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OBTAINING, RHEOLOGICAL CHARACTERIZATION AND THERMAL DEGRADATION OF SOME NEW MEDICINAL CREAMS

BY

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Abstract. In this work was to prepared, reological characterized and thermical degradation of creams with imidazoline and pyrazole derivatives with various pharmacological actions. The newly obtained creams including active substances were submitted to rheological tests by means of a modular rheometer to made evident their properties in time and also under the influence of certain parameters. The TG, DTG and DTA thermal analysis study revealed the temperature range where the creams containing the active components are thermally stable and properly used as well as the degree of embedding of the active principle.

Keywords: imidazoline and pyrazole derivatives; rheological tests; thermal analysis.

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1. Introduction

Both imidazoline and pyrazole derivatives are used as cardiovascular, anti-histamine, vasoconstrictive drugs, vasodilators, local anestethetics, anti-septics, bacteriostatics, fungicides, etc. (Congiu *et al*., 2008; Kumar *et al*., 2008; Nitulescu *et al*., 2019; Saeed and Batool, 2007;Ueno *et al*., 1995; Worzakowska *et al*., 2019).

Starting from these premises the opportunity was taken into account of obtaining some pharmaceutical creams containing synthesized products with potential biological activity including 2-imidazoline or pyrazole groups as farmacofors and showing low side effects, a good tolerability and significant anti-bacterial and anti-inflammatory effects (Alam *et al*., 2012; Apotrosoaei *et al*., 2014; Holla *et al*., 2000; Liu *et al*., 2008; Sharpe *et al*., 1985).

The analysis of the thermo-gravimetric (TG), derived thermo-gravimetric (DTG) and differential thermal (DTA) curves are indicative of a complex degradation mechanism of the creams under nitrogen atmosphere proceeding into two or three decomposition stages. The thermal stability is correlated to the temperature where the sample weight loss begins subsequently to the moisture removal (Burescu *et al*., 2014; Chaudhary *et al*., 2015; Mocanu *et al*., 2013; Mocanu *et al*., 2017).

2. Experimental

Preparation of active principles

The imidazoline derivative was obtained as follows: 3g (0.01 mol) of 2-chloro-4-ethylamidosulfonyl-phenoxyacetic acid ester were solved in 10 mL anhydrous methanol and then 0.01 g p-TsOH and 1g (0.016 mol) EDA solved in 5 mL anhydrous methanol added. The resulting reaction mixture was refluxed for 4 h and the methanol then removed under vacuum. The remaining residue was treated with 25 mL water and let to stay till crystallization. After repeated recrystallizations in water the resulting 2-chloro-ethylamidosulfonyl phenoxymethyl-2-imidazoline was finally obtained as an amorphous white substance melting at 117^{o}C, in a yield of 78%.

The pyrazole derivative was obtained by the condensation of the sulfonamidated 2-methyl-3-chloro-phenoxyacetic acid hydrazide with acetyl-acetone as follows: 3.30 g (0.01 mol) sulfonamidated 2-methyl-3-chloro-phenoxyacetic acid hydrazide was solved in 20 mL dimethylformamide under heating and then 1.1 g (0.011 mol) acetylacetone added. The reaction mixture was refluxed under heating for 30 min followed by cooling and addition of 29 mL water when N-hydrazide finally precipitated. The crude product was solved in 20 mL methanol, treated with charcoal and diluted with 25 mL water when 3.42 g of the final pure product resulted. To achieve the ring closure reaction the

intermediate was solved in 20 mL ethylic alcohol, then 0.1 mL of 10% HCl aqueous solution added and the mixture refluxed for 1 h. The solvent was partially distilled under vacuum, the reaction mixture cooled when the 3,5-dimethylpyrazole resulted as a precipitate. The final pure product was obtained after solving in acetone under heating, treating with charcoal, cooling and crystallization (Șoldea *et al*., 1992, Dumitrascu, 1998; Mocanu *et al*., 2017).

Rheological characterization

Oscillatory and rotational tests were run on a Testele Physica MCR 501 modular rheometer provided with a Peller system for temperature control. In order to avoid the sample slip in all measurements the geometry with paralel plates of 50 mm diameter with ribbed plates was used. Rheology of the creams was studied by means of the both oscillatory (amplitude sweep and frequency sweep) and rotational tests. Every experiment was carried out at the temperature of 25^{o}C (Lungu and Ibănescu, 2008) aiming the obtained data to reveal the properties of the creams in time and also under the influence of certain parameters. The amplitude sweep tests were performed at a constant frequency and variable amplitude between 0.001-100%.

Method of DTG analysis

The thermogravimetric analysis was carried out on a Mettler Toledo TGA-SDTA851 derivatograph under nitrogen atmosphere at a flow rate of 20 mL/min, a heating rate of 10^{o}C/min (25-700^{o}C) working with sample weights over the 2.8-4.13 mg. range. The thermal analysis cell is one of a high performance with a weighting precision below 1 microgram requiring quite low sample amounts which is very important for the organic and inorganic fine synthesis. The oven works within the 25-1100^{o}C range with a precision of temperature control of 0.01^{o}C and a heating rate starting from 1^{o}C/min and attaining 200^{o}C/min. The cell of thermal analysis is controlled by a computer when analysis programs of a high complexity can be generated. The soft (STAR) afferent to the cell allows also the mathematical processing of the weight loss curves as well as the kinetic processing (Mettler Toledo STAR^{e} System TGA/SDTA851^{e}, 2006).

3. Results and Discussions

The newly synthesized derivatives taken for obtaining the medicinal creams are of the following structures (Fig. 1):

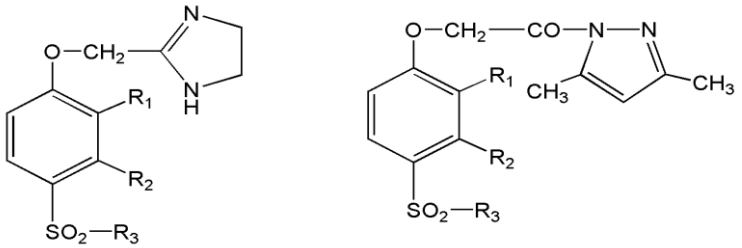

Fig. 1 – Structures of compounds.

Synthesis of the 2-chloro-4-ethylamidosulfonyl-phenoxymethyl-2-imidazoline derivative was performed by the condensation of the 2-cloro-4-ethylamidosulfonyl phenoxyacetic acid methylic ester with ethylenediamine and acid catalyst (p-toluenesulfonic acid p-TsOH) while the pyrazole derivative was synthesized by the condensation of the sulfonamidated R_1,R_2-fenoxyacetic acid hydrazide with acetylacetone (Fig. 2).

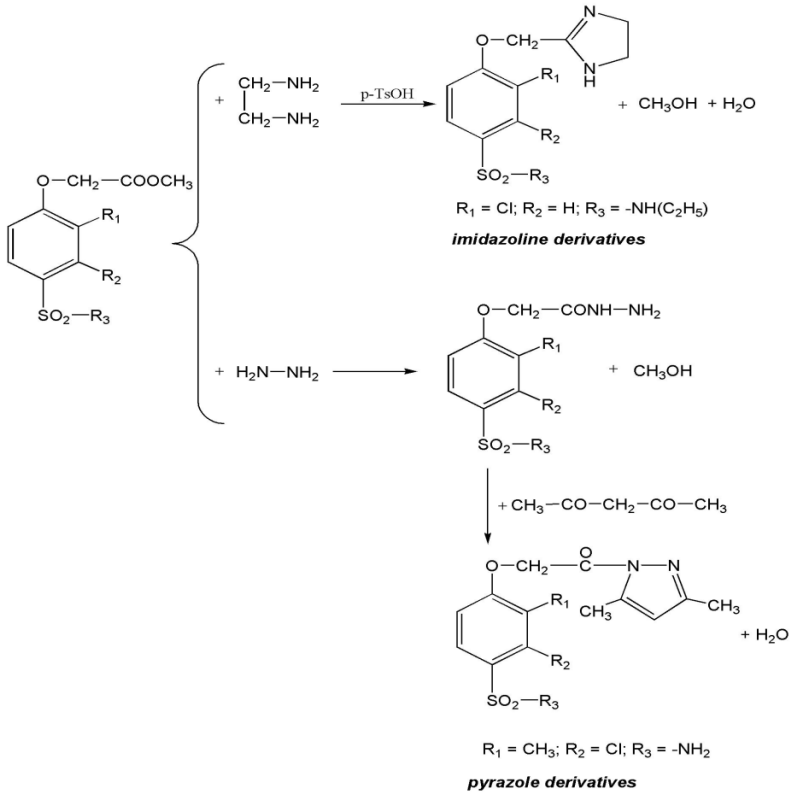

Fig. 2 – Synthesis of the imidazoline and pyrazole derivatives.

The creams were prepared as follows: the bee wax (7 g) and the cocoa butter were heated to obtain a homogeneous mixture. Meanwhile the borax (1 g) was solved in distilled water (50 mL) and the active principle (imidazoline and pyrazol, 0.2 g) in ethylic alcohol (10 mL). When the wax-cocoa butter mixture was homogeneous the water-borax mixture was added and and the resulting mass mixed vigorously with a glass bar till a creamy texture appearance. Finally the active principle solved in ethanol was added under continuous mixing till a creamy well thickened texture appears. This cream was prepared under a working temperature of 68-70^{o}C.

Rheological characterization

As can be seen in Fig. 3 all samples under study show structural stability within the range of small deformations. The accumulation module (G') higher than the loss module (G") is indicative of a well-developed network and a gel behavior (G'>G"). At 25^{o}C, all samples have a high accumulation module, are rigid and sensitive to small deformation variations. The components added into the basic cream do not influence significantly the rheological behaviour of the product under study the resulted dynamic modules being thus of similar values. The limit value of the linear viscoelastic domain (LVE) of γ_{LVE} = 0.005% was estimated for all samples under study.

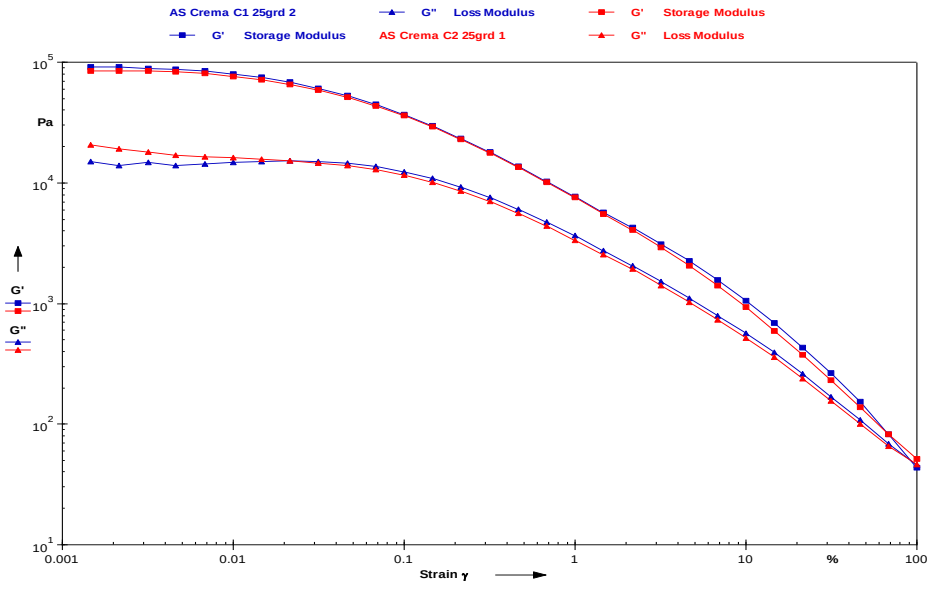

Fig. 3 – Amplitude sweep tests.

The frequency sweep tests were carried out at a constant amplitude (within the LVE domain limit) and variable frequency between 0.1-100 L/s.

The frequency sweep test was made to get information on the structural stability, to estimate the consistency in the resting state, long term behavior as well as that of the product separation. The both creams are noticed to show a characteristic behaviour of the gel type (G' higher than G" over the entire experimental frequency domain), so that all samples have stable structures with no separation of components (Fig. 4).

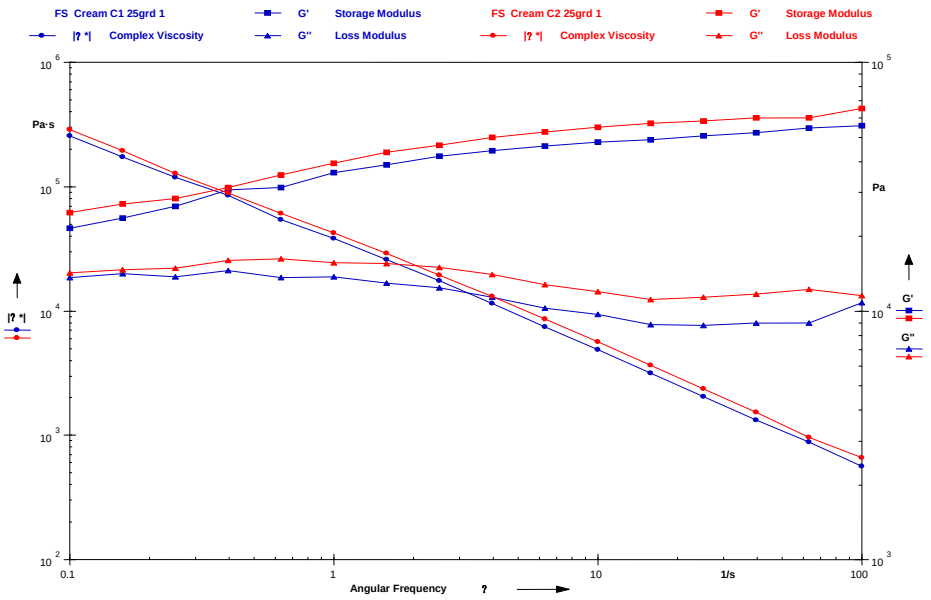

Fig. 4 – The frequency scanning tests.

The flow tests were made with variations of the shear speed between 0.001-100 L/s. Since the viscosity, η, decreases with increasing shear speed the both creams containing imidazoline and pyrazole, respectively, show a pseudo-plastic behaviour at 25°C. The high viscosity values at zero shear estimated by means of the Carreau-Yasuda model (η_0 = 2.58 x 10^4 Pa for the imidazoline cream and η_0 = 3.53 x 10^4 Pa for the crem with pyrazole) are indicative of the long term structural stability of the samples under study (Fig. 5).

The quality of a pharmaceutical product depends on its formulation and the rheological behaviour could indicate its suitability for a certain purpose. The preparation and proper selection of the ingredients allow the product to flow easily from the container (flow point, τ_0), with no sedimentation of solid particles during storage, to show a high stability (viscosity zero in case of shear, η_0) and to be easily applicable on the skin (pseudo-plastic behaviour).

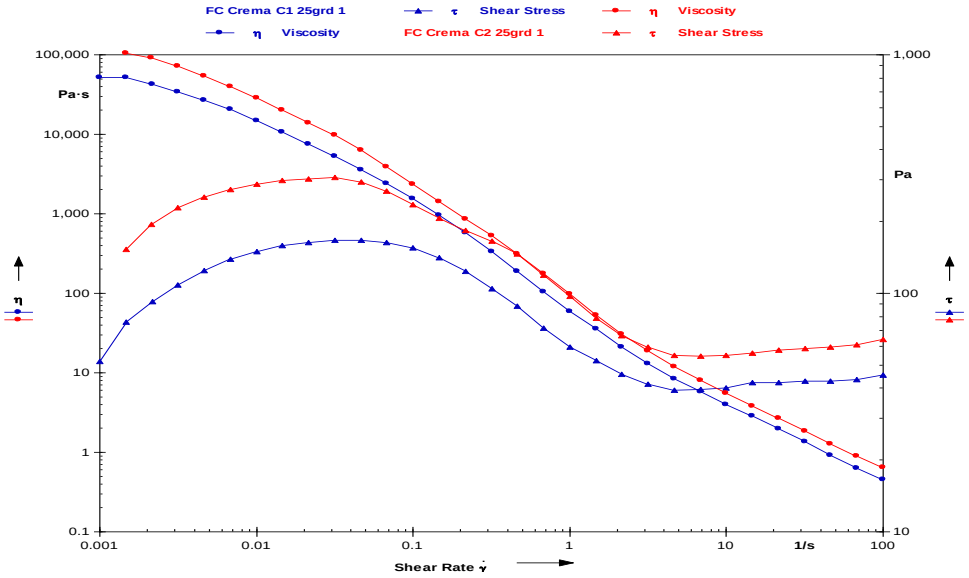

Fig. 5 – The flow tests.

Thermal analysis data

The thermal analysis study TG, DTG and DTA made evident the temperature range where the obtained creams containing active principles are thermally stable and suitable for use. The thermal degradation mechanism of the creams under nitrogen atmosphere is rather complex and proceeds into two or three decomposition stages. The thermal stability is correlated to the temperature where the weight losses of the samples begins after moisture removal (Chaudhary *et al*., 2015; Mocanu *et al*., 2013; Mocanu *et al*., 2017; Swiderski *et al*., 2018).

The thermo-gravimetric (TG) and derived thermo-gravimetric (DTG) curves recorded with the creams prepared under inert atmosphere, such as nitrogen, are depicted comparatively in Figs. 6-9.

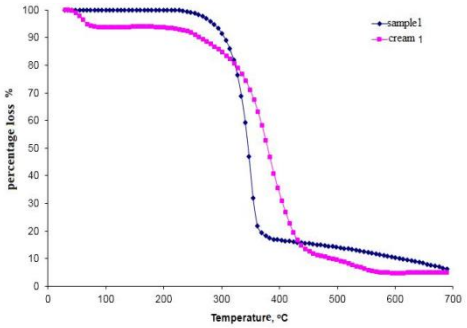

Fig. 6 – TG curve for imidazole cream.

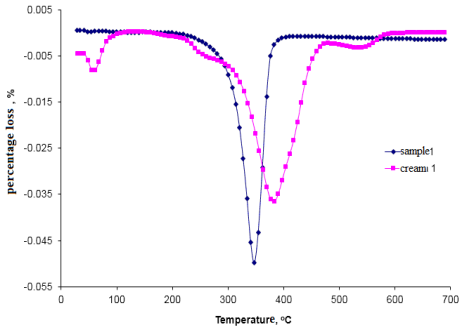

Fig. 7 – DTG curve for imidazole cream.

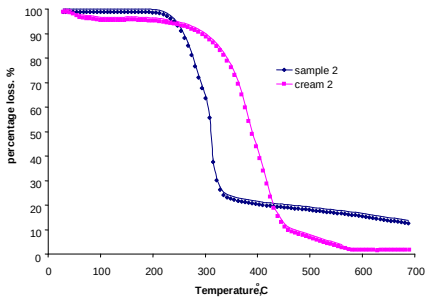

Fig. 8 – TG curve for pyrazole cream.

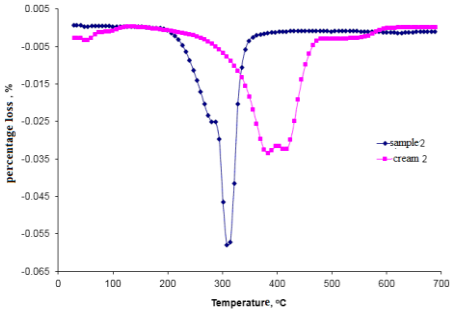

Fig. 9 – DTG curve for pyrazole cream.

The main thermo-gravimetric characteristics of the samples under study are given in Table 1. The residue amount resulting at 700°C as well as the DTA characteristic are also specified. According to the obtained results the imidazoline derivative is thermally degraded into one exothermal stage at the temperature where degradation rate is the highest at 347°C. The residue amount corresponding to the temperature of 700°C is of 3.86%. As mentioned in literature the imidazoline ring is opened within the 255–370°C temperature range in the presence of oxygen (Swiderski *et al*., 2013) and within the 280–390°C range under inert atmosphere (Jin *et al*., 2012). Consequently the fact is noticeable that our results fall within the temperature range mentioned by other scientists for imidazoline derivatives. After moisture removal between 45–71°C, the thermal decomposition of the imidazoline containing cream proceeds into two exothermic stages, the resulting residue amount of 4.27% being noticed at 700°C. The imidazoline ring opening proceeds within the 249–448°C temperature range along with the degradation of other ingredients taken for the cream preparation.

Table 1

Characteristic Amounts from TG-DTG Analysis

Samples	*Degradation stage*	$T_{onset}{}^{o}C$	$T_{peak}{}^{o}C$	$T_{endset}{}^{o}C$	*W%*	*DTA Characteristics*	*Residue*
imidazoline derivatives	I	309	347	364	96.14	Exo	3.86
imidazoline cream	I	45	53	71	6.38	Endo	4.27
	II	249	381	448	81.22	Exo	
	III	448	543	568	8.13	Exo	
pyrazole derivatives	I	236	282	306	37.54	Endo	12.37
	II	306	311	323	50.09	Exo	
pyrazole cream	I	43	50	104	3.18	Endo	2.48
	II	326	383	389	47.28	Exo	
	III	389	415	454	38.18	Exo	

As revealed by the data in Table 1 the thermal degradation of the pyrazole derivative develops into two stages, one endothermic and the other exothermic, at the temperature where the decomposition rate is the highest,

namely 282 and 311°C, respectively. As mentioned (Mocanu *et al*., 2017), along these stages the pyrazole ring is opened with release of NH_3, HNCO, C_2H_4 and CH_2-NH-.

After moisture removal the degradation of the pyrazole containing creame under nitrogen atmosphere develops into three stages. The final degradation stage develops between 400°C and 600°C being similar to that in case of imidazoline containing cream and the percentage weigh loss is of about 8.5%. This weight loss is probably caused by the decomposition of an ingredient common to both creams. The pyrazole containing cream is thermally more stable than that with imidazoline as revealed by the temperatures where the thermal degradations begin, about 320°C and 240°C, respectively.

4. Conclusions

The obtained imidazoline and pyrazole derivatives showing potential anti-microbial action were subsequently embedded into two creams showing drug action.

The obtained creams were submitted to thermal and rheological analyses. The rheological analysis made evident a structural stability of the samples within the domain of small deformations, the network being well developed, with a gel character, stable structures and no separation of the components over long time.

The thermal analysis data are indicative of a higher thermal stability of the pyrazole cream than that with imidazoline, the thermal decomposition starting at temperatures higher than about 80°C after moisture removal.

The mechanism of the thermal decomposition of the two creams is rather complex, developing into two or three stages depending on the presence of either imidazole or pyrazole derivatives.

The rheological and thermal analyses were indicative of a well embedded active principles into the two obtained creams.

REFERENCES

Alam S.M., Choi J.H., Lee D.U., *Synthesis of Novel Schiff Base Analogues of 4-Amino-1,5-Dimethyl-2-Phenylpyrazol-3-One and their Evaluation for Antioxidant Andanti-Inflammatory Activity*, Bioorg. Med. Chem., **20**, 4103-4108 (2012).

Apotrosoaei M., Vasincu I., Dragan O., Buron F., Routier S., Profire L., *Design, Synthesis and the Biological Evaluation of New 1,3-Thiazolidine-4-Ones Based on the 4-Amino-2,3-Dimethyl-1-Phenyl-3-Pyrazolin-5-one Scaffold*, Molecules, **19**, 13824-13847 (2014).

Burescu A.I., Sava I., Bruma M., Lisa G., *Study of the Thermal Decomposition of Some Azopolyimides*, High Performance Polymers, 26, 81-88 (2014).

Chaudhary R.G., Junejab H., Pagadalac R., Gandhared N., Gharpure M., *Synthesis, Characterisation and Thermaldegradation Behaviour of Some Coordination Polymers by Using TG–DTG and DTA Techniques*, J. of Saudi Chem., Soc.,19, 442-453 (2015).

Congiu C., Cocco M.T., Onnis V., *Design, Synthesis, and in Vitro Antitumor Activity of New 1,4-Diarylimidazole-2-Ones and their 2-Thione Analogues*, Bioorg. Med. Chem. Lett., **18**, 980-993 (2008).

Dumitrascu A., *Studies on Obtaining New Derivatives of Sulfamoyl-R-Phenoxy-Acetic Acids with Potential Biological Action*, Doctoral Thesis, Iaşi, 1998.

Holla B.S., Gonsalves R., Shenoy S., *Synthesis and Antibacterial Studies of a New Series of 1,2-Bis(1,3,4-Oxadiazol-2-Yl) Ethanes and 1,2-Bis(4-Amino1,2,4-Triazol-3-Yl) Ethanes*, Eur. J. Med. Chem., 35, 267-271 (2000).

Jin Xinghui J., Hu Bingcheng, Liu Zuliang, *Thermal Stability and Quantum Chemistry Study on Octahydro-2,5-Bis(Nitroimino)Imidazo[4,5-d]Imidazole*, Proced. Engin, 45, 558-561 (2012).

Kumar A., D'Souza S.S., Gaonkar S.L., Rai K.M.L., Salimath B.P., *Growth Inhibition and Induction of Apoptosis in MCF-7 Breast Cancer Cells by a New Series of Substituted-1,3,4-Oxadiazole Derivatives*, Invest. New Drugs, 26, 425-435 (2008).

Liu F., Luo X.Q., Song B.A., Bhadury P.S., Yang S., Jin L.H., Xue W., Hu D.Y., *Synthesis and Antifungal Activity of Novel Sulfoxide Derivatives Containing Tri-Methoxyphenyl Substituted 1,3,4-Thiadiazole and 1,3,4-Oxadiazole Moiety*, Bioorg. Med. Chem., 16, 3632-3640 (2008).

Lungu M., Ibănescu C., *Rheological Properties of Polymer Systems*, Ed. Performantica 2008.

Mocanu A.M., Luca C., Luca A.C., *Thermal Degradation of Some New Azomethines and Environmental Impact Assessment*, Rev. Chim. (Bucharest), 64, 1182-1186 (2013).

Mocanu A.M., Luca C., Luca A.C., *Synthesis, Characterization and Thermal Degradation of Some New 3,5-Dimethyl Pyrazole Derivatives*, Rev. Chim. (Bucharest), 68, 319-355 (2017).

Nitulescu G.M., Matei L., Aldea I.M., Draghici C., Olaru O.T., Bleotu C., *Ultrasound Assisted Synthesis and Anticancer Evaluation of New Pyrazole Derivatives as Cell Cycle Inhibitors*, Arabian J. of Chem., **12**, 816-824 (2019).

Saeed A., Batool M., *Synthesis and Bioactivity of Some New 1-Tolyl-3-Aryl-4-Methyl-Imidazole-2-Thiones*, M. Med. Chem. Res., **16**, 143-154 (2007).

Sharpe T.R., Cherkofsky S.C., Hewes W.E., Smith D.H., Gregory W.A., Haber S.B., Leadbetter MR., Whitney JG., *Preparation, Antiarthritic and Analgesic Activity of 4,5-Diaryl-2-(Substituted Thio)-1H-Imidazoles and their Sulfoxides and Sulfones*, J. Med. Chem., 28, 1188-1194 (1985).

Swiderski G., Wilczewska A.Z., Swisłocka R., Włodzimierz Lewandowski M.K., *Spectroscopic (IR, Raman, UV–Vis) Study and Thermal Analysis of 3d Metalcomplexes with 4-Imidazolecarboxylic Acid*, J.Therm. Anal. and Calorim., 134, 513-525 (2018).

Șoldea C., Oniscu C., Sunel V., *On Hypotensive Action of Some Imidazoline Derivatives of Sulphonamidated Aryloxyalkyl Carboxylic Acids*, Rev Med. Chir. Soc. Med. Nat., 96, 265-268 (1992).

Ueno M., Imaizumi K., Sugita T., Takata I., Takeshita M., *Effect of a Novel Antirheumatic Drug, TA-383, on Type II Collagen-Induced Arthritis*, Int. J. Immunopharmac. 17, 597-603 (1995).

Worzakowska M., Sztanke M., Sztanke K., *Decomposition Course of Anticancer Active Imidazolidine-Based Hybrids with Diethyl Butanedioate Studied by TG/FTIR/ QMS-Coupled Method*, J. of Analytical and Applied. Pyrolysis, 143, 104686-104691 (2019).

** Mettler Toledo STARe System TGA/SDTA851e, Operating Instructions, Mettler-Toledo GmbH, 2006.

OBȚINEREA, CARACTERIZAREA REOLOGICĂ ŞI DEGRADAREA TERMICĂ A UNOR NOI CREME MEDICAMENTOASE

(Rezumat)

În această lucrare au fost preparate, caracterizate reologic şi degradate chimic creme cu derivați de imidazol şi pirazol cu multiple acțiuni farmacologice. Cu ajutorul reometrului modular s-au realizat teste reologice ale noilor creme cu substanțele active sintetizate, urmând ca datele obținute să reflecte diferite proprietăți ale acestora în timp sau sub acțiunea unor parametri. Studiul de analiză termică TG, DTG şi DTA a permis identificarea intervalului de temperatură în care cremele cu principii active sunt stabile termic şi pot fi utilizate, cât şi gradul de înglobare al principiului activ.