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Review Article

A Review on Different Analytical Methods: Letrozole

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Abstract

Letrozole is a third-generation aromatase inhibitor used for hormonal-sensitive breast cancer in postmenopausal women. Several analytical methods were developed to analyze Letrozole. The present review clearly covers all the analytical techniques used for the analysis of Letrozole available till date, which helps the researchers in developing new methods for estimation of Letrozole by considering the pros and cons of the previously developed methods.

Keywords: Aromatase Inhibitor; UPLC; LC-MS/MS; Capillary Zone Electrophoresis

Introduction

Letrozole (Figure 1) is chemically known as 4-[(4-cyanophenyl)-(1, 2, 4-triazol-1-yl) methyl] benzonitrile, with molecular formula $C_{17}H_{11}N_5$ and is freely soluble in dichloromethane; slightly soluble in ethanol; practically insoluble in water. It is a third-generation aromatase inhibitor used for hormonal-sensitive breast cancer in postmenopausal women. A very low daily dose of Letrozole is sufficient for unveiling antitumor activity and it is highly potent and selective and well tolerated [1]. Aromatase inhibitors can be classified based on their chemical structure as steroidal (type I inhibitors) and nonsteroidal (type II inhibitors), where anastrozole and Letrozole are nonsteroidal inhibitors and exemestane is a steroidal inhibitor [2]. Catalysis of enzyme aromatase was the final step in biosynthesis of estrogen so this step can be inhibited for inhibition of estrogen production [3].

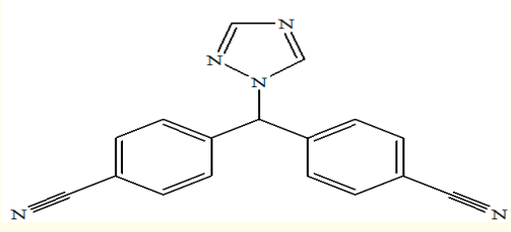

Figure 1: Structure of Letrozole.

Letrozole which is a nonsteroidal type II aromatase inhibitor, interacts noncovalently with the heme moiety of aromatase and occupy its substrate-binding site, thus it inhibits binding of androgens to the catalytic site. It is a reversible antagonism in which the compound can be competitively displaced from the active site by endogenous substrate. According to pharmacodynamics studies the recommended dose of Letrozole is 2.5 mg daily once. Pharmacokinetically, Letrozole was rapidly and completely absorbed after oral administration with bioavailability of 99.9%. Apparent volume of distribution was 1.87 l/kg (range, 1.47-3.24). About 60% of Letrozole gets bound to plasma protein mainly to albumin (55%). The half-life of Letrozole is 42 hours and is longer with great AUC in breast cancer patients. Letrozole gets metabolized by CYP 450 isoenzyme (CYP3A4 and CYP 2A6) and gets eliminated from the body. Steady-state concentrations of Letrozole are reached after 2–6 weeks and maintained for long periods with no evidence of drug accumulation.

Method development and validation can be done using different instrumentation techniques such as spectrophotometric techniques, chromatographic techniques and by some hyphenated techniques. The aim of present work is to review different instrumentation techniques such as HPTLC [4], spectrophotometry (Table 1) [5-10], RP-HPLC (Table 2) [11-24], UFLC [25], UPLC [26] in pharmaceutical formulations and biological samples (Table 3) [27-31], LC-MS/MS (Table 4) [32-39] and Capillary zone electrophoresis [40] for the quantification of Letrozole.

Reagent	λ (nm)	Linearity (µg/ml)	Ref
Ethanol	240	1-10	[5]
Acetonitrile	240	1-24	[6]
Methanol	238	2–20	[7]
Phosphate buffer (pH 6.8) Phosphate buffer (pH 3.8)	240 245	0.5-20	[8]
Methanol (Zero order, First derivative Second derivative and AUC)	240, 224 241 and 235.0–245.0	0.25-20.0	[10]

Table 1: Review of spectrophotometric methods.

Mobile phase (v/v)	λ (nm)	Linearity (µg/ml)	Ref
Water: Acetonitrile: Phosphate buffer (pH 5.8)(70:20:10)	230	600-1400	[11]
Methanol: Tetrabutyl ammonium hydrogen sulfate (80:20)	240	0.5–150	[12]
0.01 M Potassium dihydrogen phosphate : Methanol	230	0.01-80	[13]
Water: Acetonitrile (30:70)	230	0.0115-1.278	[14]
Deionized water: Acetonitrile: Methanol (50:30:20)	240	1-50	[15]
Acetonitrile:50.0 mM Phosphoric acid solution (pH-7) (50:50) (Fluorimetric detection)	256 (Ex) 585 (Em)	50-700 ng/ml	[16]
Potassium dihydrogen phosphate (pH 3.5 ± 0.2) with orthophosphoric acid: methanol (85:15)	230	20-120	[17]
Glacial acetic acid: Acetonitrile: Water (0.1: 50: 50)	240	1–100	[18]
Mixture of Acetonitrile: Water (50:50).	265	160-240	[19]
Acetonitrile : Phosphate buffer (pH 7.8) (70:30)	232	10-100	[20]
Acetonitrile: Water (50:50).	265	160-240	[21]
Acetonitrile: Water: Methanol (50:35:15)	289	4-24	[22]
Water: Acetonitrile (60:40)	240	0.25-16 mg/L	[23]
Acetonitrile: Acetate buffer (pH 4.5) (50:50)	240	5-2500 ng/ml	[24]
UFLC Acetonitrile: Phosphate buffer (pH 6.8) (50:50)	241	20-100	[25]
UPLCAcetonitrile: Water (35:65)	240	2.5-200	[26]

Table 2: Review of liquid chromatographic methods for dosage forms.

Mobile phase (v/v)	λ (nm)	Linearity	Sample	Ref
Methanol: Water (70:30)	239	0.15–100 µg/ml	Wistar rat serum	[27]
Acetonitrile: Phosphate buffer (35:65) (Fluorescence technique)	230 (Excitation) 295 (Emission)	0.5 - 80 ng/ml	Human plasma	[28]
75% 0.02 M Phosphate buffer (pH 5.5): 25% Acetonitrile	-	50.55-120.0 ng/ml	Human plasma	[29]
Acetonitrile: Phosphate buffer (41:59)	239	2.48-99.2 µg/L	Human plasma	[30]
Phosphate buffer (pH 6.8): Acetonitrile (56:44).	242	0.2-20 µg/ml	Blood plasma	[31]

Table 3: Review of liquid chromatographic methods for biological samples.

Mobile phase	Linearity (ng/ml)	Sample	Ref
0.1% formic acid in water (pH 3.3): 0.1% formic acid in methanol	1.0 - 60.0	Human plasma	[32]
Acetonitrile - 0.1% formic acid in water	2 - 2000	Rat plasma	[33]
Methanol: 10 mM Ammonium acetate (65:35)	0.40 - 50.0	Human plasma	[34]
Acetonitrile: Formic acid (0.2% aqueous) (70:30)	0.25 - 100	Human blood plasma	[35]
10mM Ammonium acetate: Acetonitrile (pH 3.0) (10:90)	0.2 - 100	Human plasma	[36]
Methyl terta - butyl ether (TBME) with methanol	1.56 - 200	Human plasma	[37]
15 mM ammonium format containing 0.1% formic acid: Acetonitrile	10 - 500	Human Urine	[38]
Methanol: 0.1% Formic acid in water (85:15)	0.10 - 100	UPLC Human plasma	[39]

Table 4: Review of LC - MS/MS methods.

Conclusion

Different analytical methods such as HPTLC, UV, HPLC, UPLC, UFLC, Capillary electrophoresis and hyphenated techniques such as LC-MS and LC-MS/MS methods were reported for the estimation of Letrozole in bulk, pharmaceutical formulations and biological samples. This review article will be very useful for the researchers to compare any new analytical method developed with that of the previously available methods for the estimation of Letrozole.

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