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DEVELOPMENT OF NEW ANTIMICROBIAL COMPOSITIONS OF THIOSULFONATE STRUCTURE

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Abstract. The antimicrobial composition based on the substance of thiosulfonate structure (ETS) and surfactants of microbial origin (biosurfactants) in the form of stable suspensions and ointments were developed and investigated for their effectiveness. The application of biosurfactants in the preparation enhances the antifungal and antibacterial activity of ETS and reduces its active concentration. The economic calculations have shown that the developed antimicrobial composition has a low cost and is competitive compared with antifungal agents present in the pharmaceutical market.

Keywords: S-esters of thiosulfoacids, biosurfactants, antimicrobial activity of medicinal agents, antifungal agents, price formation.

1. Introduction

Nowadays, according to the World Health Organization data more than 20 % of the world population are affected by chronic fungal diseases, that is why the control against such infections is an urgent problem. Growth of mycotic diseases and complications caused by them (secondary infections, allergic reactions, eczemas) causes the trend of the emergence of pathogens resistant to existing medicinal agents. Important pharmaceutical, epidemiological and therapeutic challenge is the expansion of the range of soft medicinal agents for treatment of chronic and recurrent dermatoses, particularly tinea pedis, onychomycosis, for which the treatment process is time consuming and inefficient. Therefore, the search for new effective antifungal substances, the optimization of their production and the development of formulations of medicinal agents are extremely important.

Thiosulfoacids and their esters are structural analogs of natural antibacterial substances such as phytoncids of garlic *Allium sativum*, onion *Allium cepa*, sea urchin *Echinocardium cordatum* [1-3]. It is known that synthetic esters of thiosulfoacids possess the biological activity, which often exceeds the efficiency of natural analogues [4]. Some synthetic thiosulfonates are proposed for the use as medicinal agents [5-11].

The prospects of surface-active substances (surfactants) use in the development of effective forms of antibacterial and antifungal agents is based on their ability to reduce the surface and interfacial tension, solubilization of hydrophobic substances, regulation of surfaces wetting, sorption-desorption processes, *etc*. [15, 16]. The unique properties of biogenic surfactants (biosurfactants), produced by microorganisms, namely: their high efficiency, activity in a wide range of temperatures and pH, the possibility of production using inexpensive substrates (including industrial waste), along with the low toxicity, biodegradability determine their priority in modern technologies [12-14].

Considering the amphiphilic nature of biosurfactants, they have the ability to form stable suspensions with hydrophobic substances indicating the feasibility and potential of their use in creating effective complex antimicrobial preparations. Biosurfactants have the ability to influence the microbial cell membrane components, to improve the pharmacokinetic parameters of biologically active compounds in joint application, contributing to their targeted transport to the appropriate receptors. This allows the acceleration of the expected pharmacological effect and reduction of the active

ingredient concentration, and enables the creation of active pharmaceutical compositions containing poorly soluble substances with a micellar dispersion.

The aim of our work was the development of antimicrobial compositions based on the synthetic substance of thiosulfanate type using the surfactants of microbial origin (biosurfactants).

2. Experimental

The structure of the target product and intermediates was confirmed by the spectroscopic methods and the elemental analysis data. IR spectra were recorded on the spectrophotometer "SPECORD M 80" in tablets with KBr. H^1 NMR spectra were recorded on a spectrometer "Varian VXR-300", operating frequency – 300 MHz, standard – TMS. The course of reactions and the individuality of the compounds were controlled by TLC method.

4-Acetylaminobenzensulfochloride (2a). 125 ml (1.88 mol) of chlorosulfonic acid were supplemented with 50 g (0.3703 mol) of acetaldehyde (1) at 273–281 K and vigorous stirring. The reaction mass was kept at 273 K for 2 h and at 338 K – for 4 h. The sulfomass was decomposed gently pouring onto ice. The precipitate was filtered, washed with cold water to neutral reaction by Congo and dried at room temperature. Yield 65 g (75 %). Melting point 442 K. Elemental analysis $C_8H_8NSO_3Cl$. Determined, %: N 5.85; S 13.13; Cl 15.01. Calculated, %: N 6.00; S 13.70; Cl 15.20.

Sodium 4-acetylaminobenzenthiosulfonate (3a). Solution of 80 g (0.3340 mol) of 9-hydrogen sodium sulfide in 80 ml of water was supplemented with 65 g (0.2784 mol) of 4-acetylaminobenzensulfochloride at 273–281 K. After 2 h exposure at 273–277 K the reaction mixture was heated to 338–340 K and kept for 1 h; 2 g of activated carbon were added to dissolve the formed sulfur (pH 9–10). The hot reaction mixture was filtered, cooled, the precipitate was dried and recrystallized from 2-propanol. Yield 65 g (75 %). Melting point 442 K. Elemental analysis $C_8H_8NS_2O_3Na$. Determined, %: C 37.72; N 5.67; S 25.41; H 3.38. Calculated %: C 37.94; N 5.53; S 25.30; H 3.16. H^1 NMR 3.461(s,3H, CH_3), 7.198(d, 2H, Ar), 7.427(d, 2H, Ar), 8.510(s,1H,NH).

S-Ethyl-4-acetylaminobenzenthiosulfonate (4a). The solution of 15 g (0.0593 mol) of sodium 4-acetylaminobenzenthiosulfonate in 100 ml of water was supplemented with 4.44 ml (0.0593 mol) of ethyl bromide at pH 7 and 293 K and kept for 2 days. The precipitate was filtered, washed with water, dried, recrystallized from benzene. Yield 7 g (46 %). Melting point 358 K. Elemental analysis $C_{10}H_{13}NS_2O_3$. Determined, %: N 5.37; S 24.56. Calculated, %: N 5.41; S 24.74. IR spectrum (ν, cm^{-1}): 1144, 1328 (SO_2); 1570, 1582, 1604 (Ar); 1636 (NH); 1688 (CO).

4-Aminobenzenthiosulfoacid ethyl S-ester (6). 4 ml (0.0195 mol) of 40 % sulfuric acid were supplemented with 1 g (0.0039 mol) of 4-acetylaminobenzenthiosulfoacid ethyl S-ester. The reaction mass was heated to 351 K and kept for 3 h. The reaction mixture was supplemented with 1 g of activated carbon, the hot reaction mixture was filtered and the filtrate was cooled. Excess acid was neutralized with sodium bicarbonate to pH 6–7. The precipitated 4-aminobenzenthiosulfoacid ethyl S-ester was filtered and washed with water. Yield 0.69 g (82 %). Melting point 350–352 K. Elemental analysis $C_8H_{11}O_2S_2N$. Determined, %: N 6.37; S 29.62. Calculated, %: N 6.45; S 29.49; infrared spectrum (ν, cm^{-1}): 1132, 1328 (SO_2); 1572, 1588, 1602 (Ar); 1636 (NH); 3376, 3472 (NH2). ^{1}H NMR δ 1.225(t,3H,CH_3), 2.848 (m,2H,CH_2), 6.619(d,2H,Ar), 7.459 (d,2H,Ar), 6.198(s_{broad},2H,NH_2).

Biosurfactants were obtained by culturing the strain *Pseudomonas* sp. PS-17 in Erlenmayer flasks on an orbital shaker (220 rpm) at 300 K in a liquid nutrient medium with glycerol (2 wt %) as the carbon source [12]. Surface-active biocomplex PS was isolated from the cell-free culture liquid in the acidic medium and pH 3 (10 % HCl), kept overnight at 277 K and separated by centrifugation.

The criteria for the selection of ETS-biosurfactant ratios were the formation of stable emulsions and biological activity of the obtained compositions, namely, antifungal and antibacterial activity. The biological activity of ointment preparations was assessed by the diameter of growth delay zones of test organisms (on agar nutrient medium using the method of discs and cylinders). The ETS ointment composition without biosurfactants was used as a control. The study of the biological activity of new ointment compositions with biosurfactants was conducted with the following concentrations of active substance (ETC) – 0.1 %, 0.5 % and 1 %. Biological activity of ointment compositions was determined on different taxonomic groups of microorganisms: *Bacillus mesentericus*, *Aspergillus niger*, *Penicillium chrysogenum*, *Escherichia coli*, *Candida lipolytica*. To meet the standard testing conditions the suspensions of microorganisms were used with cell titer 10^6 CFU/ml.

The biological activity of the ointment composition containing the active substance ETC (1 %) and biosurfactant was evaluated in comparison with the known commercial antifungal agents, namely Clotrimazole ointment, Econazole gel, Nystatin ointment, Lamisil cream, Gentamicin ointment. The strains of microorganisms *Staphylococcus aureus* and *Escherichia coli* with cell titer 10^9–10^{10} CFU/ml (by the turbidity standard) were used as

test cultures. The microorganisms were grown on Mueller-Hinton agar (MHA). 1 ml of a test culture suspension was evenly applied over the surface of MHA in Petri dishes, the holes in an agar layer were made with a sterile tube (8 mm). The studied preparations were heated in a thermostat to 313 K and transferred to the holes in the agar. The dishes were kept in the thermostat (310 K, 24 h). The antimicrobial effect of the preparations was assessed by the conventional criteria: absence of growth delay zones of a test-culture or the zone with a diameter less than 10 mm indicates the insensitivity of the test-culture to the tested agent, 11–15 mm growth delay zone indicates the low sensitivity, more than 15 mm – high sensitivity.

The economic calculation of the obtained ointment composition value and market research were carried out for comparative analysis of price positions of the medicinal agents used as antifungal agents: Clotrimazole ointment, Econazole gel, Nystatin ointment, Lamisil cream, Gentamicin ointment. The internet search of the registered prices of medicinal agents was conducted according to "Register of wholesale and retail prices for medicinal agents and products, purchased at the expense of the state and local budgets". However, on 23.10.2012, the registration price could be set only for Nystatin ointment 1 % – 15 g. The results of internet search for other medications prices were compared with actual prices in Lviv pharmacies. The weight average prices for the products were calculated for 100 g of an agent. The weight average prices for medicinal preparations that are registered and used in the Ukrainian market were used in the calculations. Prices of preparation in UAH were equivalent translated into EUR currency according to the official exchange rate on 23.10.2012.

3. Results and Discussion

When developing the antimicrobial compositions and the methods of their production the following criteria were considered: high antimicrobial activity, compatibility with additional ingredients and low cost.

Based on the previous studies of the biological activity of 4-aminobenzenthiosulfoacid S-alkyl esters the synthesized insoluble ester (ETC) – a synthetic analogue of the natural antibiotic allicin [17] was used as an antimicrobial agent and the biosurfactant produced by the bacterial strain *Pseudomonas* sp. PS-17 was used as a surfactant component in the composition [12].

The synthesis of antimicrobial substance ETC (6) can be performed in two ways (A, B) corresponding to the following transformations (Fig. 1).

Aniline derivatives (1a, 1b) were used as starting materials for the synthesis of 4-aminobenzenthiosulfoacid S-alkyl esters. Through their sulfochlorination with the chlorosulfonic acid the appropriate sulfochlorides were obtained (2a, 2b); their redox reaction with sodium sulfide solution resulted in the formation of sodium 4-carbmethoxyaminobenzen- and 4-acetylaminobensenthiosulfonates (3a, 3b). These salts were converted into sodium 4-aminobenzenthiosulfonates via deacylation with aqueous sodium hydroxide (4a). S-alkyl esters of 4-aminobenzen- (6) and 4-acetylaminobenzenthiosulfoacids (4a) were obtained in the water-acetone solution *via* alkylation with haloalkyls. 4-Aminobenzenthiosulfoacid S-alkyl ester sulfate (5) was obtained *via* acid hydrolysis of the ester acetylamino group (4a) with the sulfuric acid. The sulfate (5) under the influence of sodium bicarbonate solution was converted into the corresponding ester (6).

The ETS synthesis by the path A includes 5 chemical stages unlike the path B in which the product (6) is obtained in four stages. However the ETC (6) obtained by the path A, has a higher degree of purity and does not require additional purification step [17].

The synthesis of aminobenzenthiosulfoacid S-alkyl ester (6) by the path B requires the additional purification of sodium salt (4b) and the final product, since the target ester (6) may decompose even in diluted alkaline solutions to the corresponding sulfinic acid and disulfide due to alkaline hydrolysis. On the other hand, sulfochlorides (2a, b) are the intermediates of sulfonamide synthesis; that is why the analysis of their price positions in the market of intermediates of chemical and pharmaceutical industries was conducted. It was established that the average price of 1 kg of sulfochloride (2a) is 116.7 USD, and the average price of 1 kg of sulfochloride (2b) – 470 000 USD. Taking into account that sulfochloride (2a) is available in the market of chemical raw materials and product (2b) is virtually absent and expensive, the best method of the substance synthesis of thiosulfonate type ETS is A path, which has a number of significant advantages. Our studies have revealed that the obtained ETS is a low toxic compound (LD_{50} = 2000 mg/kg) and exhibits a wide range of antimicrobial activity, including the high antifungal activity against pathogenic fungi of different genera and moderate antibacterial activity against gram-positive and gram-negative bacteria. An important property of ETS is its keratolytic action, which provides advantages comparing to other medicinal agents for the treatment of fungal skin diseases, such as tinea pedis, onychomycosis and other diseases of epithelial tissues.

It was shown that the presence of biogenic surfactants enhances the bactericidal, sporocidal and fungicidal action of S-alkyl-4-aminobenzenthiosulfonates (ETS and MTS) [18, 19]. Since the antimicrobial substance ETS is poorly soluble in aqueous systems, the surface-active products of microbial synthesis of the strain

Pseudomonas SP. PS-17 in various forms were used when creating compositions in suspension and ointment forms to enhance water solubility of ETS and its permeability through cell membranes. The ability of biosurfactants to create stable fine emulsions in a wide pH range (5.5–10) allows their application for solubilization of thiosulfanilates, including ETS, which is stable in the pH range 5–7.

Biosurfactant was used in the form of surface-active lipids or biocomplex PS – these are rhamnolipids, composed of rhamnose residues and 1-b-oxydecanoic acid and biopolymer (polysaccharide of alginate structure which adsorbs lipid molecules) (Figs. 2 and 3).

The physico-chemical properties of the strain culture liquid were determined: emulsification index (E_{24}) in the system biosurfactant solution-hydrophobic compound makes 75–85 %, the surface tension σ_s is 28.5–31.1 mN/m. The values of the minimum surface tension and the critical micelle concentration (CMC) of biosurfactant aqueous solutions testify to their significant activity (Table 1).

High efficiency of biogenic surfactants was ascertained in the comparison with the synthetic surfactant – sodium dodecyl sulfate (lower values of surface tension and high emulsifying activity).

The influence of the developed ointment compositions (ETS and biosurfactant) on the growth of the test-cultures of microorganisms *Bacillus mesentericus*, *Aspergillus niger*, *Penicillium chrysogenum*, *Escherichia coli*, *Candida lipolytica* was studied (Table 2).

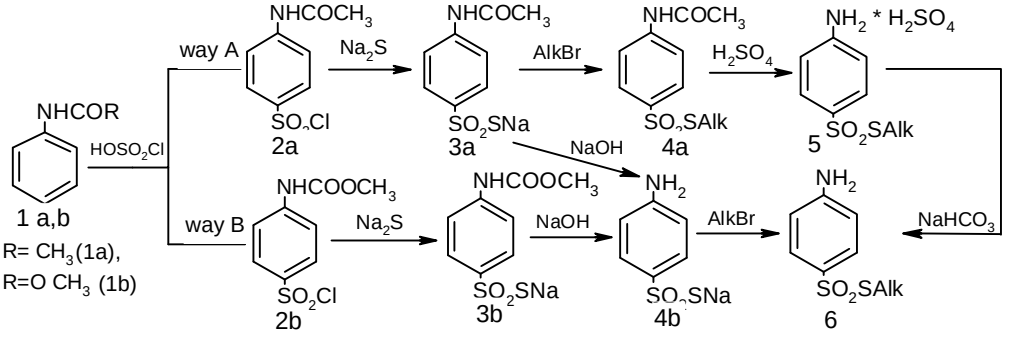

Fig. 1. Synthesis of 4- aminobenzenthiosulfoacid S-alkyl ester (6)

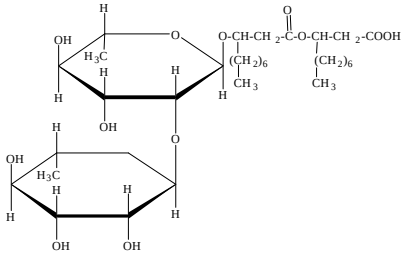

Fig. 2. Structural formula of *Pseudomonas* sp. PS-17 dirhamnolipid

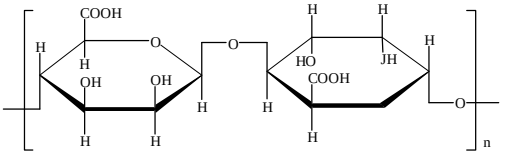

Fig. 3. Structural formula of *Pseudomonas* sp. PS-17 biopolymer

Table 1

The physico-chemical properties of biogenic surfactants

Surfactants	Surface tension, mN/m	Interfacial tension (*n*-heptane), mN/m	Emulsification index (E_{24}), %
Rhamnolipids	28.8	0.2	70
Rhamnolipid biocomplex PS	29.9	0.9	75
Sodium dodecyl sulfate	35.0	0.2	50

Note: Surface and interfacial tension was determined for biosurfactant solutions in concentration 1 g/l; emulsification index (in system biosurfactant-kerosene) – in concentration 5 g/l.

Table 2

Influence of the type of ointment compositions on the growth of microorganisms (growth delay zones, mm)

Microorganisms	ETC concentration, %					
	0.1		0.5		1.0	
	ETC	ETC + biosurfactant	ETC	ETC + biosurfactant	ETC	ETC + biosurfactant
Bacillus mesentericus	17	20	20	23	22	24
Escherichia coli	20	24	25	28	28	31
Aspergillus niger	40	50	48	55	40	65
Candida lipolytica	18	30	23	35	33	38

Note: Biosurfactants were used in concentration 0.01 %; the mixture of polyethylene glycols (PEG 400 and PEG 500) was used as a base for the ointment compositions.

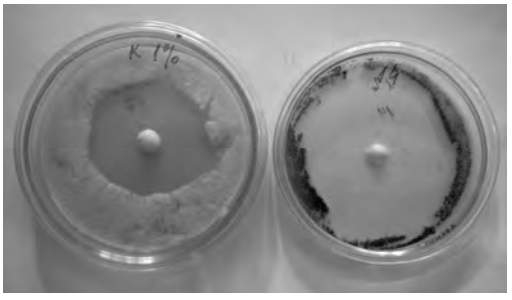

Fig. 4. The effect of the ointment compositions ETC and ETC + biosurfactant on the growth of A. niger (ETS concentration – 1 %)

Table 3

Antimicrobial action of the medicinal agents on *Candida albicans, Staphylococcus aureus* and *Escherichia coli*

Agent name	Test-culture growth delay zone (d, mm)		
	Candida albicans	*Staphylococcus aureus*	*Escherichia coli*
Oinment composition ETS	32.2±0.1	30.0±1.0	23.2±0.8
Clotrimazole ointment	26.5±0.2	18.6±0.4	20.3±0.7
Econazole gel	--	17.5±0.5	16.4±0.6
Nystatin ointment	24.2±0.5	0	0
Lamisil cream	--	0	0
Gentamicin ointment	13.5±0.2	26.3±0.7	25.5±0.5

Table 4

Weighted average prices for antifungal agents

Agent name	Dosage form	Price for 1 pc., UAH	Price for 100 g, UAH	Weighted average price per 100 g	
				UAH	EUR
Oinment composition ETS	Oinment composition ETS 1% - 100 g	-	44.25	44.25	4.21
Clotrimazole ointment	Clotrimazole ointment 1% - 25 g	7.91	31.64	41.08	3.91
	Clotrimazole ointment 1% - 15 g	7.71	51.40		
	Clotrimazole ointment 1% - 20 g	9.55	47.75		
	Clotrimazole ointment 1% - 25 g	8.38	33.52		
Econazole gel	Econazole gel 1% - 15 g	10.40	69.33	71.50	6.81
	Econazole gel 1% - 15 g	11.05	73.67		
Nystatin ointment	Nystatin ointment 1% - 15 g	7.00	46.67	46.67	4.44
Lamisil cream	Lamisil cream 1% - 15 g	58.87	392.47	383.15	36.49
	Lamisil cream 1% - 15 g	47.60	317.33		
	Lamisil cream 1% - 15 g	68.77	458.47		
	Lamisil cream 1% - 30 g	109.30	364.33		
Gentamicin ointment	Gentamicin ointment 1% - 15 g	20.00	133.33	97.47	9.28
	Gentamicin ointment 1% - 25 g	15.40	61.60		

It was determined as a result of microbiological studies that the introduction of biosurfactants into ointments promoted the increase of the antimicrobial action of ETS (determined by the diameter of growth inhibition zones of microorganisms). The greatest activity of the developed agent was observed for *Aspergillus niger* and *Candida lipolytica* (Fig. 4).

The results of the conducted studies of new antimicrobial ointment composition ETS + biosurfactant (ETS – 1 %) indicate the significantly higher activity of the developed composition in comparison with known antifungal agents – Clotrimazole ointment, Econazole gel, Nystatin ointment, Lamisil cream, Gentamicin ointment (Table 3).

The results of economic calculation of the proposed ointment composition value based on ETS, biosurfactants and marketing research using internet search methods and fieldwork on prices for drugs used as antifungal agents are presented in Table 4.

The economic calculation for the created compositions based on ETS and biosurfactant was performed for 100 g of ointment. Cost of the ointment composition obtained in the laboratory was 14.75 UAH. Since its production has not been tested on an industrial scale, the calculation was performed taking into account the average general expenses and costs, which typically make 100 % in total. Accordingly, the calculated value of the developed ointment composition is 29.50 UAH.

Comparative analysis of the economic calculations and market research clearly shows that even with 100 % markup on the proposed agent, its price does not exceed, and in some price positions is much lower than the prices for existing drug analogues by the pharmacological action.

4. Conclusions

It was established that the thiosulfanilate ETS, developed at Lviv Polytechnic National University, is suitable for the creation of effective medicinal agents with antimicrobial action in soft dosage forms.

The expediency of the use of the biogenic surfactants, obtained at the Department of Physico-Chemistry CM L.M. Litvinenko InPOCC NAS of Ukraine, in composition of antimicrobial agents, was ascertained. If compared with their synthetic analogues the biosurfactant advantages are their high efficiency, low toxicity and environmental safety.

The antimicrobial compositions based on ETS and biosurfactants in the form of stable fine suspensions and ointments were developed. The introduction of biosurfactants into the compositions allowed the reduction of the active antimicrobial agent concentration in the resulting product. The ointment composition exhibits high antifungal and antibacterial activity in comparison with known medicinal agents such as Clotrimazole ointment, Econazole gel, Nystatin ointment, Lamisil cream, Gentamicin ointment.

The economic and market research have shown that the developed antimicrobial composition has prospects for the use in medicine and other areas of economy, due to its high efficiency, low cost and will be competitive in the global and domestic markets of antimicrobial agents.

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РОЗРОБЛЕННЯ НОВОЇ АНТИМІКРОБНОЇ КОМПОЗИЦІЇ ТІОСУЛЬФАНІЛАТНОЇ СТРУКТУРИ

Анотація. *Розроблено антимікробну композицію на основі субстанції тіосульфонатної структури (ЕТС) і поверхнево-активних речовин мікробного походження (біоПАР) у формі стабільних суспензій і мазі та досліджено її ефективність. Застосування біоПАР у препараті сприяє підвищенню протигрибкової та антибактеріальної активності ЕТС та дає можливість зменшити його діючу концентрацію. Економічні розрахунки засвідчили, що розроблена антимікробна композиція має низьку собівартість та є конкурентоспроможною у порівнянні з протигрибковими препаратами, представленими на фармацевтичному ринку.*

Ключові слова: *S-естери тіосульфокислот, біоПАР, антимікробна активність лікарських засобів, протигрибкові препарати, ціноутворення.*