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THEORETICAL STUDY OF THE POSSIBILITY OF DECAMETHOXIN COMPLEXES WITH THIOTRIAZOLINE TO BE FORMED

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Over the last decade, much attention has been paid to the prevention and treatment of chronic diseases of the oral mucosa. This is primarily due to the increase in the number of patients who seek dental care for diseases of the oral mucosa (DOM).

Currently, due to the lack of special epidemiological studies, information on the pathology of the oral mucosa in the literature is almost non-existent. The etiology and pathogenesis have not been definitively elucidated. It is established that a significant role in the pathogenesis of chronic inflammatory processes belongs to the state of the microbiocenosis of the oral mucosa.

One of the most striking examples of domestic drugs of the antioxidant group is thiotriazoline, developed by the staff of the NGO "Pharmatron", as well as specialists of the Department of Pharmaceutical Chemistry of Zaporozhye State Medical University under the leadership of professor Mazur I. A. This drug has an antioxidant and membrane-stabilizing effect.

The aim. *The combined use of several drugs can be complicated by the formation of their supramolecular complexes. Therefore, before the introduction of several substances in it is necessary to model the possibility of intermolecular interactions between them. For this purpose, methods of quantum chemistry are used.*

Material and methods. *We examined the structures and energy characteristics of the complexes, formed thiotriazoline and decamethoxin, also carried out analysis and established at what temperature the formation of a substance from two active components was possible.*

Results. *As a result, the probability of the formation of intermolecular hydrogen bonds is reduced, which is very well seen in the trend of interactions between acid and morpholine.*

Conclusions. *Quantum chemical study of a two-component system consisting of thiotriazoline and decamethoxine showed that the most energetically advantageous three-component complexes have a sufficiently low interaction energy of thiotriazoline and decamethoxine. In addition, the data that are provided in the analysis of the tree diagram suggest that in the technological process in the manufacture of dosage forms, it is advisable to use a temperature not higher than 115 °C*

Keywords: *thiotriazoline, decamethoxine, molecular compounds, diseases, quantum chemical calculations, interaction energy*

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1. Introduction

Due to the fact that this mixture consisting of decamethoxin and thiotriazoline is a new pharmaceutical development. Which is directly dealt with by a group of scientists together with the NVO "Pharmatron" under the leadership of Vice President L. I. Kucherenko. All data are presented in the sources. There are also developments of successful use in combinations of thiotriazoline, namely with piracetam, amiodorone and carbatril. This indicates the successful use of thiotriazoline in combinations.

Over the last decade, considerable attention has been paid to the problem of the prevention and treatment of chronic oral mucous membrane diseases [1].

This is primarily due to the increasing number of patients seeking dental care with oral mucous membrane diseases (OMMDs).

The OMMDs represent one of the most difficult problems in dentistry due to difficulties in diagnosis and treatment. The problem is complicated by the fact that so far no communal disease prevention measures have been developed.

It was found that the age of most patients ranged from 20 to 40 years. Before puberty, both sexes are equally ill, but among adults, women predominate.

At present, due to the lack of special epidemiological studies, the information about the pathology of oral mucosa is practically not found in the literature. The etiology and pathogenesis have not been finally clarified. It has been established that a significant role in the pathogenesis of chronic inflammatory processes belongs to the state of microbiocenosis of the oral mucous membrane.

At present, antiseptic drugs are widely used in medicine, especially compounds that have bactericidal properties to reduce the effect of microbes on the oral mucosa.

Decamethoxin is a chemical compound which is used for the treatment of OMMDs [2, 3].

Because decamethoxin is a surfactant, it changes the permeability of the microbial cell membrane, resulting in the destruction and death of microorganisms, which causes its bactericidal action.

The antiseptic action of the substance is based not only on the bactericidal activity but also on bacteriostatic activity. Bacteriostatic action is due to the following mechanisms:

- a) Inactivation of exotoxins of microorganisms.
- b) The decrease in the adhesion of pathogenic microorganisms.

One of the brightest examples of domestic preparations of the group of antioxidants is thiotriazolin, which was developed by the staff of NGO "Pharmatron", as well as specialists of the Department of Pharmaceutical Chemistry of Zaporizhzhia State Medical University under the guidance of professor I. A. Mazur. The intermolecular interaction of thiotriazoline with the formation of complexes with amino acids was previously studied [4].

This drug has antioxidant and membrane-stabilizing effects.

It is known that the combined use of several drugs can be complicated by the formation of their supramolecular complexes. Therefore, before introducing several substances into a drug, it is necessary to simulate the possibility of the formation of intermolecular interactions between them. To do this, use the methods of quantum chemistry is useful.

The aim of the work. We examined the structures and energy characteristics of the complexes, formed thiotriazoline and decamethoxin, also carried out thermogravimetry analysis and established at what temperature the formation of a substance from two active components was possible.

2. Planning of the research

Since we are planning to use two active ingredients in one dosage form, we need to exclude their intermolecular interactions. To confirm and eliminate the risks of physical interaction between active substances, it is advisable to conduct thermogravimetric studies. The article presents thermogravimetric studies and quantum chemical analysis, which showed that these two components could be used together. If it were proven that these active substances form stable supramolecular complexes, we would have to abandon further research. This was the risk identification of our study.

The combined use of several drugs can be complicated by the formation of supramolecular complexes in them. Such a complexation can change the physico-chemical characteristics of a drug and as a consequence its biological activity. Therefore, before introducing several substances into PhF (PF), it is necessary to simulate the possibility of the formation of intermolecular interactions between them. For this, methods of quantum chemistry. Since our study takes two components, we needed to conduct an analysis – DTA. All substances

have an individual thermal characteristic, which reflects its behaviour during heating (cooling), depending on the composition, properties, structure, mechanism and kinetics of transformation.

Thus, according for substance analysis, we received a high-quality characteristic of the investigated substances. Qualitative phase display that thermal effects and their characteristic temperatures remain unchanged, therefore, these two components do not enter into an interaction reaction, which gives us the right to use them in a joint combination.

3. Material and methods

For modelling the structure and stability of thiotriazoline complexes with decamethoxine (Fig. 1) a technique similar to that used earlier in the study of thiotriazoline complexes. The following scheme was used to search for the most stable complexes of isoniazid with MTTA and morpholine:

– by the method of genetic conformational search using the force field MMFF94, which is implemented in the AutoDock Vina program, possible complexes differing in mutual orientation were found molecules and their conformation. In total, for each system, about 10,000 complexes were calculated, which for such systems guarantees a complete covering the variation space; 478 – from the complexes obtained at the previous step, 100 were selected the most energetically favourable, for them a preliminary geometry optimization by (SMD-) B97D / 6-31G *; – final optimization of the 10 most energy-efficient complexes obtained in the previous step was carried out by the method (SMD-) B97D / 6-311G [5–7].

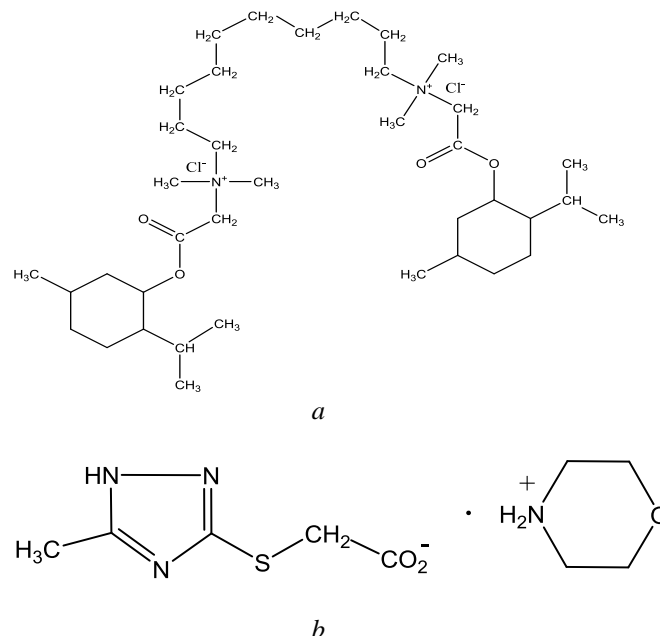


Fig. 1. Chemical formulas:
a – decamethoxin; b – thiotriazoline

Initial approximation to geometry of the complexes was obtained using a molecular docking procedure with the help of the AutoDock Vina program. The 2-(5-methyl-1H - 1,2,4-triazol-3-ylsulfanyl)acetate in the thiotriazoline exists in only one tautomeric form (Fig. 1) that was confirmed by

X-ray diffraction study [8]. For the construction of three-component complexes, 2-(5-methyl-1H-1,2,4-triazol-3-ylsulfanyl) acetate MTA and morpholine docking was conducted at the first stage, and 50 structures with the low energies were selected. Then docking of the obtained salt complexes with decamethoxin molecule was carried out, and the further 50 structures with the low energies were also selected. Thus, for the study of possible three-component complexes, 2500 initial structures were obtained.

At the second stage, the obtained three-component complexes were preliminarily optimized by the semi-empirical PM7 method by modelling the influence of the polarizing environment using the COSMO method (water was used as a solvent). Calculations were made using the MOPAC2012 program.

Based on the results of these calculations, 100 structures with the lowest energy were selected for the three-component complex, which were then optimized by the density functional method with the empirical dispersion correction B97-D3/SVP+COSMO (water) by applying a geometric correction to the incomplete gCP base set [9–11].

DTA analysis was performed on a Shimadzu DTG-60 derivatograph (Japan) with a platinum-platinum-rhodium thermocouple while heating the samples in aluminium crucibles (from 25 to 250 °C). Al_2O_3 was used as a reference substance. The heating rate was 10 °C per minute. The derivatograph graphically recorded the obtained data in the form of T, DTA, TGA curves. The T curve in the derivatogram shows the change in temperature, and the TGA curve shows the change in the mass of the sample during the study period.

4. Results

The large size of the decamethoxine molecule and the presence of two quaternized nitrogen atoms in this molecule (which gives a double positive charge) lead to a significant increase in nonspecific interactions (general electrostatics and dispersion) compared to the three-component complexes of thiotriazoline with aminoacids. As a result, the probability of the formation of intermolecular hydrogen bonds is reduced, which is very well seen in the trend of interactions between amino acid and morpholine. In many cases, the intramolecular O-H...N hydrogen bond in acid is more preferable than the intermolecular hydrogen bond between acid and morpholine. In addition, in no complex is the interaction of the deprotonated carboxylic group with the protonated morpholine nitrogen atom forming organic salt.

The prevalence of non-specific interactions is confirmed by comparison of interaction energies in complexes calculated by two methods: a) in vacuum using density functional, parametrized for intermolecular interactions; b) taking into account the polarizing environment using density functional, taking into account dispersion interactions. In most complexes, these energy values differ more than twice. They become comparable only in complexes where weak intermolecular hydrogen bonds are formed.

The formation of intermolecular hydrogen bonds is critical for the stability of the complexes, that can be shown by the example of the most and least energy-efficient complexes from the selected ones.

The most energetically advantageous complex (given under number 1 in Fig. 2) is formed by two intermolecular hydrogen bonds besides non-specific interactions. One of these bonds is quite strong and binds acid to morpholine. The second hydrogen bond was found between the triazole acid cycle and decamethoxin. However, this bond is weaker according to its geometric characteristics. The least stable of the selected complexes was formed only due to non-specific interactions, primarily dispersion.

Structure of the most stable complex and the least stable complex of thiotriazoline with decamethoxin, their interaction energy in the complex (E_{int} , kcal/mol), and characteristics of the hydrogen bonds (H...A, Å, and D-H...A, deg.) according to B97-D3/ def2-tzvp+COSMO (water) method.

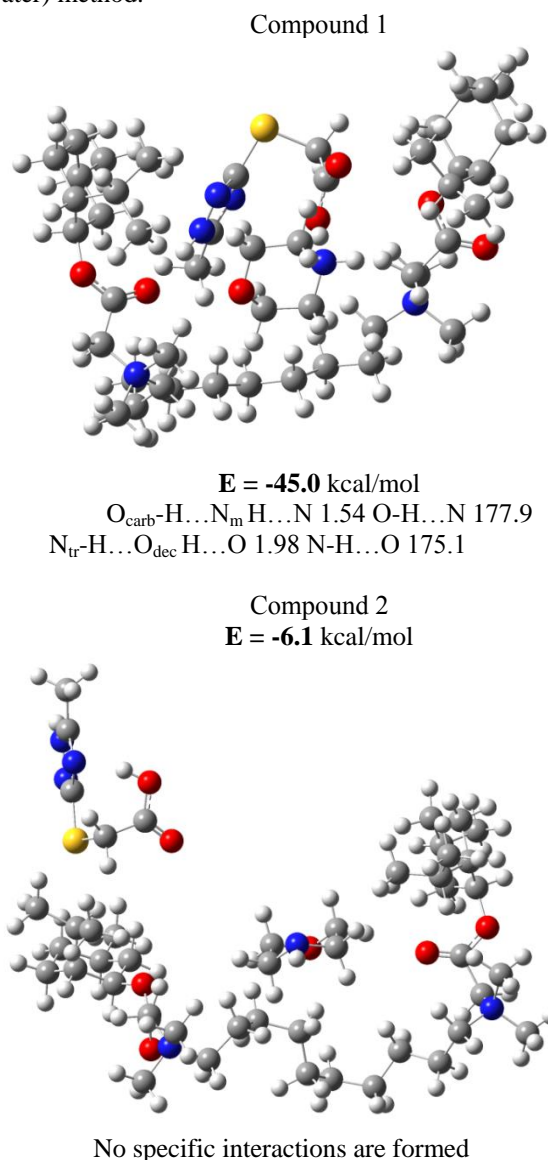


Fig. 2. Structure of the most stable complex and the least stable complex of thiotriazoline with decamethoxin, their interaction energy in the complex (E_{int} , kcal/mol), and characteristics of the hydrogen bonds (H...A, Å, and D-H...A, deg.) according to B97-D3/ def2-tzvp+COSMO (water) method

The structure of the most stable complex and the least stable complex of thiotriazoline with deca-

methoxin, the energy of their interaction in the complex (Eint, kcal/mol) and characteristics of hydrogen bonds (H...A, Å and D-H...A, deg.) calculated by the B97- D3 / def2-tzvp + COSMO (water) method showed that these complexes are instable. These results confirm the possibility of combining the studied components in the dosage form.

The DTA curve reflects the differentiation of thermal effects, contains information on endothermic and exothermic peaks, and could be used for a qualitative assessment of the derivatogram.

As can be seen from the data presented (Fig. 3), thiotriazoline is a thermally stable compound in the temperature range from 30.08 °C to 116.73 °C. After the eleventh minute of the experiment, the endothermic effect (-367.22 µV) was observed at a temperature of 148,

49 °C and a slow weight loss of almost 183 °C (5.6 %). As the temperature rises to 200 °C, this process intensifies somewhat, and by the end of the experiment, the change in the sample mass was 17.8 %.

The thermogravimetric behavior of decamethoxin behaves similarly. The derivatogram (Fig. 4) shows the thermal stability of the compound up to almost 167 °C with a slight weight loss (3.63 %). Nevertheless, at a temperature of 185.62 °C, an endothermic effect is observed with a more significant (by 17 %) decrease in the mass of the test substance. Moreover, at the end of the experiment, the test sample weighed 11.48 mg, which is 66.3% of the original weight.

On the derivatography of the combined dosage form, there is a coincidence of its thermal effect with its active pharmaceutical ingredients (Fig. 5).

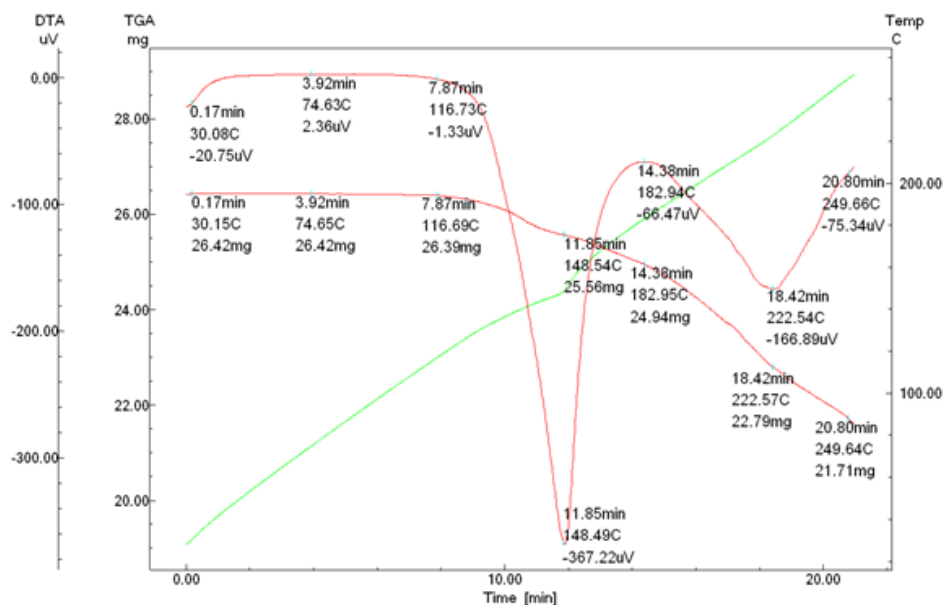


Fig. 3. Thiotriazoline derivatography

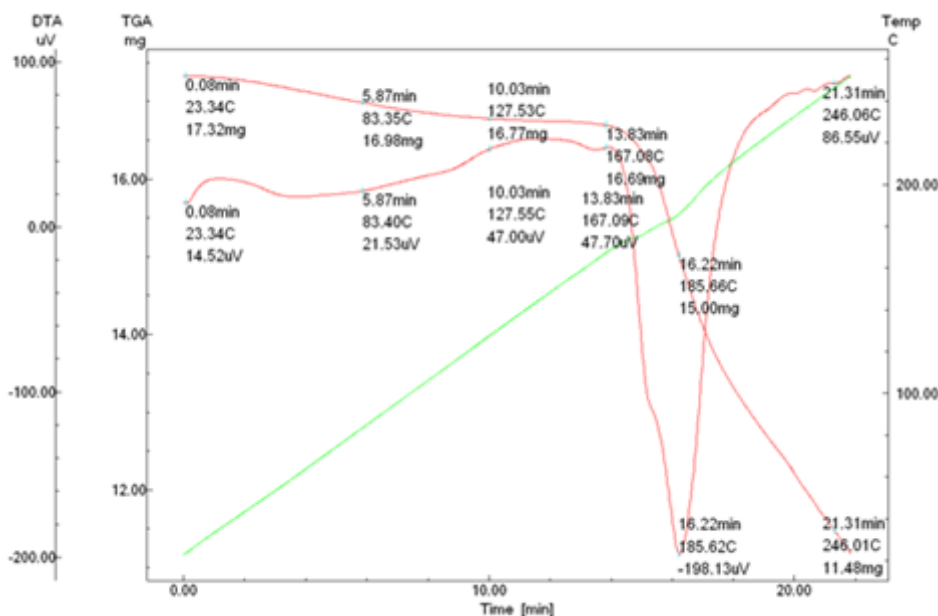


Fig. 4. Decamethoxin derivatography

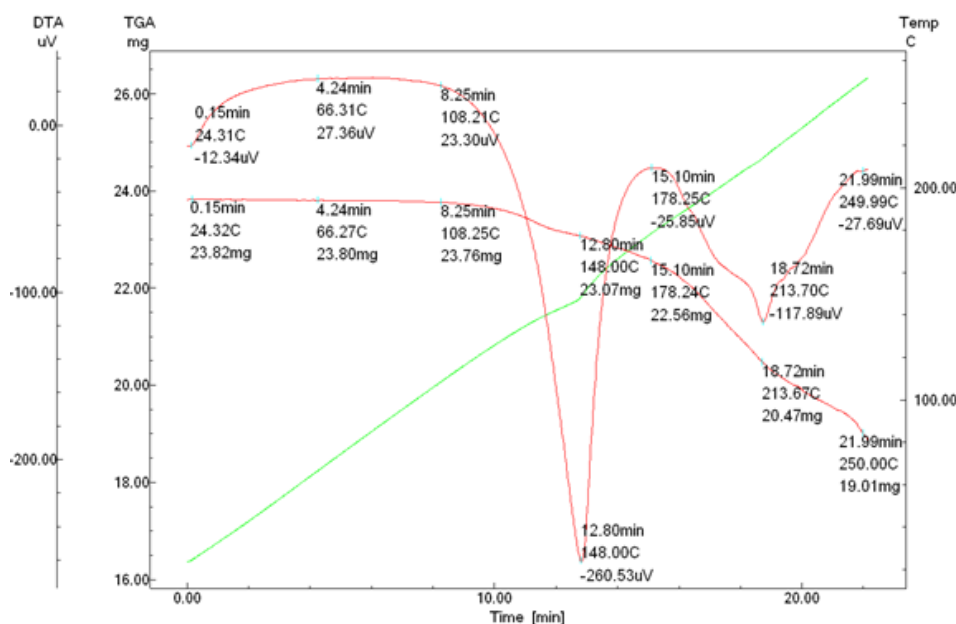


Fig. 5. Derivatography of the combined dosage form

It indicates the absence of chemical interaction between.

5. Discussion

The research data used the method of quantum chemistry and derivatogram.

These methods allow us to talk about the possible interactions of the components. Further research is needed for their further joint interaction.

From the obtained structures of three-component complexes, the 10 best in energy were selected, for which the final calculation of the geometry and energy of interaction of thiotriazoline with decamethoxin was carried out according to the B97-D3 / def2-tzvp + COSMO method. Density functional calculations were performed using the ORCA 3.0.3 software.

The nature of the derivatogram of the mixture of thiotriazoline with decamethoxin indicates a slight weight loss (3.14 %) and thermal stability of the test sample up to a temperature of 148 °C. A pronounced endothermic thermal effect is observed at the thirteenth minute of the experiment, after which the weight loss of the composition is 20.19 % [12, 13].

On the derivatogram of the model mixture of decamethoxin and thiotriazoline, its thermal effect coincides with its active pharmaceutical ingredients. This indicates a lack of chemical interaction between them.

In addition, derivatographic studies show that these components decamethoxin and thiotriazoline can be used to develop a new complex drug for the treatment of diseases of the oral mucosa.

As a result of the quantum-chemical calculations, derivatographic studies, it was shown that the possibility

of combining decamethoxin and thiotriazoline in one dosage form. This can be used to further develop tablets. [13–15].

Study limitations. The study was not carried out in the case of detection of changes in statistical processing when determining the hydrogen bond.

Prospects for further research. The obtained theoretical data on the possibility of the formation of complexes of two active ingredients, namely decamethoxin and thiotriazolin, could be used to develop a new complex drug for the treatment of oral mucosa disease.

6. Conclusions

A quantum-chemical study of a two-component system consisting of thiotriazoline and decamethoxin showed that the most energetically favourable three-component complexes have a rather low interaction energy of thiotriazoline and decamethoxin.

We have found that taking into account the analysis of the thermal effect of biologically active substances of the developed tablets for oral use, the process temperature up to 115 °C does not significantly affect the structure of active pharmaceutical ingredients.

These results allow the use of a combination of decamethoxin and thiotriazoline in one dosage form.

Conflict of interests.

The authors declare that they have no conflicts of interest.

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