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LUMINESCENT MARKER FOR DETERMINATION OF OROTIC ACID IN DRUG FORMULATIONS

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Luminescent properties of orotic acid (OA), vitamin B_{13}, a known bioactive substance, have been studied in this research work. It is shown that inside a coordination complex of orotic acid with Tb (III) an intermolecular excitation energy transfer from a ligand to a lanthanide ion happens which causes sensitized luminescence of Tb (III) ion. Luminescence intensity (I_{lum}) of Tb (III) increases in the presence of nonionic and cationic surfactants (SA). It is found that as a result of attachment of analyte in question onto a solid-phase sorbent with an increase of its molecular rigidity, more efficient excitation energy transfer is observed followed by the elevation of luminescence intensity of the coordination complex in the sorbent solid phase. Luminescence intensity of Tb (III) complex with orotic acid adsorbed onto the sorbent is estimated by the use of different types of sorbents. The optimum

results are achieved using Silicagel Merck as a solid-phase sorbent. The removal rate of the complex from the solution in this case reaches to 97%. The optimum conditions for isolation of orotic acid are specified. On the basis of presented research work a new analytical procedure technique is developed for the solid-phase luminescence determination of orotic acid and its salts in medicinal dosage forms.

Keywords: luminescence, complex, terbium, orotic acid, solid-phase, sorbent.

Orotic acid (OA) (2,6-dihydroxypyrimidine-4-carboxylic acid), vitamin B13, is a pyrimidine derivative and possesses bioactive activity. OA is formed as one of the intermediate products in the synthesis of nucleic acid pyrimidine bases in the living organisms. Medicinal drugs made on the basis of orotic acid potassium and magnesium salts are prescribed in medical practice as a stimulator of metabolism in humans.

Polarographic method[1], high-performance liquid chromatography[2], ion-exchange chroniatography, and methods of enzymatic analysis are in use for analytical determination of orotic acid[4,5]. Some research papers [6-8] propose method of sensitized luminescence of Tb (III) ion in the complex with orotic acid for the detection of the latter.

The aim of the presented research work is the development of sorption-luminescence determination of orotic acid in medicinal drugs with the using of sensitized luminescence of Tb (III) ion in the sorbent solid phase.

Instruments And Experimental Technique

Solutions of potassium orotate (0,01 mol/l) and surfactants (ethonium, Neonol 9-12, Triton X-100) were prepared by dissolution of precisely weighed quantities of chemical substances in distilled water. Standard solution of Terbium chloride (0.01 mol/l) was prepared by dissolving the high purity oxide (99.988%) in hydrochloric acid (1:1), followed by removal of excess through the evaporation. The concentration of Tb (III) was determined through the complexometric titration with complexone III solution using arsenazo I as the indicator in the presence of urotropine..Terbium ions luminescence was recorded at the 470-640 nm spectral region with the help of ISP-51 spectrograph with a photoelectric adapter (FEP-1) and FluoroLog FL 3-22 spectrofluorimeter (Horiba Jobin-Yvon, France) equipped with 450 Watt Ozone Free Xenon lamp. Luminescence decay kinetics was investigated using oscillograph recordings. While luminescence was excited by impulse nitrogen laser at the wavelength 337 nm. Solution pH values were measured by biological pH-meter (Radelkis OP-211/1, Hungary). All the measurements were performed at 20±2°C temperature.

Results And Discussion

Our recent study [6] revealed that inside a coordination complex of orotic acid with Tb (III) an intermolecular excitation energy transfer from a ligand to a lanthanide ion occured which causes sensitized luminescence of Tb (III) ion. It was found out that luminescence intensity (I_{lum}) of Tb (III) increases in the presence of nonionic and cationic surface-active agents (SAA).

In this case, luminescence excitation spectra of Tb (III) ions featured emission bands corresponding to the electronic transitions: ${}^5D_4 \rightarrow {}^7F_6$ ($\lambda = 487{,}5$ нм), ${}^5D_4 \rightarrow {}^7F_5$ ($\lambda = 545$ нм), ${}^5D_4 \rightarrow {}^7F_4$ ($\lambda = 585$ нм) and ${}^5D_4 \rightarrow {}^7F_3$ ($\lambda = 620$ нм), most efficient elecro-dipole transition ${}^5D_4 \rightarrow {}^7F_5$. with the greatest luminescence intensity at $\lambda = 545$ nm. In the presence of cationic SAA ethonium (1,2-ethylene-bis-(N-decyloxycarbomethyl-N.N-dimethylammonium) dichloride) luminescence intensity increases by 2 times (Fig. 1).

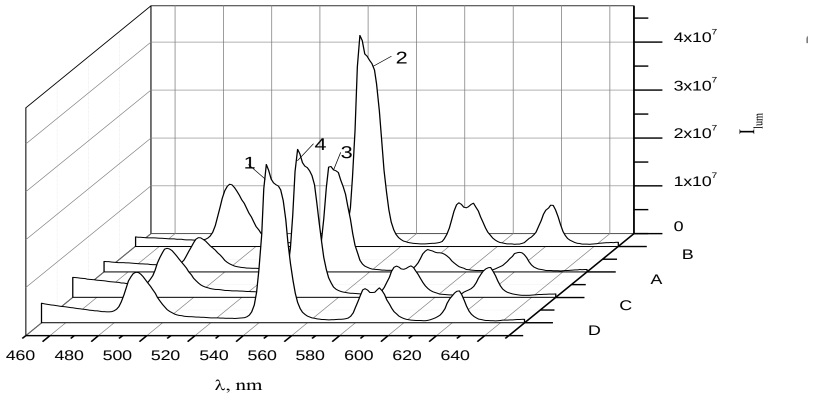


Fig. 1. The luminescence emission spectra of Tb (III) complex with orotic acid (1) in the presence of Etonium (2), Neonol 9-12 (3), Triton X-100 (4); ($C_{Tb\,(III)} = 1 \times 10^{-2}$ mol /l; pH 7,0; $\lambda_{ex} = 365$ nm)

Luminescence excitation spectrum of Tb (III) complex with orotic acid demonstrates one emission band with maximum intensity at λ = 323 nm (Fig. 2).

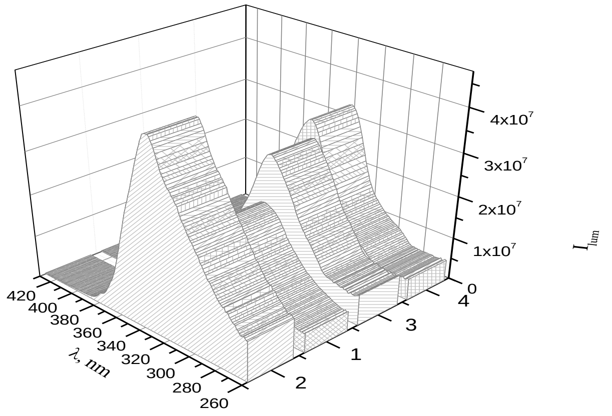


Fig.2. . Luminescence excitation spectra of Tb (III) in complex with orotic acid (1) in the presence of Etonium (2), Neonol 9-12 (3), Triton X-100 (4);

($C_{Tb\ (III)}$ = 1 × 10^{-2} mol /l, C_{surf} = 5 × 10-5 mol / L, λ_{ex} = 365 nm)

Addition of SA doesn’t change the pattern of emission of luminescence excitation spectrum but the intensity of emission bands increases.

I_{lum} elevation of emission bands of luminescence excitation spectra results from water molecules displacement from inner coordination sphere of the coordination complex which leads to decrease of nonradiative electron energy dissipation and its more efficient transfer to the lanthanide ion.

Luminescence intensity of terbium orotate increases significantly when it is adsorbed on a sorbent. Advantages of sorption-luminescence method include not only the combination of concentrating of analyte with the creation of an analytical form of analyte suitable for testing, but also with an increase of kinetic stability of complexes on sorbent in comparison with their stability in the solution [9]. The well-established consequence of this is a reinforcement of analyte molecular rigidity in response to its fixation on the solid-phase sorbent, which causes more efficient excitation energy transfer, and respective elevation of luminescence intensity. Study of I_{lum} of potassium orotate, adsorbed on various types of sorbents (posphalugel, sofraderx Sf G-75, calflo E, celite 545, Silicagel Merk), revealed the fact that the most intense luminescence is observed by the use of Silicagel Merk.

Is was established that the greatest value of luminescence intensity was achieved when the sorption from 5 mL solution with the help of 100 mg of sorbent was done. Evaluation of sorption kinetics of terbium orotate from a solution revealed that the maximum value of luminescent signal from the sorbate is achieved after 10-15 minutes of shaking. The more intense shaking of the complex on sorbent doesn’t show any significant differences in I_{lum}.

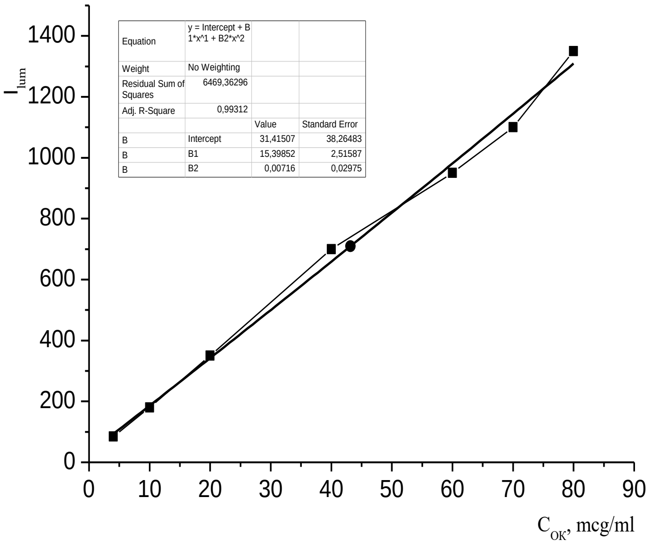
Sorption of terbium (III) orotate on the Silica gel surface occurs at a pH of 4.5-9; maximum sorbate I_{lum} is observed at a pH of 7.0.Optimum value of pH during process of sorption was established due to addition of urotropine. I_{lum} of sorbate complexes increases with an elevation of metal ions concentration in the solution, from which sorption is performed. For further research the terbium (III) concentration of 1×10^{-2} mol/l was selected which showed maximum I_{lum}. It was established that the most intense analytical signal from terbium sorbate complex with orotic acid was achieved after 10-15 minute drying process at the temperature of 60°C. It was found that luminescence intensity of sorbate complexes demonstrates its maximum values when sorption is done from water solutions .

Luminescence intensity of sorbate complex increases when dimeric surfactant ethonium is added into the solution; the same is observed during the process of sorption with the presence of ethonium as well. Sorbates of complexes, absorbed from the solutions in the presence of other SA, exhibited decrease of luminescence intensity which may be linked to solubilisation of complexes in the solution and due to that decrease of sorption degree. On the basis of obtained results a new analytical procedure was developed for the sorption-luminescence determination of analyte in medicinal drugs: potassium orotate and magnesium orotate.

Quantitative determination of orotic acid. Calibration Curve Plotting.

Put per 100 mg of Silica gel into the series of dose-measuring cups; then put there 0.2, 0.5; 1.0; 2.0; 2.5; 3.0; 3.5; 4.0 ml respectively of working solution of orotic acid (100 mcg/ml). In each dose-measuring cup put per 1 ml of terbium chloride solution (0,01 mol/l); then add 0.4 ml of ethonium solution (0.01 mol/l); after that put 0.2 ml of 4%-aqueous solution of urotropine. The volume of solutions bring up to 5 ml by adding distilled water and perform sorption by constant stirring during 10 minutes. Then make filtration and drying during 15 min at 60°C temperature in the drying oven.

Simultaneously prepare solution of blank control sample which contains all of the ingredients except for orotic acid. Luminescence intensity of terbium (III) sorbate measure at λ_{lum} = 545 nm (λ_{ex}= 365 nm). Plot a calibration curve for the relationship between luminescence intensity of sorbate complex and concentration of orotic acid (Fig.3).



Equation	y = Intercept + B 1*x^1 + B2*x^2		
Weight	No Weighting		
Residual Sum of Squares	6469,36296		
Adj. R-Square	0,99312		
		Value	Standard Error
B	Intercept	31,41507	38,26483
B	B1	15,39852	2,51587
B	B2	0,00716	0,02975

Fig. 3. Calibration curve for determination of orotic acid;

($C_{Tb\ (III)}$ = 1 × 10^{-2} mol/l; pH 7,0; λ_{ex} = 365 nm)

Determination Orotic Acid Salts In Tablet Dosage Form

Detrmination of orotic acid salts was performed in medicinal drugs “Magnerot” and “Potassium orotate”.

2 tablets of medicinal drug were pounded with a pestle till obtaining of powder-like state. A weighed amount of 100 mg of powder was placed in a 500 ml capacity measuring flask, then 250 ml of distilled water was added; the solution was stirred and diluted to the volume mark with distilled water and then filtrated. From obtained solution 1 ml of filtrate was taken to analysis; it was placed in the beaker

and then the sequence of events was the same as in the case of plotting of calibration curve.

The amount of OA was calculated on the calibration curve; amount of OA in each tablet was calculated using the equation:

$$C_x = \frac{C \cdot V_0 \cdot V_1 \cdot b}{10^6 \cdot V \cdot a}$$

C – concentration of OA found with help of calibration curve, mcg/ml

V_0 – volume of prepared solution (500 ml), ml;

V_1 – dilution volume, ml

b – average tablet mass, g; 10^6 – conversion into gramms;

a – weighed amount of medicinal drug, g.

The results of "Magnerot" and "Potassium orotate" medicinal drugs analysis calculated with reference to magnesium and potassium salts are presented in the Table 1.

Table 1.

Results of determination of orotic acid salts in tablet dosage form (n = 5, P = 0,95)

Dosage form	Found, X_i	Found, $X_{cp} \pm \Delta X$	S_r
Magnerot 500 mg, №50 (Woerwag Pharma, Germany**)**	0,5023	0,4999±0,0110	0,036
	0,4972		
	0,4961		
	0,5014		
	0,5028		
Potassium orotate 500 mg, №10 (Borschagovskiy ChPhF "(Ukraine, Kiev)"	0,5008	0,5003±0,0142	0,043
	0,4998		
	0,5012		
	0,5010		
	0,4989		

The presented method is characterized by satisfactory metrological characteristics and is rather simple in performance. At n = 5 and P = 0.95 the relative standard deviation is of 3.0 ... 4.0%.

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