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Analytical Profile of Epalrestat and Pregabalin: A Review

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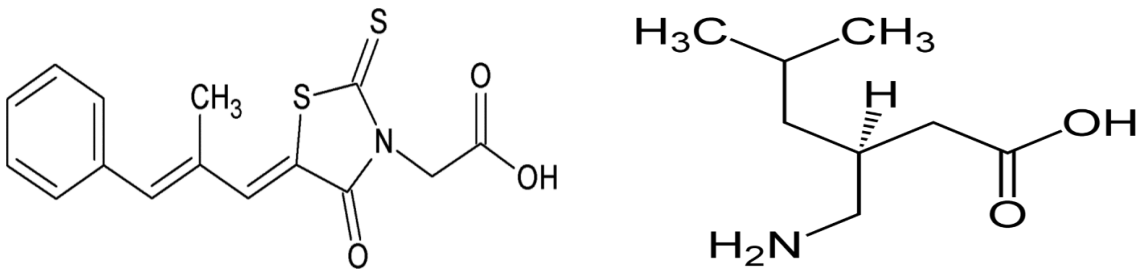
ABSTRACT

Epalrestat is an aldose reductase inhibitor that is used in the treatment of diabetic peripheral neuropathy. Aldose reductase enzyme is present in most tissues and has a significant physiological role in our body for producing an electrically neutral, non-diffusible osmolyte in cells generally exposed to hypertonicity. Under normal conditions, the enzyme has less affinity to produce sorbitol, but in the case of diabetes, increasing the level of intracellular glucose in some cells leads to the accumulation of sorbitol causes neuropathy pain. Epalrestat produces some improvement in the late-onset neuropathy associated with Diabetes mellitus. Pregabalin is a structural analog of gamma-aminobutyric acid and it's a non-opioid drug. It is used as an anti-epileptic and Anti-anxiety agent which is generally used to treat neuropathic pain associated with diabetic neuropathy pain, spinal cord injury & post-therapeutic neuralgia. Generally, Pregabalin slows the impulses in the brain that cause seizures. A combination of Epalrestat and Pregabalin is widely used to overcome neuronal damage in Diabetes mellitus. This review is provided to compile the different analytical methods of the Epalrestat and Pregabalin developed by using Ultraviolet Spectrophotometer, RP-HPLC Reverse Phase High-Performance Liquid Chromatography, and Liquid Chromatography-Mass spectrometry to identify and quantify the drug content in bulk, Pharmaceutical, and biological samples.

INTRODUCTION:

Epalrestat (Figure 1a) is a carboxylic acid derivative & non-competitive, reversible 'Aldose reductase inhibitors' used for the treatment of diabetic neuropathy which is one of the common long-term complications in patients with Diabetes mellitus. It reduces the accumulation of intracellular sorbitol which is believed to be the cause of Diabetic neuropathy, Retinopathy, and Neuropathy [1]. Chemically Epalrestat is {(5Z)-5-[(2E)-2-Methyl-3-phenylprop-2-en-1-ylidene]-4-oxo-2-sulfanylidene-1,3-thiazolidin-3yl} acetic acid [2]. Pregabalin (Figure 1b) was FDA-approved in 2004 as an anti-epileptic drug also called 'Anti-convulsant'. Chemically Pregabalin is a (S)-3-(Amino-methyl)-5-methyl hexanoic acid [3]. It works by slowing down the impulses in the brain that cause seizures. Pregabalin also affects chemicals in the brain that send pain signals across the nervous system. It is used to treat pain caused by fibromyalgia or nerve pain in people with diabetes, post-hepatic neuroglia, or spinal cord injury is also used with other medications to treat partial-onset seizures in adults & children aged at least a month [4].



(a) **(b)**

Figure 1: Chemical Structures of (a) Epalrestat and (b) Pregabalin

Table 1: Physicochemical properties [5]

S.No.	Parameters	Epalrestat	Pregabalin
1	Solubility	Soluble in organic solvents such as DMSO & DMF	Soluble in water
2	Pka	3.62	4.2
3	Melting point	210^0C [410^0 F], 483 K	186^0 C to188^0 C
4	Boiling Point	516.8^0C [962^0 F], 789.9K	274° to 276° C
5	Density	1.43 gm/cm^3	0.097±0.06 g/cm^3
6	Storage temperature	-20^0 C	40^0 C & 20^0 C
7	Form	Powder [Crystalline]	Crystal
8	Color	Yellow to Orange	White
9	Half-life	0.8 to1.1h	4.6 to 6.8 h
10	Dose	50 mg [3 times daily before meals]	150 to 600 mg/day

Mechanism of action of Epalrestat: It is a carboxylic acid derivative & a non-competitive agent and is mainly involved in the Polyol pathway. In general, glucose converts to sorbitol which is further processed to fructose. Epalrestat inhibits the conversion of glucose to sorbitol by using an aldose reductase enzyme. It reduces the accumulation of intracellular sorbitol in our neurons [6].

Mechanism of action of Pregabalin: Pregabalin involves the binding to the alpha-2-delta subunits of voltage-gated calcium channels in the CNS. This reduces the release of certain neurotransmitters, such as glutamate, and norepinephrine. Pregabalin helps in managing nerve-related pain [7].

Table 2: Pharmacokinetic parameters

S. No.	Pharmacokinetics	Epalrestat	Pregabalin
1	Absorption	Oral route	Oral route
2	Distribution	Binds to plasma proteins& distributed into body fluids	Binds to plasma proteins& distributed into body fluids
3	Metabolism	Hepatic metabolism, primarily through glucuronidation	Minimal hepatic metabolism
4	Excretion	Through urine	Through urine

Side Effects: Nausea & vomiting, irregular heartbeat, diarrhea, abdominal pain, dry mouth, weakness, and genital discomfort, chills, dizziness, headache, allergic reactions of Epalrestat and dizziness, blurred vision, weight gain, ataxia, dry mouth, constipation, vertigo, dizziness, headache, and euphoria of Pregabalin [8-9].

Table 3: Available market Formulations of Epalrestat [10]

Trade name	Dosage form	Dose Available	Manufacturer
Aldonil	Tablets	50 mg	Zydus Medica, Ahmadabad, India.
Alrista	Tablet	150 mg	Macleods India.
Listap-150SR	Tablet	150 mg	Schem, Hyderabad India
Epimeth	Tablet	150 mg	Zaiva Life Sciences, Hyderabad India
Aldorin	Tablet	150 mg	Bangladesh
Epalrica-M	Tablet	150 mg	Ordina Globai, Londan, UK.
Eplistat150-SR	Tablet	150 mg	Schem, Hyderabad India
Xetostat-SR	Tablet	50 mg	Amor Pharmaceuticals, Kolkata, India
Tanglin	Tablet	20 mg	Yangtze River Pharmaceutics group, Taizhou
Palestat-ER	Tablet	150mg	Druto laboratories, New Delhi, India.
Epo	Tablet	150 mg	Frankfurt Pharma Private Limited, New Delhi, India
Nurestat-150SR	Tablets	150 mg	Chemo healthcare, Changodar, Gujarat
Epialrigise	Tablet	150 mg	East-west pharma, Chennai, Tamilnadu
Epalpex-150 SR	Tablet	50 mg	Shilpex Pharmysis, Delhi, India

Table 4: Available market formulations of Pregabalin [11]

Trade Name	Formulation	Dosage Available	Manufacturer
Pregalin 75	Tablet	75 mg	Torrent pharmaceutical Pvt. Ltd., Ahmedabad
Nervzone 300	Capsules	300 mg	Zeelab Pharmacy Pvt. Ltd, Delhi
Lyrica	Capsules	75 mg	Pfizer Ltd, AP
Maxgalin 75	Capsules	75 mg	Sun Pharmaceutical industries, Bangalore, Vizag
Pregabid CR	Tablet	82.5 mg	Intas Pharmaceuticals Ltd, Ahmedabad, Hyderabad
Pregabanyl-300	Capsules	300 mg	Leeford Healthcare Ltd, Ludhiana Punjab
Pregeb 75	Capsules	75 mg	Torrent Pharmaceuticals Ltd, Ahmedabad
Pbren 50	Capsules	50 mg	Larenon Healthcare Pvt. Ltd, Ahmedabad
Nova 75	Capsules	75 mg	Cipla Ltd, Vishakhapatnam & Mumbai
Gabawin 75	Tablets	75 mg	Icon life sciences, Secunderabad, Telangana
Sonaxa 75	Capsules	75 mg	Eris life sciences, Guwahati, Assam
Renrica 50	Capsules	50 mg	Osren Healthcare Pvt. Ltd, New Delhi, India
Pregiva 75	Tablets	75 mg	Kuresys labs, New Delhi, India.
Mecocorn-p	Tablets	75 mg	Medipol Pharmaceuticals India Pvt. Ltd, Noida, Uttar-Pradesh
Pregastare	Capsules	75 mg	Lupin Pvt. Ltd. Hyderabad, Telangana

Table 5: UV, RP-HPLC, LC-MS, UHPLC-MS/MS methods for Epalrestat

S. No.	Method	Column	Mobile Phase /Solvent	Flow Rate (ml/ min)	Linearity (µg/ ml)	Wave-length (nm)	RT (min)	LOD (µg/ ml)	LOQ (µg/ ml)	Ref.
1	UV	-	Phosphate Buffer $P^{H:}$ 5,7 and [9]	-	A: 0.1-20, B: 0.1-20, C: 0.1-15	387	-	-	-	12
2	RP-HPLC	Qualisil C_8 column	Methanol:(0.01ml^{-1}) potassium di hydrogen phosphate (75v/v:25v/v), P^H:4.5 with ortho phosphoric acid	1	2-12	294	6.64± 0.02	0.15	0.46	13
3	RP-HPLC	C_{18}column (250mm×4.6 mm,5µm)	Buffer (potassium dihydrogen phosphate in water) at P^H 3.2 with orthophosphoric acid	1	2-120	294	15.9	0.005	0.015	14
4	LC-MS	C_{18} (100mm×4.6 mm,3.5µm)	Ammonium acetate: Acetonitrile (68%: 32%)	1	2-5000	-	2.6	-	-	15
5	UHPLC-MS/MS	C_{18} reversed-phase column (2.1mm×50mm,1.7µm)	Acetonitrile& 5mmol/L ammonium acetate in water	0.2	-	-	5.5	--	-	16

Table 6: UV, HPLC, RP-HPLC Methods for Pregabalin

S.No.	Method	Column	Mobile Phase/Solvent	Flow Rate (ml/min)	Linearity (µg/ml)	Wavelength (nm)	RT (min)	LOD (µg/ml)	LOQ (µg/ml)	Ref.
1	UV	Kromasil® 100-C18[250×4.6 mm]	Phosphate buffer & acetonitrile [96:4 v/v]	1	1-25	210	4.6	10 & 17 ng/mL	0.04 & 0.12 ng/mL	17
2	HPLC	C18[100×4.6 mm]	Phosphate buffer acetonitrile [90:10]	1	-	-	-	-	-	18
3	HPLC	C18[250×4.6 mm]	Disodium hydrogen phosphate: acetonitrile: methanol [80:10:10 v/v/v]	-	1-25	210	4.6	10	17	19
4	RP-HPLC	C18[250×4.6 mm]	A-10mM NH_4OAC in H_2O B-Acetonitrile & methanol [80:20 v/v]	0.8	150-850	210	-	-	-	20
5	HPLC	C8[150×4.6 mm]	Phosphate buffer& acetonitrile [95:05v/v]	1	0.5-1.5	200	4.66	0.23	0.6	21
6	LC-MS/MS	Gemini C18 [150*2.0 mm]	Methanol&H_20 [98:02 v/v] with 0.5%v/v formic acid	-	-		-			22

Table 7: RP-HPLC and UPLC methods for Epalrestat and Pregabalin combination

S.No.	Method	column	Mobile phase	Flow rate (ml/min)	Linearity (µg/ml)	Wavelength (nm)	RT (min)	LOD (µg/ml)	LOQ (µg/ml)	Ref.
1	RP-HPLC	STD Discovery column 250×4.6mm,5 µm)	0.1% orthophosphoric acid: Acetonitrile (45:55% v/v)	1	E-37.5 P-225	244	E-2.407 P-3.272	E-0.78 P-0.18	E-2.38 P-0.55	23
2	RP-HPLC	Chromatogram column (250× 4.6mm)	Buffer: Acetonitrile (60:40)	0.8	E-1500 P-750	274	E-2.515 P-3.741	E-0.153 P-0.376	E-0.464 P-1.139	24
3	UPLC	HSS Column (100mm×2.1 mm,1.8 µm)	0.1% orthophosphoric acid buffer: Acetonitrile (55:45% v/v)	0.3	37.5-225	210	E-1.704 P-1.081	-	-	25
4	UPLC	Agilent Zorbax SB_{18} (2.1×100MM, 18 µm)	0.1% Formic acid & Acetonitrile (60:40% v/v)	1	E-7.5-150 P-3.75-75	226	E-0.97 P-1.27	-	-	26

CONCLUSION:

The present review provides a summary of a deep understanding of the pharmacological action, pharmaceutical aspects, and Various analytical methods reported for the determination of Epalrestat and Pregabalin. The reported analytical methods consisting of Spectrophotometry, RP-HPLC, UPLC, LC-MS/MS, and UHPLC-MS/MS were employed for the determination of Epalrestat and Pregabalin. Based on the reports the Analytical method is preferred RP-HPLC is major used for the estimation of the Epalrestat and Pregabalin. This review will be useful in the further development of the analytical methods for the Epalrestat and Pregabalin estimation and also gives a glimpse of the drug Profile.

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CONFLICT OF INTEREST: Nil

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