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A Quantitative Ultraviolet (UV) Spectrophotometric Analysis of ZOPICLONE as a Cyclopyrrolone Sedative Hypnotic Drug in Pharmaceutical Tablets

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INTRODUCTION & AIM

Zopiclone is a Cyclopyrrolone sedative hypnotic drug, which considerably increases the normal transmission of gamma-aminobutyric acid (GABA) in the Central Nervous System, via modulating GABA-A-type receptors. Zopiclone is a novel hypnotic agent used in the treatment of insomnia. Its mechanism of action is based on modulating benzodiazepine receptors. In addition to zopiclone's benzodiazepine pharmacological properties it also has some barbiturate-like properties. Zopiclone as a nonbenzodiazepine hypnotic from the pyrazolopyrimidine class is indicated for the short-term treatment of insomnia. While Zopiclone is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic properties, it interacts with the gamma-aminobutyric acid-benzodiazepine ($GABA_BZ$) receptor complex. Subunit modulation of the $GABA_BZ$ receptor chloride channel macromolecular complex is hypothesized to be responsible for some of the pharmacological properties of benzodiazepines, which include sedative, anxiolytic, muscle relaxant, and anticonvulsive effects in animal models. Zopiclone binds selectively to the brain alpha subunit of the GABA A omega-1 receptor. Zopiclone exerts its action by binding on the benzodiazepine receptor complex and modulation of the $GABA_BZ$ receptor chloride channel macromolecular complex. Both zopiclone and benzodiazepines act indiscriminately at the benzodiazepine binding site on α1, α2, α3 and α5 GABAA containing receptors as full agonists causing an enhancement of the inhibitory actions of GABA to produce the therapeutic (hypnotic and anxiolytic) and adverse effects of zopiclone. Extensively metabolized in the liver via decarboxylation (major pathway), demethylation, and side chain oxidation. Metabolites include an N-oxide derivative (weakly active; approximately 12% of a dose) and an N-des-methyl metabolite (inactive; approximately 16%). Approximately 50% of a dose is converted to other inactive metabolites via decarboxylation. Hepatic microsomal enzymes are apparently not involved in zopiclone clearance..The main purpose of this research was to exactly find and quantify the amount of pure Zopiclone, as an active substance in tablets. *Main objective consisted in the improvement, optimization and experimental application of a new proposed spectrophotometric method for Zopiclone quantitative analysis in Ultraviolet (UV) range. A second objective consisted in comparing the obtained results with Romanian Pharmacopoeia and European Pharmacopoeia, X-Th Standards, regarding the maximum percentage deviations allowed, compared to the official declared content of Zopiclone in pharmaceutical tablet.*

METHOD

Method description

Zopiclone. (RS)-[8-(5-chloropyridin-2-yl)-7-oxo-2,5,8-triazabicyclo [4.3.0]nona-1,3,5-trien-9-yl] 4-methyl-piperazine -1-carboxylate dissolved in Dioxane p.a. as a solvent, showed a maximum absorption A = 0.265 for a standard solution 0.726 µg/mL in the UV range at λ= 282 nm and could be appropriately dosed at this wavelength .

Working method applied to draw the calibration graph

From the initially prepared Zopiclone pew stock solution 500 µg/mL, a working standard solution of 150 µg/mL was obtained following the exact measurement of 30 mL of Zopiclone 500 µg/mL, which were brought quantitatively into another volumetric flask V= 100 mL. Dioxane p.a. was added and the content was well homogenized and filled with Dioxane p.a. right up to the mark. From the standard working Zopiclone solution 150 µg/mL, a number of eleven standard solutions were prepared in the concentration range 0.60 µg/mL – 16.80 µg/mL (Table 1). These pure standard solution were used directly to calibrate the spectrophotometer at the wavelength corresponding to the maximum absorption of the active substance, λ= 282 nm. Standard solutions were prepared in volumetric flasks of volumes Ve = 25 mL, by measuring the corresponding volumes of standard working solution 150 µg/mL of Zopiclone in each volumetric flask followed by homogenization and the subsequent filling up o the mark with Dioxan p.a. as chosen solvent and blank sample. The absorbances of the resulting standard solutions were read against Dioxane p.a. as a control, at λ= 282 nm. Three measurements were made for each of standard solutions and the average absorbance A (λ) was calculated With the obtained values (Table 1), the calibration graph was then plotted: A (λ) = f (C), Calibration graph was represented in Fig. 2.

Table 1. Measured absorbance values of Zopiclone standard solutions in direct relation with their concentrations

Nr. det.	mL standard solution of Zopiclone, 150 µg/mL	Reagent added	C (µg/mL)	A (λ)
1.	0,1	Filling up to the mark with Dioxane p.a. → V_E = 25 mL in volumetric flasks.	0.60	0,262
2.	0,3		1,80	0,298
3.	0,5		3,00	0,331
4.	0,7		4,20	0,363
5.	0,9		5,40	0,395
6.	1,2		7,20	0,446
7.	1,4		8,40	0,487
8.	2,0		12,00	0,589
9.	2,2		13,20	0,617
10.	2,5		15.00	0,673
11.	2,8		16,80	0,725

RESULTS & DISCUSSION

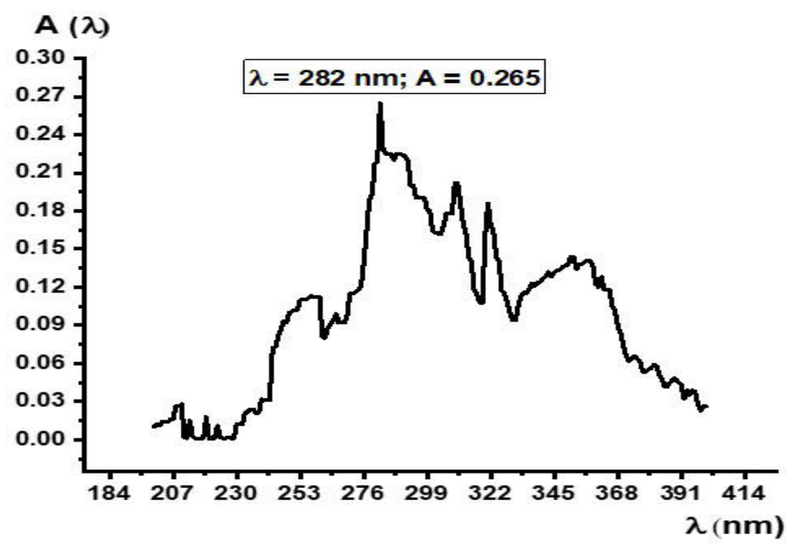

Fig. 1 Absorption Spectrum of Zopiclone in Ultraviolet (IV) Range

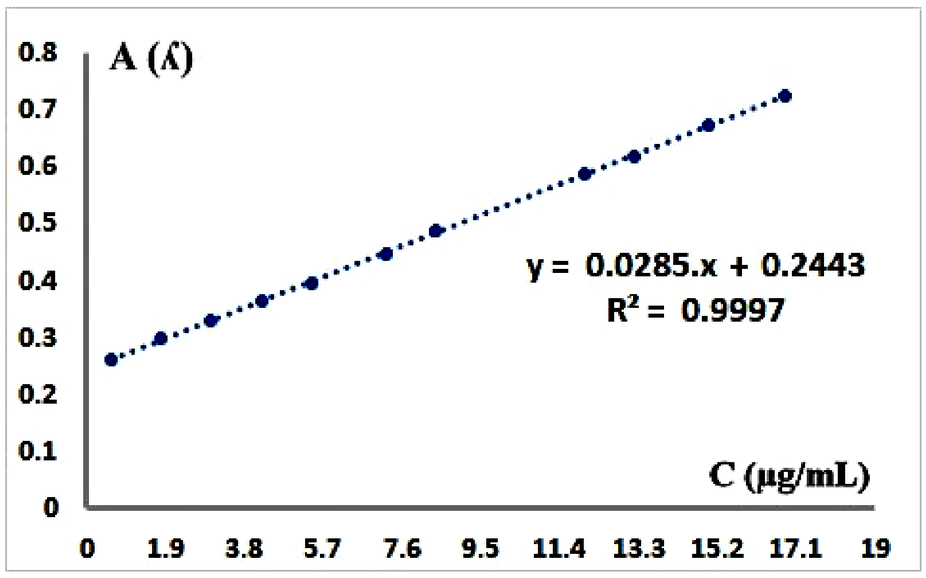

Fig. 2. Calibration graph of Zopiclone standard solutions

Sample Zopiclone dosing solution	A_p	Cp (µg/mL)	µg Zopilclone /tablet	mg Zopilclon/ tablet
	0,281	1,287 µg/mL	7210,403µg	7,2104 mg

Regression Statistics	
Multiple R	0.9998693
R Square, R^2	0.9997386
Adjusted R Square, R^2	0.9997096
Standard Error of the Regression Line (SE)	0.0027056
Observations	11

CONCLUSION

As a result of this experiment, **7,2104 mg** of pure Zopiclone/ tablet were obtained, which corresponded to a percentage content of **104.016 %** of Zopiclone in pharmaceutical tablet . This value was close enough to the official declared content of pure Zopiclone **(7.5 mg),** with a relative percentage deviation of only **(-) 4.016%.** compared to the declared content of active substance. This value was found below the value of maximum percentage deviation allowed **(± 10 %)** from the declared content of active substance **(7.5 mg)** and successfully fell within the perfect normal limits of values, provided by the Romanian Pharmacopoeia and the European Pharmacopoeia, 10th Editions.

FUTURE WORK / REFERENCES

1. Nutt DJ, Stahl SM: Searching for perfect sleep: the continuing evolution of GABAA receptor modulators as hypnotics. J. Psychopharmacol. 2010 Nov;24(11):1601-12. doi: 10.1177/0269881109106927. Epub 2009 Nov 26. [

32 https://go.drugbank.com/drugs/DB01198 , accessed Thursday 26.09.2024, at 20.00 hour.