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Review Article

A Systematic Review on the Analytical Techniques for the Quantification of Piracetam

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Abstract

Piracetam is a cyclic analogue of γ-amino butyric acid which is an inhibitory neurotransmitter. Piracetam is used as a nootropic agent. Much of research work has been done on Piracetam regarding the synthesis, pharmacology, mechanism of actions etc. but in the present article the authors have focused only on the analytical techniques so far published for the estimation of Piracetam in biological fluids as well as pharmaceutical formulations in the literature and these analytical methods were thoroughly reviewed in a systematic manner by considering the analytical instruments used by different authors and some of the validation parameters.

Keywords: Piracetam; Alzheimer's Disease; Myoclonus

Introduction

Piracetam, chemically is 2-oxo-1-pyrrolidine acetamide is a prototype nootropic agent used clinically for the treatment of memory impairment in aged patients, alcoholism, epilepsy, Alzheimer's disease, dementia etc. [1-4]. Piracetam has a molecular weight 142.156 g/mol and molecular formula $C_6H_{10}N_2O_2$. Piracetam is soluble in methanol, ethanol, DMSO and water. Piracetam has a pKa value 15.67. UK has approved the license for Piracetam even for the treatment of myoclonus. Myoclonus is an unexpected muscle spasm (Muscle jerks) which may involve a single muscle or group of muscles and the movements are involuntary and cannot be controlled. Piracetam is also used to increase cognitive impairment [5].

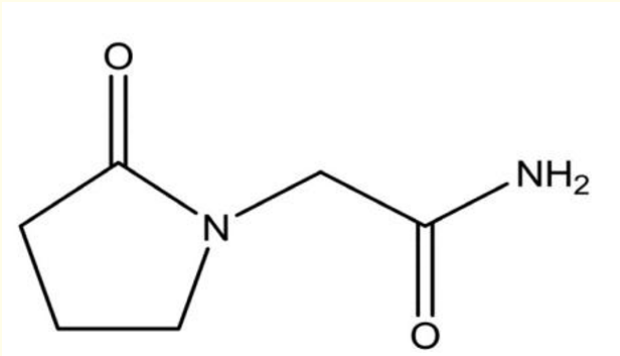

Figure 1: Chemical structure of Piracetam.

Piracetam is available as tablet, injection, syrup and capsule with brand names Neurocetam (Micro Labs Ltd), Perceptal (Pulse Pharmaceuticals Pvt Ltd), Cerecetam (Intas Pharmaceuticals Ltd.), Nirocet (Bondane Pharma), Alcetam (Alkem Laboratories), Normenta (Ipca Laboratories Ltd), Nootropil (UCB Pharma Limited)

etc. with label claim 200, 400, 500, 800 mg in India. Piracetam is available in combination with Citicoline, Cinnarizine, Levetiracetam, Brivaracetam, and Carbamazepine etc. In the present study the authors have reviewed exclusively the analytical methods developed for the quantification of Piracetam in biological samples as well as pharmaceutical dosage forms.

Discussion

Most of the analytical method were established basing on the chromatographic technique as it takes less time to quantify the drug either in pharmaceutical formulations or in biological fluids. Bhowmick., *et al.* [6] have developed a validated first derivative spectrophotometric method using methanol for Piracetam pharmaceutical formulations and API in which the λ_{max} was reported as 214 nm and in this method the linearity was observed over the concentration range 10-80 µg/ml. Karamancheva and Staneva [7] have determined the possible impurities in Piracetam using FTIR spectroscopy and a capillary electrophoresis method was developed in human plasma by Lamparczyk [8] in which the wavelength was chosen at 200 nm and the linearity observed was 4-24 µg/ml. The impurities of Piracetam were estimated by Ovalles., *et al.* [9] using TLC and densitometry in which the mobile phase was a mixture consisting of pentyl acetate: ethyl acetate: ethanol: glacial acetic acid (10:10:9:1) and the detection was carried using Gibb's reagent–ammonia vapor. Lengyel., *et al.* and Alebic-Kolbah., *et al.* developed gas chromatographic techniques for the determination of Piracetam in human and rat plasma [10] and serum [11] respectively.

Kapendra Sahu., *et al.* established two stability indicating UPLC and HPLC methods [12] using two different columns Acquity UPLC BEH C18 and Phenomenex C18 columns respectively with two different mobile phases acetonitrile: water (25:75) and acetonitrile: 10 mM ammonium acetate (pH 5.0) (20: 80) mixture and the two method were compared. In both UPLC and HPLC methods Beer-Lambert's law was obeyed over the concentration range 10 - 50 µg/ml. Ardhani DwiLestari., *et al.* used Lichrospher® (100 RP-18) column methanol: water (5: 95) as mobile phase with detection at 215 nm for the RP-HPLC method [13]. But in this method the linearity was very narrow and is found to be 0.005 - 0.1 µg/ml. Arayne., *et al.* developed liquid chromatographic method for the simultaneous determination of Piracetam and its four impurities by RP-HPLC with UV detection at 206 nm with a very narrow linearity range 0.05 - 10 µg/ml. A mixture of 0.02% tri ethyl amine: acetonitrile (85:15) was used by adjusting the pH to 6.5 with ortho phosphoric acid with C18 Nucleosil column [14]. Piracetam was estimated by liquid chromatography technique by Louchahi., *et al.* [15] using methanol: water (5: 95) as mobile phase in human plasma and urine. The assay was carried out by liquid-liquid extraction using hexane-2-propanol at pH 9.2 and the liquid chromatographic method was performed on isocratic mode with UV detection at 206 nm. The method has shown linearity response over the concentration 3 - 40 mg/l and 100 - 2000 mg/l in human plasma and urine respectively [15]. Augustin Curticapean and Silvia Imre [16] established a validated HPLC method on gradient mode for the determination of Piracetam in human plasma using Aq. 0.01% $HClO_4$: Acetonitrile: Methanol as mobile phase and a linearity of 5 - 80 µg/ml was observed. This experiment was conducted on plasma which was a supernatant layer obtained after proteins precipitation with perchloric acid and they have also proved that Piracetam was stable in plasma for about 4 weeks at -20°C and for 36 hours at 20°C in the supernatant after the protein precipitation.

Doheny., *et al.* [17] developed a specific HPLC method for the estimation of Piracetam using only 25 µl of plasma and 10 µl of cerebrospinal fluid in presence of internal standard i.e. α-ethyl-2-oxo-1 -pyrrolidine acetamide and the linearity was observed over the concentration range 4 - 256 µg/ml. The authors performed the pharmacokinetic profile using the typical plasma and cerebrospinal fluid of Piracetam after intra peritoneal administration of Piracetam to a single male Sprague-Dawley rat.

Nalbandian., *et al.* [18] performed the chromatographic study on the methanol extracts of serum and aqueous humor using Bondapak C18 and a mobile phase mixture consisting of methanol: 0.1 M KH_2PO_4 solution where the pH was adjusted to 4.8 with 0.1 M HCl and the linearity was shown as 5 - 15 nmol. A LC-MS/MS method was developed for the pharmacokinetic study of Piracetam in rat plasma [19] using acetonitrile: 1% formic acid (10:90) as mobile phase in presence of an internal standard Oxiracetam. Protein precipitation was achieved with trichloro acetic acid (5%) and the linearity was observed over the concentration range 0.1 - 20 µg/ml. Different analytical methods were established by different authors for the quantification of Piracetam in pharmaceutical formulations as well as the biological fluids. Table 1 highlights some of the important parameters observed during this systematic review.

Reagent/Column/Mobile phase (v/v)	Linearity (µg/ml)	Comment	Ref
Methanol (First derivative spectroscopy)	10-80	λ_{max} = 214 nm	[6]
FTIR spectroscopy	0.1-1.3 mg/mg	Impurities	[7]
Capillary electrophoresis	4-24	**λ = 200 nm** Human plasma	[8]
TLC and Densitometry Pentyl acetate: Ethyl acetate: Ethanol: Glacial acetic acid (10:10:9:1) Detection: Gibb's reagent–Ammonia vapor	-	Impurities Sample: 210 nm; Reference: 230 nm	[9]
Gas Chromatography	0.1-100/0.5 ml plasma	Human plasma and Rat plasma	[10]
Gas Chromatography	-	Serum	[11]
UPLC: Acquity UPLC BEH C18/Acetonitrile: Water (25:75) HPLC: Column-Phenomenex C18/ Acetonitrile: 10 mM Ammonium acetate (pH 5.0) (20: 80)	10-50 10-50	UPLC Stability-indicating HPLC (Isocratic mode)	[12]
Lichrospher® **(100 RP**-18) column/ Methanol: water (5: 95)	0.005-0.1	HPLC 215 nm	[13]
C18 Nucleosil/0.02 % Tri ethyl amine: Acetonitrile (85:15) (pH adjusted to 6.5 with ortho phosphoric acid)	0.05-10	HPLC 205 nm	[14]
Hibar LiChrosorb RP-18/Methanol: water (5: 95)	3-40 100-2000	HPLC Human plasma and Urine 206 nm	[15]
RP-18 LiChroSpher 100/Aq. 0.01% $HClO_4$: Acetonitrile: Methanol (Gradient mode)	5-80	HPLC Human plasma 200 nm	[16]
215 nm Spherisorb S5CN/Acetonitrile: Water (98 : 2) **α**-ethyl-2-oxo-1 -pyrrolidine acetamide (Internal standard)	4- 256	HPLC Plasma or Cerebrospinal fluid	[17]
Bondapak C18/Methanol: 0.1 M KH_2PO_4 (pH adjusted 4.8 with 0.1 M HCl)	5-15 nmol	HPLC Rabbits serum and Aqueous humor 208 nm	[18]
Zorbax SB-Aq/Acetonitrile: 1% Formic acid (10:90) Oxiracetam (Internal standard)	0.1-20	LC-MS/MS Rat plasma	[19]

Table 1: Review of analytical techniques for the estimation of Piracetam.

Conclusions

The present review helps the readers to understand the existing analytical techniques so far proposed for the estimation of Piracetam.

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Volume 5 Issue 7 July 2021