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DEVELOPMENT OF THE COMPOSITION OF ORALLY DISINTEGRATING ANTIVIRAL TABLETS WITH THIOSULFONATE COMPONENT, ALLYL ESTER OF 4-METHACRYLOYLAMINOBENZENETHIOSULFONIC ACID

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The development of the optimal composition of solid dosage forms for using in the oral cavity with new antimicrobial active ingredients has become a particular issue nowadays. Orally disintegrating tablets occupy a special place in the pharmaceutical market, considering the demand from many categories of patients. Compounds with thiosulfonate pharmacophores are promising active pharmaceutical ingredients for the development of new drugs due to their wide range of biological activity and compound stability.

The aim of the study is to develop an optimal composition of orally disintegrating tablets based on allyl ester of 4-methacryloylaminobenzenethiosulfonic acid that has antiviral, antibacterial and antifungal effects, as well as to select excipients to achieve the required pharmaco-technological parameters.

Materials and methods. The target ester was synthesised according to the authors' method. The structure and individuality of the synthesised compound were confirmed by elemental analysis, IR and NMR spectroscopy. While studying the development of the composition of tablets, tentatively called "Virulin", the effect of 16 excipients was investigated. Mathematical planning of the experiment was used to obtain the optimal combination. The direct compression method was used to manufacture the tablets.

Results. A new method for the synthesis of the allyl ester of 4- methacryloylaminobenzenethiosulfonic acid has been developed, which involves 3 stages via preparation of 2 important intermediates. The structure and individuality of the compound were confirmed by elemental analysis, IR and NMR spectroscopy. The conducted studies enabled us to determine the impact of excipients on the main pharmaco-technological parameters of powder masses for tableting, as well as tablets based on them, obtained by direct compression. The optimal excipients were selected for the introduction to the dosage form.

Key words: formulation optimization, synthesis, antiviral activity, thiosulfonates, tablets, mathematical planning of the experiment, Virulin.

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РОЗРОБЛЕННЯ СКЛАДУ АНТИВІРУСНИХ ТАБЛЕТОК, ЩО ДИСПЕРГУЮТЬСЯ У РОТОВІЙ ПОРОЖНИНІ, ІЗ ТІОСУЛЬФОНАТНИМ СКЛАДНИКОМ, АЛІЛОВИМ ЕСТЕРОМ 4-МЕТАКРИЛОЇЛАМІНОБЕНЗЕНТІОСУЛЬФОКИСЛОТИ

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Статтю присвячено розробленню твердої лікарської форми у вигляді таблеток, що диспергуються у ротовій порожнині, під умовною назвою «Вірулін», на основі алілового естеру 4-метакрилоїламінобензентіосульфокислоти. Методика синтезу потенційної діючої речовини з антимікробною дією розроблена авторами і включає три хімічні стадії. Будова та індивідуальність сполуки підтверджені даними елементного аналізу, ІЧ та ЯМР-спектроскопії. Авторами було використано математичне планування експерименту. Результати досліджень із розроблення складу таблеток «Вірулін» дали змогу встановити вплив допоміжних речовин на основні фармако-технологічні показники порошкових мас для таблетування і сформованих таблеток. Вибрано оптимальні допоміжні речовини для таблеток з антимікробною дією.

Ключові слова: розроблення складу, синтез, антивірусна дія, тіосульфонати, таблетки, математичне планування експерименту, «Вірулін».

Introduction. One of the most promising approaches to developing new drugs is the synthesis of structural analogues of biologically active compounds (BAC) of natural origin and their further use as potential active pharmaceutical ingredients (APIs) in dosage forms. Newly synthesised compounds may have equivalent or higher effiectiveness and be less toxic than well-known biologically active molecules.

A large number of disulfur-containing compounds of the general formula $RS(O)_n SR$, where R is alkyl/alken thiosulfinates (n = 1) and thiosulfonates (n = 2) are phytoncides obtained from plants of the genus *Allium* and *Brassica*. They demonstrate antioxidant, anti-inflammatory, antimicrobial activity, participate in

the regulation of lipid metabolism, glucose metabolism and protect the cardiovascular and nervous systems [1, 2]. Synthetic thiosulfonates also have a wide range of biological activities and are stable compounds compared to thiosulfinates. These sulfur-containing compounds are potential active ingredients for the development of drugs of various pharmacotherapeutic groups, demonstrating fungicidal [3, 4], anthelmintic [5, 6], antithrombotic [7], and anticancer [8, 9] effects; there are some substances among them that have been proposed for the treatment of Alzheimer's disease [10]. It has been established that S-alkyl thiosulfonate esters have bactericidal properties against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Staphylococcus aureus* [11].

A study on the the antibacterial and antiviral effects of various thiosulfonate derivatives, including those derived from 4-acetylaminobenzenethiosulfonic acid and 4-methacryloylaminobenzenethiosulfonic acid, revealed S-allyl-4-methacryloylaminobenzene sulfonate (AMABT) as the most potent compound against viruses. It demonstrated significant inhibition of *in vitro* replication of herpes simplex virus strains (HSV-1 and HSV-2) compared to other studied compounds [12]. This ester is also effective against *Escherichia coli* and *Staphylococcus aureus* [12].

In our opinion, orally disintegrating tablet (ODT) is a promising dosage form as a drug delivery system that is a good alternative to traditional tablets, particularly in paediatrics, geriatrics and psychiatry, in cases of dysphagia, helping to achieve better patient compliance by combining the advantages of liquid drugs and the positive characteristics of tablets [13].

During the process of a drug development, it is necessary to go through all the stages from the primary idea to the final product, including the development of the composition and technology. It is important to substantiate the composition and number of excipients and choose the optimal technology. To conduct the research, it is recommended to use an experimental design that allows you to determine the impact of various factors on the quality of the final product. For this purpose, various mathematical and statistical methods are used, united by the concept of mathematical planning of the experiment (MPE) [14].

The aim of the work is to develop an optimal composition of a solid dosage form based on AMABT with antiviral, antibacterial and antifungal effects and to select the excipients to achieve the required pharmacological and technological parameters.

Materials and methods. The following reagents were used for the reaction: sodium sulfide nonahydrate Na_2S*9H_20 95% ('Sfera Sim'), 4-acetamidobenzenesulfonyl chloride 98% ('Alfa Aesar'), sodium hydroxide NaOH 99% ('Sfera Sim'), allyl bromide 98% ('Ukrorgsintez'), methacryloyl chloride 97% ('Sigma-Aldrich'), tetrahydrofuran 99% ('Sigma-Aldrich'), triethylamine 99% ('Sigma-Aldrich').

The structure of the active compound has been confirmed by ^{13}C-, ^{1}H-, IR spectroscopy and elemental analysis. The spectral studies of the compounds were carried out using the following instruments: spectrometer for IR spectra ('PerkinElmer'); spectrometer Bruker Avance DRX-500 for ^{1}H and ^{13}C NMR spectra (500 MHz, chemical shifts of ^{1}H are expressed in δ scale relative to tetramethylsilane, DMSO-D6 as a solvent). The elemental analysis was carried out using Euro Vector EA-3000 microanalyzer (Italy).

For manufacturing tablets by direct compression (DC), 16 excipients were selected and classified into 4 groups: sugar-based fillers (Factor A), disintegrants (Factor B), microcrystalline cellulose (MCC)-based fillers (Factor C), and lubricants (Factor D), each consisting of four compounds.

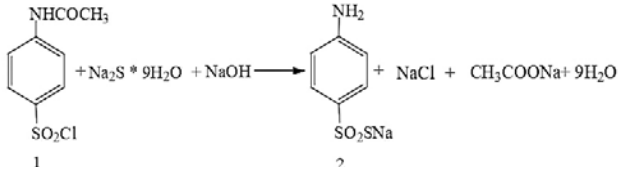
"Virulin" powder masses and tablets based on them, obtained by DC method, were investigated by 6 parameters: bulk and tapped density of powder masses, angle of repose, resistance to crushing, abrasion and disintegration time in accordance to generally accepted methods of the State Pharmacopoeia of Ukraine (SPhU). Tablets were pressed with a laboratory hydraulic press at a specific pressure of 180 MPa, tablet diameter – 12 mm, average weight – 0.5 g.

A 4x4 Greco-Latin square of the fourth order was used as an experimental plan. The results were subjected to analysis of variance.

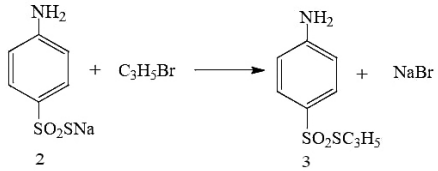
The determination of the bulk density and tapped density was carried out in accordance to the SPhU (2.9.34. Bulk density and tapped density. SPhU 2.0). The angle of repose was determined using the VP-12A device (2.9.36. Flowability of powders. Angle of repose. SPhU 2.0). The resistance to crushing of tablets was determined using ERWEKA TBH 220 TD device. The crush resistance of 10 tablets with a diameter of 12 mm was measured (2.9.8. Resistance of tablets to crushing. SPhU 2.0). A drum-type device with one blade was used to determine the abrasion of tablets (2.9.7. Abrasion of uncoated tablets. SPhU 2.0). The disintegration time of tablets was determined using an ERWEKA ZT 502 device (2.9.1. Disintegration of tablets and capsules. SPhU 2.0).

Results and discussion. Taking into account the pronounced antimicrobial (antiviral, antibacterial, antifungal) activity of S-allyl-4-methacrylamidobenzenesu lfonothioate and the expediency of the ODTs development, we have improved a method for the synthesis of AMABT and its intermediates and selected conditions for obtaining the highest product yield. The synthesis of the allyl ester of 4-methacryloylaminobenzenethiosulfonic acid involves three stages:

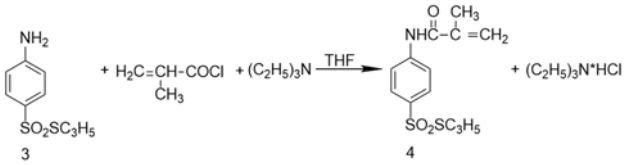
1. Preparation of the intermediate ***sodium 4-aminobenzenesulfonothioate*** **2** by redox interaction of ***4-acetamidobenzenesulfonyl chloride*** **1** with an aqueous solution of sodium sulfide nonahydrate and deacylation of the acyl group with sodium hydroxide:



2. Preparation of ***S-allyl 4-aminobenzenesulfonothioate*** **3** by alkylation of sodium 4- aminobenzenethiosulfonate 2 with allyl bromide:



3. Preparation of ***S-allyl 4-methacrylamidobenzenesulfonothioate* 4** by acylation of S-allyl 4-aminobenzenesulfonothioate 3 with methacroyl chloride:



Optimising the reaction involves increasing the yield and economic efficiency as well as reducing the process time.

The structure and identity of the synthesised compound were confirmed by elemental analysis (Table 1), IR and NMR spectroscopy.

Results of IR and NMR spectroscopy of the synthesised compound. Yield: 76 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm: 10.46 (s, 1H, NH), 7.85 (s, 4H, ArH), 5.67 (dd, *J* = 15.5, 7.7 Hz, 1H, allyl), 5.51 (s, 1H, CH_2 methacryl.), 5.43 (s, 1H, CH_2 methacryl.), 5.19 (d, *J* = 16.7 Hz, 1H, allyl), 5.05 (d, *J* = 9.4 Hz, 1H, allyl), 3.42 (br.s, 2H, CH_2 allyl), 2.10 (s, 3H, CH3 methacryl). ^{13}C NMR (126 MHz, DMSO-d_6) δ, ppm: 169.25 (C=O), 144.30 (C, Ar), 137.66 (C, Ar), 131.39 (CH allyl), 128.21 (2CH, Ar), 119.61 (CH_2 methacryl), 118.74 (2CH, Ar), 38.27 (CH_2 allyl), 24.18 (CH_3 methacryl). IR : 1138, 1316 (SO_2); 1582 (Ar); 1624 (C=C); 1630 (NH); 1670 (C=O); 3232 (NH).

Taking into account the physical properties of the synthesised substance S-allyl 4-methacrylamidobenzenesulfonothioate (particle size, fluidity), the direct compression is a rational method for manufacturing tablets with this compound.

In recent years, considerable attention has been paid to the development of tablets characterised rapid dissolution and/or disintegration in the oral cavity. Thus, medicines can be absorbed by sublingual, buccal or local delivery. Such tablets combine the benefits of liquid drugs (speed of delivery, onset of action, high bioavailability) with the positive characteristics of tablets (dosing accuracy, ease of use, avoidance of pain, masking of organoleptic characteristics, stability over a longer period of time compared to liquid drugs). They are also attractive for busy people or travelers who have limited access to water [13].

Orally disintegrating tablets are defined in the SPhU as uncoated tablets that are placed in the mouth where they disperse rapidly before entering the stomach. Samples of this oral dosage form should disintegrate within 3 minutes according to the SPhU 2.0. The Food and Drug Administration (FDA) sets the disintegration time at no more than 30 seconds [15].

Substances transported from the stomach and intestines enter the liver through the portal vein system, where they are inactivated by enzymes. This process is called the first-pass effect. Unlike drugs that pass through the gastrointestinal tract in full, the active substances of the ODTs, dispersed in the oral cavity, begin to be absorbed through the mucous membrane, thus mitigating the above-mentioned effect and, consequently, the toxic effect on the liver [16].

Successful drug development of the ODTs requires consideration of certain specific requirements: sufficient mechanical strength along with rapid disintegration in a small amount of liquid, pleasant tactile and taste sensations. Moreover, ODTs are mostly packaged in moisture-protective packaging to ensure stability of them and protect the tablets from humidity and other environmental factors [17, 18].

Direct compression is widely used because it is cost-effective and is constantly being improved as the market of excipients expands and new approaches to pharmaceutical formulation are developed.

It is known that excipients used in pharmacy have a significant impact on the effectiveness of drugs. It can vary depending on the chemical structure of excipients and biologically active substances, their size, shape, ability to intermolecular association and other characteristics, directly affecting pharmacological, pharmacodynamic and pharmacokinetic parameters [19, 20]. Hence, we have studied a number of combinations of excipients to determine the optimal composition of new ODTs.

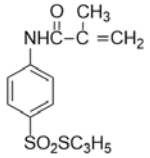
Table 2

Excipients studied in the development of tablets

Factors	Levels of factors
A – sugar-based fillers	a_1 – lactose monohydrate 200 a_2 – ludipress a_3 – mannitol 60 a_4 – sorbitol
B – disintegrants	b_1 – corn starch b_2 – croscarmellose sodium b_3 – sodium carboxymethyl starch b_4 – sodium starch glycolate
C – MCC-based fillers	c_1 – MCC 102 c_2 – MCC 200 c_3 – MCC 500 c_4 – Prosolv SMCC 90
D – lubricants	d_1 – calcium stearate d_2 – magnesium stearate d_3 – sodium stearyl fumarate d_4 – sodium lauryl sulfate

Table 1

Results of elemental analysis of the synthesised compound

Compound	Yield, %	Melting point, °C	Found, % / Calculated, %				Brutto-formula
			C	H	N	S	
	83.1	112–113	52.22	5.41	4.48	21.26	$C_{13}H_{15}NO_3S_2$
			52.53	5.05	4.71	21.55	

During the development of the composition of dosage form, the authors used MPE that significantly reduces the number of experiments, saving time and resources. A crucial stage of the MPE is the analysis of variance. It analyses the influence of qualitative factors that is known for its great variety in the sphere of tablet manufacturing. The list of all considered excipients we studied is given in Table 2. The study of 4 quantitative factors, each of which is taken at four levels, was carried out using a Greco-Latin square.

According to the results of microbiological studies, the recommended concentration of AMABT in the tablet is 2%. The weight of AMABT in the tested tablet samples was 0.01 g. The composition of excipients and their concentration (Table 3) were selected on the basis of literature data [12].

The experimental plan and the results of the study of powder masses and tablets based on them are given in Table 4. Each series of experiments was carried out in 2 repeats. We estimated three properties of the powder masses: bulk and tapped density, angle of repose. Additionally, tablets of "Virulin" were assessed for three parameters: abrasion, resistance to crushing and disintegration time. The results were subjected to analysis of variance.

The analysis of variance for bulk density showed the significance of the factors studied and the interaction between them in such a way: C > A > B > D > res.

The suitability of powder masses for direct compression is significantly determined by their tapped density. The analysis of variance for the study of the bulk density of powder masses after showed a similar significance of the studied factors and the interaction between them: C > A > B > D > res.

One of the parameters that characterises the propensity of powder masses to be pressed is the angle of repose. A decreased value of this indicator suggests an increased probability of obtaining tablets by the chosen method. The angle of repose should be less than 41 degrees. The influence of the studied factors on the above-mentioned indicator is illustrated by the following range of advantages: B > A > C with statistical insignificance of factor D and interaction between factors.

Resistance to crushing plays a crucial role in the manufacturing of the ODTs. For manufactured tablets with the diameter of 12 mm this criterion should be at least 40 N. The studied factors impacted the resistance of "Virulin" to crushing as follows: C > A > D > B.

Table 3

Composition of components per 1 tablet of Virulin

Component name	Amount of compound in 1 tablet, g	Compound concentration in 1 tablet, %
AMABT	0.01	2
Fillers based on sugars (factor A)	0.1	20
Disintegrants (factor B)	0.04	8
Fillers based on MCC (factor C)	0.345	69
Lubricants (factor D)	0.005	1

Table 4

Experimental planning matrix and results of the study of powder masses for tableting and "Virulin"

№*	A	B	C	D	y_1	y'_1	y_2	y'_2	y_3	y'_3	y_4	y'_4	y_5	y'_5	y_6	y'_6
1	a_1	b_1	c_1	d_1	0.439	0.431	0.594	0.591	43	46	111.2	117.3	0.04	0.05	15	17
2	a_1	b_2	c_2	d_4	0.438	0.438	0.592	0.591	45	49	85.8	87.9	0.12	0.13	20	22
3	a_1	b_3	c_3	d_2	0.556	0.551	0.715	0.712	37	40	67.5	66.9	0.71	0.74	24	20
4	a_1	b_4	c_4	d_3	0.398	0.401	0.555	0.552	40	36	230.3	233.1	0.08	0.09	35	30
5	a_2	b_1	c_2	d_3	0.451	0.457	0.592	0.590	43	47	112.5	109.7	0.21	0.26	14	17
6	a_2	b_2	c_1	d_2	0.450	0.454	0.584	0.586	42	39	121.5	126.3	0.21	0.18	23	26
7	a_2	b_3	c_4	d_4	0.412	0.417	0.524	0.527	39	36	295.2	304.3	0.06	0.05	56	59
8	a_2	b_4	c_3	d_1	0.554	0.551	0.644	0.642	36	31	76.3	77.5	0.28	0.23	27	34
9	a_3	b_1	c_3	d_4	0.584	0.589	0.667	0.655	40	36	91.8	87.4	0.24	0.28	11	15
10	a_3	b_2	c_4	d_1	0.407	0.409	0.586	0.584	35	37	220.5	231.8	0.14	0.11	25	32
11	a_3	b_3	c_1	d_3	0.477	0.472	0.626	0.623	35	34	115.2	113.8	0.18	0.19	26	23
12	a_3	b_4	c_2	d_2	0.500	0.504	0.646	0.644	40	37	77.7	80.4	0.38	0.26	27	29
13	a_4	b_1	c_4	d_2	0.417	0.414	0.527	0.526	38	40	326.3	319.7	0.52	0.59	189	176
14	a_4	b_2	c_3	d_3	0.501	0.504	0.667	0.668	40	37	137.7	143.4	0.18	0.15	50	55
15	a_4	b_3	c_2	d_1	0.499	0.494	0.624	0.621	35	36	168	164.8	0.22	0.24	101	107
16	a_4	b_4	c_1	d_4	0.455	0.451	0.588	0.585	40	37	212.3	217.5	0.17	0.15	122	131

Note:

$\mathbf{y_1}$ and $\mathbf{y'_1}$ – bulk density of powder masses of the first and second series, respectively, g/cm^3;

$\mathbf{y_2}$ and $\mathbf{y'_2}$ – tapped density of powder masses of the first and second series, respectively, g/cm^3;

$\mathbf{y_3}$ and $\mathbf{y'_3}$ – angle of repose of the first and second series, respectively, in degrees;

$\mathbf{y_4}$ and $\mathbf{y'_4}$ – crush resistance of tablets of the first and second series, respectively, N;

$\mathbf{y_5}$ and $\mathbf{y'_5}$ – abrasion of tablets of the first and second series, respectively, %;

$\mathbf{y_6}$ and $\mathbf{y'_6}$ – disintegration time of tablets of the first and second series, respectively, sec.

* – № of series.

The studied qualitative factors can be placed in the following order of preference in terms of their influence on the abrasion of tablets: D > C > res > B > A. The significant value of res indicates that there is a big interaction between the levels of the studied factors. Due to the high resistance of Virulin to crushing, their abrasion was low and did not exceed 1% in any series of experiments.

The obtained ODTs were tested for disintegration time using a disintegration tester. It was found that tablets of "Virulin" that have high resistance to crushing and low abrasion, disintegrated within 1 minute in most series of experiments. The influence of the factors studied on the disintegration time of "Virulin" is illustrated by the following order : A > C > D > res > B.

The results of the ODTs study showed that the powdered masses and tablets based on them, obtained by direct pressing, meet the pharmacopoeial requirements of Ukraine. The high value of crushing strength, low abrasion and disintegration time allowed us to select the following excipients: prosolv SMCC 90, ludipress, sodium carboxymethyl starch and sodium lauryl sulfate.

Several series of "Virulin" have been manufactured to study their stability during storage.

Conclusions. To sum up, the relevance of manufactured antiviral tablets for use in the oral cavity "Virulin" based on allyl ester of 4-methacryloylaminobenzenethiosulfonic acid, synthesized according to the author's method, was substantiated.

To obtain this compound with a potential multifunctional (antibacterial, antifungal and antiviral) effect, the method of synthesis of AMABT was improved, which is carried out in three stages through the preparation of intermediates – sodium 4-aminobenzenesulfonothioate and S-allyl 4-aminobenzenesulfonothioate. The structure and identity of the synthesized BAC were confirmed by elemental analysis, IR and NMR spectroscopy.

The studies on the development of the composition of "Virulin" made it possible to establish the influence of excipients on the main pharmaco-technological parameters of powder masses, as well as tablets based on them. Having analyzed the results of the tests, the optimal excipients were selected for the formulation of the ODTs.

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