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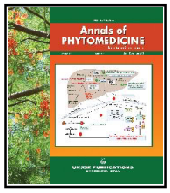

Review Article : Open Access

Analytical method development and validation of cinnarizine and piracetam: An overview

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Abstract

Nootropics, or "smart drugs", are a class of substances that can boost brain performance. They are sometimes called cognition enhancers or memory-enhancing substances. They can affect thinking and other mental functions. It is commonly used in combination with other drugs for prophylaxis of vertigo. Cinnarizine and/or its combinations in combination therapy showed a better safety profile than either of the mono-components, providing a workable therapeutic option for the treatment of vertigo. Piracetam (PRM) acts on the central nervous system and has been described as a nootropic. Piracetam shields the brain from a variety of chemical and physical insults, because its pharmacology is unusual that is, having the ability to protect the cerebral cortex against hypoxia. The combination use of cinnarizine with piracetam enhances the effect of boosting brain oxygen supply. Reviewing various analytical techniques and validating the combination medication of piracetam and cinnarizine is the main goal of this article.

1. Introduction

Cinnarizine (CIN) is a derivative of piperazine that has antihistaminic (H_1 blocker), sedative, and calcium channel-blocking activity. In 1955, Janssen Pharmaceutica synthesized cinnarizine for the first time under the name R1575. The generic ending "-rizine" for "antihistaminics/cerebral (or peripheral) vasodilators" is combined with a cinnamyl substituent on one of the nitrogen atoms to create the nonproprietary name. It has also been mentioned as one of the British Royal Navy's most popular medications for sea sickness (Lucertini *et al*., 2007). Piracetam (PRM) acts on the central nervous system and has been described as a nootropic. Corneliu E. Giurgea initially created piracetam between the 1950s and 1964. Although, some studies indicate modest benefits in certain populations, others show little to no benefit, and the evidence supporting its use is not entirely clear. Piracetam reportedly gained popularity among students in 2009 as a medication for cognitive enhancement (Winblad *et al.,* 2005). Piracetam is prescribed for various disorders such as dementia and cognitive impairment in numerous European countries. The only medication in piracetam's class that the FDA has authorized for use in the US is the antiepileptic levetiracetam (Dhirtimoni Devi and Sumithra, 2023). Although, the FDA has ruled that piracetam cannot be sold as a dietary supplement, there is little enforcement of this decision, and piracetam supplements are still obtainable (Pieter Cohen *et al*., 2020). A review of the literature revealed that only limited reports have been published on the combination of chromatographic, spectroscopic assay of piracetam and cinnarizine in the combined formulation (Navaneethan *et al.,* 2013; Ahmed *et al.,* 2020; Fadia Metwally *et al.,* 2005). Determination of piracetam individually and combined with other drugs has been reported (Payal Patil *et al*., 2018; Akhila Sivadas *et al*., 2013). Determination of cinnarizine individually and in combination with other drugs has been reported (Amal Ahmed *et al*., 2017; Dina El-Kafrawy and Tarek Belal, 2016; Walash *et al*., 2008). The major goal of this review is utilized, develop and validate newer analytical methods like spectroscopy using multivariate techniques (PLS, PCR, and CLS) and chromatography using response of surface.

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2. Mechanism of action

2.1 Cinnarizine

The mechanism of action of cinnarizine is it blocks L and T-type voltage-gated calcium channels, which prevents smooth muscle cells from contracting in the vasculature. Dopamine D_2 receptors, muscarinic (acetylcholine) receptors, and histamine H_1 receptors have all been shown to bind to it (Patel Bipin *et al*., 2010). Cinnarizine has a multimodal mechanism of action (Milind Vasant *et al*., 2019).

2.2 Piracetam

The mechanism of action of piracetam is it enhances the activity of muscarinic cholinergic (ACh) receptors, which are involved in memory processes, to produce acetylcholinergic neurotransmitter effects. Piracetam may also have an impact on NMDA glutamate receptors, which are connected to memory and learning. It is believed that piracetam increases the permeability of cell membranes (Raghavi *et al*., 2023; Jahnavi Bandla and Ashok Gorja, 2022). Piracetam may modulate ion channels (Na^+, K^+) to have a global effect on brain neurotransmission. While in the brain, piracetam seems to boost the production of cytochrome B5, which is a component of the

mitochondria's electron transport chain (Varuni *et al*., 2023). However, it also makes some Krebs cycle intermediates more permeable through the outer membrane of the mitochondria in the brain (Aaisha Ansari *et al*., 2020).

3. Dug profile

Table 1: Drug profile of cinnarizine and piracetam

Contents	Cinnarizine	Piracetam
IUPAC name	1-(diphenyl methyl)-3-(4-phenyl prop-2-enyl)-piperazine	2-(2-Oxopyrrolidin-1yl)acetamide
Appearance	White or white-like crystals or crystalline powder	The white or almost white crystalline powder
Molecular formula	$C_{26}H_{28}N_2$	$C_6H_{10}N_2O_2$
Molecular weight	368.5 g/mol	142.16 g/mol
Melting point	less than 25°C	151-152.5°C
Boiling point	154°C	259.72°C
Solubility	It is easily soluble in chloroform or benzene, and soluble in boiling ethanol (Smita Raghuvanshi and Kamal Pathak, 2014).	Freely soluble in water and soluble in ethanol (Sparsh Sharma *et al*., 2023).
Storage	2-8°C	2-8°C
pKa	7.4	15.67
Uses	Cinnarizine is used as an adjunct therapy for symptoms of peripheral arterial disease and to both prevent and cure motion sickness. Additionally, it is used to treat nystagmus, vertigo, nausea from Meniere's disease, and other vestibular disorders.	Piracetam is used to treat a variety of illnesses, including stroke and Alzheimer's disease, as well as senile dementia, vertigo, sickle cell anemia, epilepsy, and myoclonus.

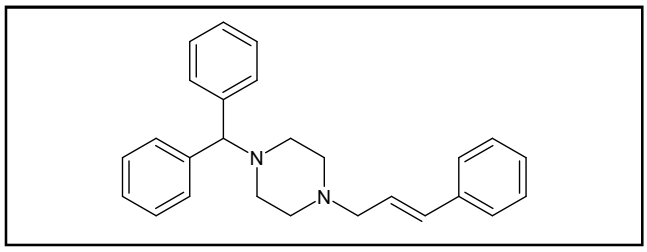

Figure 1: Structure of cinnarizine.

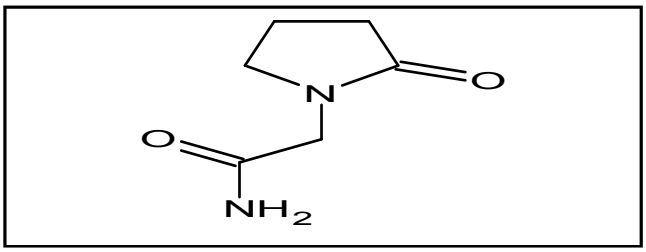

Figure 2: Structure of piracetam.

3.1 Pharmacokinetic parameters of cinnarizine and piracetam

Table 2: Pharmacokinetic parameters of cinnarizine and piracetam

Parameters	Cinnarizine	Piracetam
Absorption	It is absorbed from the gastrointestinal tract, with an absorption window in the upper gastrointestinal tract.	It is absorbed from the gastrointestinal tract quickly and widely; peak plasma concentrations are reached 1.5 h after oral doses (Margaret Vernon *et al*., 1991).
Metabolism	It is metabolized by the body and in the liver by glucuronidation and oxidation.	There is no known major metabolism of piracetam because a significant amount of the drug is eliminated unchanged after administration (Sujatha Samala *et al*., 2022).
Excretion	It excretes one-third of its metabolites in urine and two-thirds in solid waste.	The majority of piracetam excretion occurs through renal dose. elimination, with the urine recovering 80-100% of the total. Roughly 90% of the piracetam dosage is eliminated as unaltered medication in the urine (Andrei G Malykh *et al*., 2010; Mohammed Zafar *et al*., 2020).

4. Method development and validation

Alqarni Mohammed *et al.* (2023) reported an eco-friendly HPTLC method for determining CIN in brand-name formulations has been created and approved. Ethyl alcohol-water (90:10 v/v) was the environmentally friendly mobile phase used in the methods. CIN was found using a 197 nm wavelength. The analytical greenness (AGREE) approach was used to calculate the greenness score of the current method. The current method measured CIN in the 50-800 ng/band range using a linear approach. Using ICH guidelines, the current method of measuring CIN was successfully validated. It was found to be robust, sensitive (LOD=16.81 ng band^{-1} and LOQ = 50.43 ng/band), linear, accurate (% recovery=99.07-101.29%), precise (% CV = 0.80-0.95%), stable-indicating, and specific. With an AGREE score

of 0.80, the current methodology is considered to have an excellent greenness characteristic. Commercial tablet brands A and B had percentage assays of CIN of 98.64 and 101.22%, respectively. The present methodology for the pharmaceutical analysis of CIN in commercial dosage forms is deemed valid by these results. The results showed that the current method could be used to consistently determine CIN in commercial formulations.

Deepak Krishna Mhaske *et al.* (2022) described benzhydrol and cinnamyl piperazine as two degradation products; methylparaben and propylparaben are two antioxidants; and cinnarizine, five specified impurities (Impurities A-E), were all simultaneously quantified using the quick, reliable, and affordable UPHLC method. Using gradient elution mode, all analytes were eluted for 15 min at 40.0°C on an ACQUITY, UPLC, BEH C18 (150 mm x 2.1 mm, 1.7 µm) column. The concentrations of 10 m acetic acid, acetonitrile, and ammonium acetate in the mobile phases varied. Good findings were seen in the linearity curves of cinnarizine, its contaminants, and degradation products at 230 nm, with lower quantification and detection limits of 0.1875 µg/ml and 0.999, respectively, and a correlation coefficient of 0.1125 µg/ml. The proposed approach has the advantage of faster analysis, lower costs, less waste, and more environmental benefits due to its shorter run time and lower flow rate of 0.35 ml/min.

Ahmed Al-Ghani *et al.* (2020) explained the two chemometric techniques - principal component regression (PCR) and partial least squares (PLS)-were prepared using a synthetic combination comprising two medications dissolved in methanol. As a result, the quantity of cinnarizine (CIN) in both bulk and dose form could be found in a binary mixture containing piracetam (PRM). The synthetic mixture was chosen for PCR and PLS based on its zero-order spectra, which showed absorbance in the 218-230 nm range with an interval of $\Delta\lambda$=0.5 nm. The two suggested techniques showed good recovery rates of 98-102% when successfully applied to the analysis of the two drugs in dosage form and a lab-made mixture.

Lakshmana Rao *et al.* (2019) explained a straightforward, sensitive, reliable, and precise RP-HPLC method has been created. During the method development, the ODS C18 column (250 × 4.6 mm, 5 µ) was utilized. The mobile phase consisted of an 80:20 v/v ratio of acetonitrile to buffer (0.1% ortho-phosphoric acid). The buffer's pH was adjusted to 3. Cinnarizine was found to have a retention time of 4.427 min. Cinnarizine's linearity range was determined to be 10-60 µg/ml, and y=130638x + 2529.6 was the regression equation. There was a 0.52% and 0.29% RSD for intra- and inter-day precision, respectively. A mean recovery of 99.06% was found to be average. Cinnarizine's LOD and LOQ values were determined to be 1.27 and 3.25 µg/ml, respectively. A statistical analysis reveals that the results are satisfactory.

El-Adl *et al.* (2016) explained using a special isocratic HPLC method, cinnarizine, and piracetam, either in pure form or in pharmaceutical formulations, can be separated and determined simultaneously in less than 10 min. In the process of separation, a hypersil gold C18 (10 µm, 100 x 4.6 mm) column was utilized. Along with flow rate, the effects of pH and the mobile phase's composition were also looked at. For cinnarizine, the calibration range was 10-80 µg/ml, and for piracetam, it was 160-960 µg/ml. By ICH guidelines, the technique was validated and employed for the simultaneous determination of these medications in both pharmaceutical and bulk forms.

Navaneethan *et al.* (2013) reported a stability-indicating reversed-phase HPLC testing method. To accomplish the separation, gradient elution is used with the hypersil BDS C8 column (250 mm × 4.6 mm, i.d. 5 µm particle size). 2 ml of triethyl amine and 0.015 M dipotassium hydrogen phosphate, adjusted to pH 6.0 using a 990:10 v/v orthophosphoric acid and acetonitrile mixture, comprise mobile phase (A). Mobile phase (B) comprises 2 ml of orthophosphoric acid in 1000 ml of acetonitrile, flowing at a rate of 0.6 ml/min. It is discovered that the retention periods for PR and CN are, respectively, about 11 and 51 min. A diode array UV-Vis detector with a wavelength of 205 nm is used for the analysis, which is carried out at room temperature. The recommended method for simultaneously determining both medications from the capsule is found to be exact, accurate, linear, and specific (Navaneethan *et al.,* 2013).

Vania Maslarska (2013) reported a simple, fast, and reliable HPLC technique was created to measure the amount of piracetam in film-coated tablets. The mobile phase of a lichrosorb (RP-18) column was made up of acetonitrile and phosphate buffer (5:95 v/v). A quantitative analysis was done at 205 nm. Dipotassium hydrogen phosphate (5:95) at 1 g/l and a pH of 6.0 adjusted with ortho-phosphoric acid made up the mobile phase. The aqueous solution contained acetonitrile. In the concentration range of 12.5 to 100 µg/ml for piracetam, the linearity of this method was discovered. Equation Y = 5.341E7x + 1217.2, which has a correlation coefficient of 0.999, was found using the linearity curve analysis. By performing a recovery study at three distinct concentration levels (50, 100, and 150%) according to ICH guidelines, replicate analysis was used to confirm the developed method's accuracy. The accuracy of the procedure was evaluated using repeatability and intermediate precision (intra-day, inter-day), and the results were expressed as a percentage of the relative standard.

Fadia Metwally *et al,* (2005) developed four novel techniques were developed to ascertain the cinnarizine HCl concentration in its binary mixture with piracetam in pharmaceutical and pure forms. Cinnarizine hydrochloride can be separated and measured quickly and easily using a densitometric analysis, which was the first method used. The second method used a colorimetric technique to measure the drug's concentration by using $FeCl_3$ as an oxidant in a reaction with 3-methyl-benzothiazolin-2-one. The third method measured piracetam at 221.6 nm using derivative ratio spectrophotometry and measured cinnarizine HCl at 252 nm over a concentration range of 7-20 µg/ml using direct spectrophotometry. The final technique analyzed piracetam and cinnarizine HCl using liquid chromatography. It was established by quantitatively analyzing the chromatograms of piracetam and cinnarizine HCl at 252 and 212 nm, respectively, across a range of concentrations of 10-200 µg/ml for piracetam and 20-500 µg/ml for cinnarizine HCl. Recoveries quantitatively were carried out, and the outcomes matched those of previously published techniques.

5. Conclusion

This comprehensive review encompasses a diverse array of analytical techniques that have been meticulously developed and officially sanctioned for the evaluation of the piracetam and cinnarizine medication combination. The purpose of this extensive exploration is to offer a thorough examination of the methodologies employed in scrutinizing the intricate interplay between piracetam and cinnarizine, shedding light on their combined pharmacological effects and potential synergies.

This review provides readers with insights into the analytical techniques that have been proposed thus far for estimating cinnarizine and piracetam. Cinnarizine is an antihistamine drug. Piracetam is a nootropic compound often used for cognitive enhancement. Understanding the existing analytical methods is crucial for accurate and reliable estimation of cinnarizine and piracetam levels. This review aims to synthesize and present the diverse range of analytical techniques available, offering readers a comprehensive overview of the current state of methods for cinnarizine and piracetam estimation. By exploring and summarizing the existing approaches, this review equips readers with the knowledge needed to make informed decisions regarding the selection and application of analytical techniques in combination with drug research or analysis.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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