg/ml, Linearity Range: 5-50µg/ml.
2. Development and validation of UV spectroscopic method for simultaneous estimation of Doxofylline and terbutaline sulphate in combined dosage form. Q- Absorbance ratio method two wavelengths are selected, Isoabsorptive point: 294.1 nm, λ_{max} of Doxofylline 273 nm. Absorbance correction method λ_{max} of Doxofylline 273 nm for Doxofylline linearity10-50 µg/ml and terbutaline sulphate: 2-8 µg/ml.
3. A simple HPLC method for quantitation of Doxofylline in Tablet dosage form: using column intersil octyl decyl with mobile phase methanol: water (30: 70 v/v), LOD 5.152 µg/ml, LOQ 15.97 µg/ml, UV detection 274nm, linearity 160-240 µg/ml, Correlation-co-efficient (R2): 0.99892, % recovery 101.60%.
4. Development and validation of rapid HPLC method for determination of Doxofylline in bulk drug and Pharmaceutical dosage forms: Column HiQ Sil C 18 W using mobile phase Acetonitrile: buffer (50:50 v/v); pH 3 with flow rate 1 ml/min and detection at 272 nm, Linearity: 10-80 µg/ml, LOD 0.03 µg/ml, LOQ 0.1 µg/ml.

5. A validated reverse phase high performance liquid chromatographic method for the determination of Doxofylline in pure and Pharmaceutical formulations: Column Chromosil C18 (250 mm × 4.4mm, 5µm) using mobile phase Potassium dihydrogen phosphate buffer (pH 5.5): acetonitrile (75: 25 v/v), Injection volume 20 µL, flow rate 1ml/min, and retention time 4.814 min.
6. Reverse phase liquid chromatographic method for analysis of Doxofylline in presence of its degradation products: Column Supelco C 18 DB (150mm × 4.6 mm) using mobile phase Water: methanol: ethyl acetate (80:10:10 v/v/v), flow rate 1 ml/min, detection 277nm, linearity 5-25 µg/ml.
7. Spectrometric and Reversed phase High performance liquid chromatographic method for the determination of Doxofylline in Pharmaceutical formulations: UV method detection wavelength 274 nm using solvent 0.1 N HCL, linearity 0.20-30 mg/ml, co-efficient (R2) 0.999, RP-HPLC column Hypersil ODS C18 (250 × 4.6mm,5µm) using mobile phase Buffer (pH 3): acetonitrile (80:20 v/v), flow rate 1ml/min, detection 210nm, separation 7min and linearity 0.165-30 mg/ml.
8. Development and validation of liquid chromatography and spectroscopic methods for the analysis of Doxofylline in Pharmaceutical dosage form: RPHPLC method column RP-8 using mobile phase Phosphate buffer (pH 6): acetonitrile (60:40, v/v) at flow rate 1ml/min and detection at 230 nm. UV method detection at 270nm, Molar absorptivity 0.878 × 10^3 L/mol.cm.
9. Method development and Hydrolytic study of Doxofylline by RP-HPLC and LC MS/MS : Mobile phase Acetonitrile: formic acid (90:10 v/v), pH 3.0 detection at 274 nm, flow rate 1ml/min, linearity 1-200 µg/ml, 2.9min retention time. Characterization of hydrolytic degradation and pathway was done by LC-MS/MS.
10. Stability indicating RP-HPLC method development and validation of Doxofylline: column Supelco C18 DB (150 × 4.6mm) column using mobile phase Water: methanol: acetonitrile (75: 20: 5v/v) with flow rate 1 ml/min and detection at 278 nm.

OFFICIAL METHOD FOR ESTIMATION OF ERDOSTEINE

Erdosteine drug is not official in any of the Pharmacopoeia.

REPORTED METHOD FOR ESTIMATION OF ERDOSTEINE

1. Spectroscopic estimation of Erdosteine in pharmaceutical dosage form: detection wavelength 235nm in methanol having linearity 10-50 µg/ml.

2. Spectrometric method for estimation of Erdosteine in bulk and capsule dosage form: Linearity 5-90 µg/ml, detection wavelength 237.4 nm, Correlation-co-efficient (R2): 0.9998, LOD 0.595 µg/ml, LOQ 1.798 µg/ml and % recovery 98.772 ± 0.378%.
3. Simple determination of Erdosteine in human plasma using High performance liquid chromatography: Column CAPCELL PACK C18 (4.6 × 250mm) using mobile phase Acetonitrile: phosphate-heptane sulfonate buffer (5:95 v/v) (pH 2.0) detection 220nm, Linearity 0.5-8 µg/ml, LOQ 0.5 µg/ml and Correlation-co-efficient (R2): 0.999.
4. Development and validation of RP-HPLC method for estimation of Erdosteine in bulk form: column Kromasil ODS C18 (100×4.6mm, 5 µ) using mobile phase Acetonitrile: Phosphate buffer (pH 2.5), flow rate 1ml/min, detection 236 nm, linearity 2-10 µg/ml, retention time 3.02 min.
5. RP-HPLC determination of Erdosteine in human plasma and its pharmacokinetic studies: Column Luna C18 (150mm ×4.6 mm, 5 µm) using mobile phase Methanol: sodium acetate, LOD 0.01 µg/ml, Linearity 0.01-3 µg/ml, % RSD <5%, Correlation-co-efficient (R2): 0.999.
6. Stability indicating HPLC determination of Erdosteine in bulk drug and pharmaceutical dosage form: Column Ace5-C18 (250 × 4.6mm, 5µ) using mobile phase Acetonitrile: phosphate buffer (35:65 v/v), %recovery 99.78-101.25% and detection 236 nm.
7. High -performance Thin-layer chromatographic method for determination of Erdosteine in pharmaceutical dosage form: Column Aluminum-baked silica gel 60 F_{254} using mobile phase Toluene–methanol–acetone–ammonia (3.5:3.5:2.5:0.05 v/v), Detection 254 nm, Rf value 0.45 ± 0.02.
8. Stability-indicating methods for the determination of Erdosteine in the presence of its degradation products: First derivative method: Linearity 10-70 µg/ml, % recovery 100.43 ± 0.977, λ_{max} 229 nm, Ratio-spectra first derivative spectrophotometry: Wavelength 227.4, 255, Linearity 10-70 µg/ml, %recovery At 227.4 nm: 99.65 ± 1.222%, At 255 nm: 100.02 ± 1.306% Quantitative densitometric evaluation: Mobile phase Methanol: chloroform: ammonia (7: 3: 0.01v/v/v), Detection 235 nm, Linearity 2.4-5.6 µg/spot, % recovery 100.03 ± 1.015 %.
9. Stability-indicating RP-HPLC method for estimation of Erdosteine and its degradation products in pharmaceutical dosage form: Column HiQSil C18 (250 × 4.6mm, 5 µm), Mobile phase Acetonitrile: phosphate buffer (80: 20v/v) pH 5.8, Flow rate 1ml/min, detection 270 nm, linearity 5-50 µg/ml.

10. Sensitive determination of Erdosteine in human plasma by use of automated 96-well solid-phase extraction and LC-MS/MS: Column C18, mobile phase Ammonium acetate: acetonitrile (80:20, pH 3.2), Flow rate 0.3ml/min, Internal standard Letosteine, LOQ 0.2 ng/ml, linearity 0.2-5000 ng/ml, Accuracy Intraday: 99.6-105.0%, Interday: 95.0-100.5.

CONCLUSIONS

Doxofylline and Erdosteine combination used for treating bronchiectasis with less side effect and are available and frequently used in market; hence, there is great need to determine it in bulk, dosage form as well as to establish pharmacokinetic parameters. The need of analytical method validation is well reflect and highlights the aspect of analyst's personal habits, that from part of the developed methods, and on the possibility of a person getting very reproducible results when he carries out the analysis again and again in a similar set of conditions. Any developed method however, may be influenced by variable like different elapsed assay times, different days, reagent lots, instruments, equipments or apparatus, environmental condition like temperature etc.

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