

IR AND THERMAL CHARACTERIZATION OF NEW SILICOTUNGSTIC ACID COMPLEXES WITH CLEMASTINE AND TIMOLOL

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Abstract

Clemastine and timolol react with silicotungstic acid ($H_4SiW_{12}O_{40}$) and form hardly soluble ion-associations. The structures of the obtained complexes were confirmed by IR spectral analysis and thermogravimetric analysis coupled with differential calorimetric analysis. The conditions for processing the complex combinations were established in order to further assay the drugs. The chemical formula, molecular weight and solubility in water for the two complexes were determined.

Rezumat

Acidul silicowolframic ($H_4SiW_{12}O_{40}$) reacționează cu clemastina și timololul formând complecși prin asociere ionică, greu solubili în apă. Structurile complecșilor formați au fost confirmate prin analiză spectrală IR și analiză termogravimetrică cuplată cu analiză calorimetrică diferențială. Condițiile de prelucrare a precipitatelor au fost stabilite în scopul dozării substanțelor medicamentoase. S-au determinat astfel formula chimică, masa moleculară și solubilitatea în apă pentru cei doi complecși greu solubili.

Keywords: clemastine, timolol, silicotungstic acid, ion pair

Introduction

Clemastine, (2R)-2-[2-[1-(4-chlorophenyl)-1-phenylethoxy] ethyl-1-methyl pyrrolidine, is an antihistaminic drug used for reducing the effects of histamine at the level of H_1 receptors and timolol, 1-[1,1-dimethylethyl-(amino)]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol - 3-yl] oxy] 2-propanol, is a drug with antihypertensive effect useful in ocular hyper-pressure and glaucoma. Several chemical and physico-chemical methods have been reported for the quantitative determination of clemastine (CL) and timolol (TM) such as, spectral methods [1, 5, 8], electrophoresis [9, 13] and chromatographic methods [2-4, 6, 10-12, 14, 15, 17] which have been used for the assay of these drugs from bulk, pharmaceuticals and biological fluids.

The chemical structure and analytical properties of CL and TM were investigated in order to develop new methods for the quantitative determination of these drugs.

The basic properties of both compounds were determined by the pyrrolidinic nucleus in case of CL and the amino secondary group of the TM, which are easily protonable and have the capacity to form ion-pairs with some voluminous complex anions.

Silicotungstic acid abbreviated as (SiWo), multi-functional electrolyte, behaves like a polyprotic acid. It has a high molecular weight and its voluminous anion forms ion-pairs with basic drugs, with a low solubility in water. It is a reagent with a high sensibility which has been used for the assay of basic substances from batch (like alkaloids and basic drugs) and for the separation of drugs from their dosage forms.

CL and TM react with SiWo and form hardly soluble ion-associations. Complex compounds were obtained, purified and dried at room temperature and then were used for IR and thermal analysis in order to characterize the new synthesized combinations [16].

Materials and Methods

All reagents were of analytical grade and were used without further purification. Clemastine fumarate (CLF) was provided by Promedic and timolol maleate (TMM) by Merck. A 3% (w/v) SiWo solution was prepared by dissolving 3.00g in 100 mL distilled water. A 2M HCl was prepared by diluting a 38% HCl (Merck) solution with distilled water. Ethylic alcohol (Merck) was used.

An appropriate amount of substance was dissolved in alcohol (CLF) or water (TMM). The pH value

was adjusted at 1 using 2M HCl and then SiWo was added in small portions and under continuous stirring until the precipitation was completed and then a small volume of reagent was added in excess. The precipitate was separated by a filtering G₄ crucible and purified by washing at first with a saturated solution of precipitate (obtained by dissolving in water the same precipitate) and in the end with distilled water until the washing waters showed a negative reaction with AgNO₃. The precipitate was dried in a *vacuum* desiccator to constant weight.

IR spectra were registered with a Bio-Rad-Win IR spectrophotometer. IR spectra of the ion-pairs were performed in comparison with those of drugs and SiWo using KBr disks, in the range 4000 - 400 cm⁻¹.

Thermal analysis

The reagent, the two drugs and their ion-pairs were examined by using a thermogravimetric method (TG), differential thermal analysis (DTG) and differential scanning calorimetry (DSC) in a

temperature range of 20 - 700°C and 20 - 600°C. The heating rate was 20°C/minute. A Du Pont 2000 derivatograph instrument was used.

For the molecular weight determination, the maximum absorbances of the two complexes, measured by a spectrophotometric method, established by Lee Kum Tatt [7], have been used, for clemastine silicotungstate (CL-SiWo) in acetonitrile at 268.9 nm and for timolol silicotungstate (TM-SiWo), in methanol at 266.4 nm.

The solubility in water has been evaluated by measuring the absorbance of the saturated solutions of the CL-SiWo and TM-SiWo complexes in water at 25°C using a Perkin Lambda 2 UV-VIS spectrometer.

Results and Discussion

IR spectral analysis showed important changes in the characteristic bands of functional groups, which are involved in the complexation process (Table I).

Table I
IR spectral data

Compound	IR (KBr) Frequency (cm ⁻¹)
SiWo	3400; 1622; 1018 ; 980; 926; 782; 540;
CLF	3435; 3062; 2918; 2875; 2355; 1945; 1702; 1656; 1585; 1505; 1446; 1398; 1396; 1243; 1144; 1100; 979; 721; 649; 362
CL-SiWo	2361; 1446 ;1393; 1093; 1013; 973 ; 922 ; 797 ; 533
TMM	3305; 3082; 2968; 2891; 2855; 1698; 1204; 1055; 1025; 864; 770; 654; 449;
TM-SiWo	2978; 2922 ;1617 ;797

SiWo = silicotungstic acid; CLF = clemastine fumarate; CL-SiWo = clemastine silicotungstate; TMM = timolol maleate; TM-SiWo = timolol silicotungstate

The IR spectrum of SiWo is presented in Figure 1.

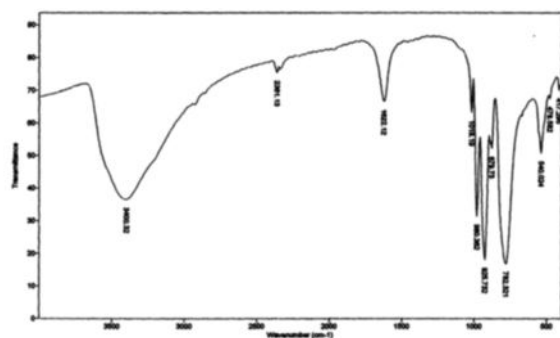


Figure 1.

The IR spectrum of SiWo

The IR spectrum of CLF (Figure 2) showed a large number of absorption bands. We attribute the most important bands to the functional groups from its structure. We attribute the bands from 3500 - 3400 cm⁻¹ and 2675 cm⁻¹ to the hydrogen fumarate ion. The band from 3500 - 3400 cm⁻¹ has a large maximum at 3435 cm⁻¹ and it results from several bands. We attribute the other bands as follow: >C=O group from fumaric acid at 1703 cm⁻¹ (valence vibration) and at 1397 cm⁻¹ (deformation vibration for -OH);

-COO- group: 1505 cm⁻¹ and 1399 cm⁻¹; >N⁺H-CH₃ group (pyrrolidinic nucleus): 2355 cm⁻¹; two benzene nucleus: 3062 cm⁻¹ (ν_{CH}), 979 cm⁻¹ (ν_{C-C}), 649 cm⁻¹ (γ_{CH}), 1585 cm⁻¹ (ν_{C-C}), 1656 cm⁻¹ (γ_{CH}); -H₂C-O-CH<: 1101 cm⁻¹; >C-O: 1243 cm⁻¹; >CH₂: 2918 cm⁻¹ (ν_{CH₂ asim}) and 2875 cm⁻¹ (ν_{CH asim}), 1446 cm⁻¹ (deformation vibration), 721 cm⁻¹ (skeleton vibration); C-N: 1362 cm⁻¹ (valence vibration). We attribute the bands from 1945 cm⁻¹ and 1144 cm⁻¹ to the ring vibration (ν_{ring}), respectively ring pulsation.

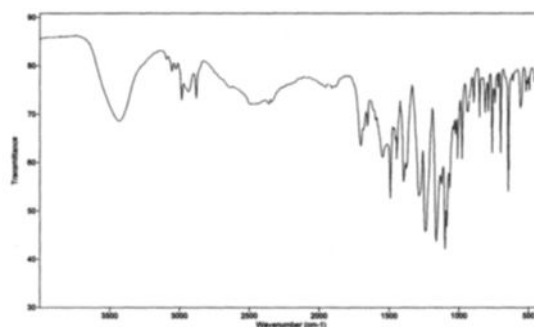


Figure 2.

The IR spectrum of CLF

The IR spectrum of Cl-SiWo (Figures 3, 4) presents the characteristic bands of the two reactants with slight changes of position, shape and intensity, taking into account the combination of cation and anion protonated of clemastine heteropolianionic. Thus, the characteristic absorbance of the heteropolianion from 540 cm^{-1} , 926 cm^{-1} , 980 cm^{-1} and 1018 cm^{-1} appears to 533 cm^{-1} , 922 cm^{-1} , 973 cm^{-1} and 1013 cm^{-1} . The band from 782 cm^{-1} appears to 797 cm^{-1} , more intense and larger.

The bands from 2361 cm^{-1} , 1446 cm^{-1} and 1393 cm^{-1} characterize the protonated cation of clemastine. In the spectrum, it is also present the characteristic band C-O-C group at 1093 cm^{-1} , slightly displaced to 1101 cm^{-1} .

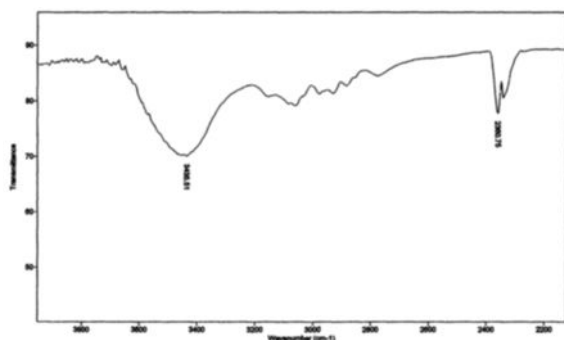


Figure 3.

The IR spectrum of CL-SiWo at a frequency of $4000 - 2000\text{ cm}^{-1}$

The IR spectrum of CL-SiWo shows the structure of ion-pairs between the protonated cation of clemastine and anion SiWo.

The complex contains crystallization water molecules.

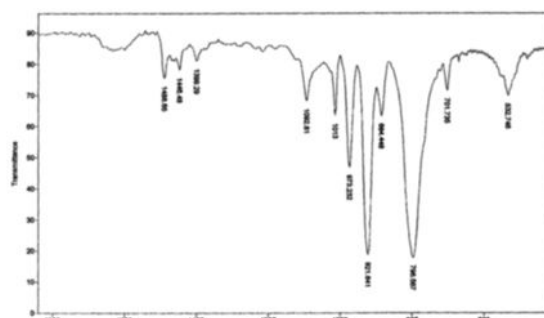


Figure 4.

The IR spectrum of CL-SiWo at a frequency of $2000 - 400\text{ cm}^{-1}$

The IR spectrum of TMM (Figure 5) is characterized by the presence of the bands from 3305 cm^{-1} and 1204 cm^{-1} which are attributed to the valence vibrations of the OH group (ν_{OH}) and C-OH group ($\nu_{\text{C-OH}}$). The band from 3082 cm^{-1} that characterizes the valence vibration for HN group (ν_{NH}) and the absorption band of valence vibrations from 1698 cm^{-1} are attributed to the C=N group. The IR spectrum showed characteristic bands for the valence vibrations of CH_3 group ($\nu_{\text{CH}_3\text{ as}}$) at 2968 cm^{-1} . The valence vibrations of the C-O-C group ($\nu_{\text{C-O-C as}}$) are characterized by the absorption band from 1055 cm^{-1} .

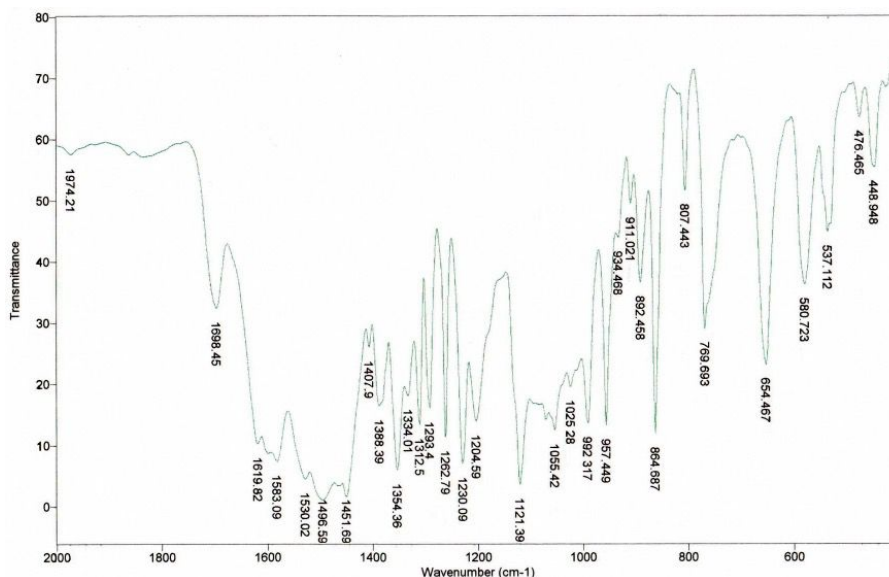


Figure 5.

The IR spectrum of TMM

The IR spectrum of TM-SiWo (Figure 6) showed the characteristic bands of protonated amino from $2978 - 2922\text{ cm}^{-1}$ and 1617 cm^{-1} with a maximum at 797 cm^{-1} . The band from 3082 cm^{-1} (ν_{NH}) no longer

appeared. In the IR spectrum of the complex, appeared characteristic bands of timolol and the heteropoliacid, unaffected by complexation.

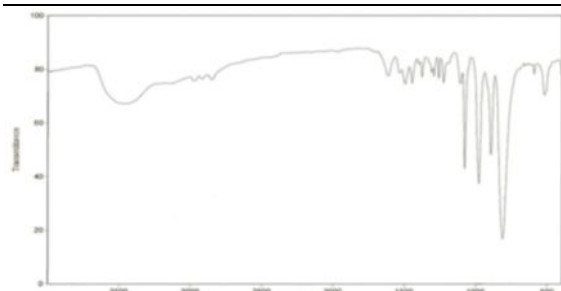


Figure 6.

The IR spectrum of TM-SiWo

Thermal analysis

TG and DTG curves of CL-SiWo (Figure 7) were determined between 0 and 700°C and the DSC curve between 20 and 260°C in an air atmosphere, with a heating rate of 20°C/minute. Up to 96°C the TG curve showed an almost constant weight with a loss of 0.2781%, followed by a continuous variation in mass, with a first maximum at 182°C (between 96 and 278°C a weight loss of 17.43% can be noted). Between 275 and 370°C it was registered a weight loss of 7.542%, with a maximum at 334°C. Between 370 and 478°C appeared a maximum at 400°C with a weight loss of 3.963% and between 478 and 655°C the loss of mass was 7.751% with two peaks at 575°C and 620°C. From 655°C it was registered a horizontal plateau.

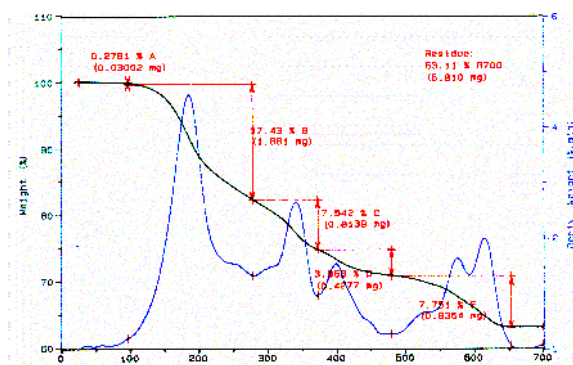


Figure 7.

The TG and the DTG curves of CL-SiWo

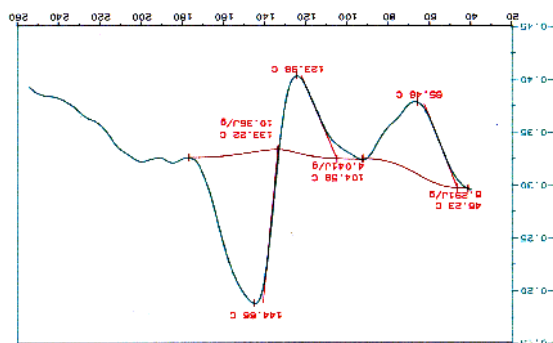


Figure 8.

The DSC curve of CL-SiWo

The DSC curve of CL-SiWo (Figure 8) showed two endothermic effects, with maximum at 65.46°C and 123.98°C, and an exothermic effect with maximum at 144.66°C.

TG and DTG curves of TM - SiWo (Figure 9) showed a slow decomposition at 95°C with a weight loss of 0.7078 %, followed in the temperature range 200 - 650°C by for a continuous variation in mass. The DSC curve evidenced the endothermic phenomenon by slightly flattened peak from 95.90°C, accompanied by an enthalpy of 28.51 j/g. Also, the DSC curve (Figure 10) showed a well-defined exothermic peak at 239.15°C. This probably corresponds to a molecular rearrangement process, for which the enthalpy is 62.72 J /g.

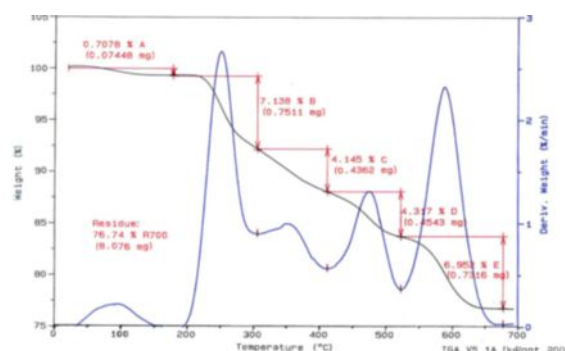


Figure 9.

The TG and the DTG curves of TM-SiWo

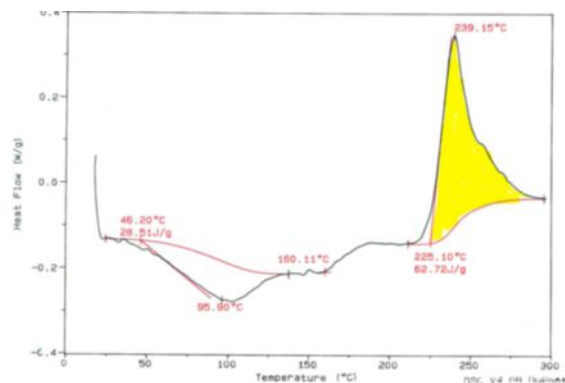


Figure 10.

The DSC curve of TM-SiWo

For the determination of the molecular weight, we used the formula established by Lee Kum-Tatt:

$$M = \frac{a \cdot \varepsilon}{A \cdot v},$$

where: M = molecular weight of the complex, a = weight (g) of the complex, ε = molar absorptivity of the complex, A = experimental absorbance, v = solution volume (mL).

The experimental molecular weight for CL-SiWo was 4285.56 versus the theoretical value, 4289.98 (corresponding to the chemical formula: $[C_{21}H_{26}ClNOH]_4^+[SiW_{12}O_{40}]^{4-} \cdot 2H_2O$) and the

experimental molecular weight for TM-SiWo was 4177.85 versus the theoretical one, 4178.28 (corresponding to the chemical formula: $[C_{13}H_{25}N_4O_3S]_4^+ [SiW_{12}O_{40}]^{4-} \cdot 2H_2O$).

The water solubility at 25°C was calculated using the formula:

$$S = \frac{A \cdot v \cdot M}{\varepsilon}$$

where S = the water solubility at 25°C (mg complex dissolved in v mL); A = experimental absorbance; v = volume of distilled water (mL), M = molecular weight of the complex, ε = molar absorptivity of the reagent in water.

The results were: 19.60 mg/L or $4.56 \cdot 10^{-6}$ mol/L for CL-SiWo and 23.15 mg/L or $5.54 \cdot 10^{-6}$ mol/L for TM-SiWo, respectively, thus demonstrating the low solubility of these complexes (Table II).

Table II

Complexes characteristics

Complex	Chemical structure	Molecular weight	Solubility	
			mg/L	mol / L
CL-SiWo	$[C_{21}H_{26}ClNOH]_4^+ [SiW_{12}O_{40}]^{4-} \cdot 2H_2O$	4285.56	19.60	$4.56 \cdot 10^{-6}$
TM-SiWo	$[C_{13}H_{25}N_4O_3S]_4^+ [SiW_{12}O_{40}]^{4-} \cdot 2H_2O$	4177.85	23.15	$5.54 \cdot 10^{-6}$

CL-SiWo = clemastine silicotungstate; TM-SiWo = timolol silicotungstate

Conclusions

The basic character reflected the capacity of the monoprotonated cations of CL and TM to form ion pairs with different reagents with voluminous complex anions. The molecular structural formulas of the complex compounds were confirmed by IR spectra, thermogravimetric and differential calorimetric analysis.

Experimental data obtained using the thermal analysis, allowed establishing the caloric effects and conditions for processing the complex combinations, in order to further assay the drugs. The molecular weight and the water solubility of the studied ion associations were determined by a spectrophotometric method.

New ion association combinations of clemastine and timolol were obtained and the study performed showed that they may be used to develop new methods for the assay of these drugs.

References

- Bedair M.M., Korany M.A., Issa A.S., Derivative spectrophotometric determination of clemastine fumarate in pharmaceutical preparations. *Analyst*, 1988; 113(7): 1137-1138.
- Boiero C., Allemandi D., Longhi M., Llabot J.M., RP-HPLC method development for the simultaneous determination of timolol maleate and human serum albumin in albumin nanoparticles. *J. Pharm. Biomed. Anal.*, 2015; 111: 186-189.
- Carlin J.R., Walker R.W., Davies R.O., Ferguson R.T., Vandenheuvel W.J.A., Capillary column GLC - mass spectrometric assay with selected-ion monitoring for timolol and [^{13}C] timolol in human plasma. *Journal of Pharmaceutical Sciences*, 1980; 69(10): 1111-1115.
- Davydova N.N., Yasuda S.U., Woosley R.L., Wainer I.W., Determination of clemastine in human plasma by gas chromatography with nitrogen-phosphorus detection. *J. Chromatogr. B Biomed. Sci. Appl.*, 2000; 744(1): 177-181.
- Du J., Quan J., Wang Y., Chemiluminescence determination of timolol maleate by gold nanoparticles-catalyzed luminol-N-bromosuccinimide system. *Talanta*, 2012; 90: 117-122.
- Gligor-Vonica A.L., Casian T., Reznec A., Tomuța I., Gligor F., Simultaneous quantification of atorvastatin and amlodipine in powder blends for tableting by NIR spectroscopy and chemometry. *Farmacia*, 2015; 63(3): 381-387.
- Kum-Tatt L., The identification and determination of nitrogenous organic bases with ammonium reineckate. *J. Pharm. Pharmacol.*, 1960; 12(1): 666-676.
- Lotfy H.M., Hegazy M.A., Rezk M.R., Omran Y.R., Novel spectrophotometric methods for simultaneous determination of timolol and dorzolamide in their binary mixture. *Spectrochim. Acta A Mol. Biomol. Spectrosc.*, 2014; 126: 197-207.
- Marini R.D., Servais A.C., Rozet E., Chiap P., Boulanger B., Rudaz S., Crommen J., Hubert P., Fillet M., Nonaqueous capillary electrophoresis method for the enantiomeric purity determination of S-timolol using heptakis(2,3-di-O-methyl-6-O-sulfo)-beta-cyclodextrin: validation using the accuracy profile strategy and estimation of uncertainty. *J. Chromatogr. A*, 2006; 1120(1-2): 102-111.
- Marley A., Connolly D., Determination of (R)-timolol in (S)-timolol maleate active pharmaceutical ingredient: validation of a new supercritical fluid chromatography method with an established normal phase liquid chromatography method. *J. Chromatogr. A*, 2014; 1325: 213-220.
- Mohamed A.M., Abdel-Wadood H.M., Mousa H.S., Simultaneous determination of dorzolamide and timolol in aqueous humor: a novel salting out liquid-liquid microextraction combined with HPLC. *Talanta*, 2014; 130: 495-505.
- Nasir F., Iqbal Z., Khan A., Ahmad L., Shah Y., Khan A.Z., Khan J.A., Khan S., Simultaneous determination of timolol maleate, rosuvastatin calcium and diclofenac sodium in pharmaceuticals and physiological fluids using HPLC-UV. *J. Chromatogr. B Analyt Technol. Biomed. Life Sci.*, 2011; 879(30): 3434-3443.
- Orlandini S., Giannini I., Navarro M.V., Pinzauti S., Furlanetto S., Dual CD system-modified MEEKC

- method for the determination of clemastine and its impurities. *Electrophoresis*, 2010; 31(19): 3296-3304.
14. Rizk M.S., Merey H.A., Tawakkol S.M., Sweilam M.N., Development and validation of a stability-indicating micellar liquid chromatographic method for the determination of timolol maleate in the presence of its degradation products. *J. Chromatogr. Sci.*, 2015; 53(4): 503-510.
15. Sboră R., Budura E.A., Nițulescu G.M., Balaci T., Lupuleasa D., Preparation and characterization of inclusion complexes formed by avobenzone with β -cyclodextrin, hydroxypropyl- β -cyclodextrin and hydroxypropyl- α -cyclodextrin. *Farmacia*, 2015; 63(4): 548-555.
16. Uivarosi V., Pahonțu E.M., Munteanu A., Synthesis, characterization and fluorescent properties of new complexes of 5-hydroxyflavone with some divalent metal ions. *Rev. Chim. (Buch.)*, 2014; 65(1): 33-38.
17. Xie Z., Liao Q., Li Z., Zhu C., Zeng Y., Liu S., Development and full validation of a sensitive quantitative assay for the determination of clemastine in human plasma by liquid chromatography-tandem mass spectrometry. *J. Pharm. Biomed. Anal.*, 2007; 44(4): 924-930.