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Research Article

Broad-Purpose Solutions of N-Chlorotaurine: A Convenient Synthetic Approach and Comparative Evaluation of Stability and Antimicrobial Activity

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Solutions of N-chlorotaurine (NCT) are effective microbiocidal agents with a broad spectrum of pharmacological activity and outstanding tolerability. The main problem limiting their medical use is their instability, which is generally inherent in solutions of all chlorine-active compounds. In this work, we developed a new synthetic approach to the synthesis of such solutions, which consists in the activation of granular and fibrous polymeric materials with immobilized N-chlorosulfonamide groups, which act here as a chlorinating agent. It was shown that when such polymers are added to taurine solutions, NCT solutions with a chemical composition suitable for immediate medical use can be obtained. The stability of such solutions under various conditions was analyzed in comparison with NCTs obtained by the classical method from sodium hypochlorite. It was confirmed that the process of decomposition of all studied solutions obeys the kinetic laws of the first-order reaction. It was proven that solutions obtained from granular polymers are more stable both in terms of active chlorine concentration and in terms of pH, and their additional buffering is not needed. The stability of solutions decreases when they are stored in the presence of polymers used, with an increase in the excess of taurine and with acidification. The high sensitivity of all obtained solutions to UV radiation was also noted. The antimicrobial properties of NCT solutions obtained from polymers are not inferior to those obtained from sodium hypochlorite at the same concentration of active chlorine. Considering the stability and compactness of the initial chlorine-active polymers, as well as the possibility of their multiple regeneration, the developed method can form the basis of the technology for obtaining multifunctional NCT solutions for medical purposes with the desired physical and chemical properties without using special equipment or specific reagents.

1. Introduction

Recent events related to the COVID-19 pandemic have demonstrated the vital need to develop new preparations and technologies for disinfection and antiseptic treatment of various surfaces and media as one of the most effective and affordable methods for preventing infectious diseases [1, 2]. Special attention should be given to microbiocidal agents that can also be used for therapeutic purposes, for example, for the treatment of pneumonia or infected wounds. In the context of the spread of multiresistant strains of microorganisms (superbugs) [3], as well as the acquired ability of some microbes to rapidly form biofilms [4], the speed and a wide range of antimicrobial actions of such preparations

are also very important. Active chlorine preparations—hypochlorous acid [5], its salts [6], and organic chloramines [7], including those immobilized on polymeric carriers [8, 9]—have all the described qualities. These compounds extremely quickly and effectively suppress bacteria, viruses, fungi, and prions due to their high oxidative capacity, as well as through the chlorination and transchlorination of proteins and nucleic acids of pathogens, so the development of true resistance to these compounds is almost impossible [10]. Another advantage of active chlorine is its endogenous nature—chlorine-active compounds are constantly formed in the body during phagocytosis and, therefore, are generally well tolerated and rarely cause allergies [11].

A special place among active chlorine compounds is occupied by chlorinated derivatives of taurine, which have been extensively studied particularly in the studies of Nagl, Gottardi, and colleagues. Taurine is an amino acid that, although not proteinogenic, is present in large quantities in the body and performs a wide range of cytoprotective and neuromodulatory functions [12]. One of the most important functions of taurine is to mitigate the action of hypochlorous acid formed during phagocytosis, forming the less toxic but at the same time quite effective antimicrobial and anti-inflammatory metabolite—N-chlorotaurine (NCT) [13, 14]. Thus, NCT is a natural microbiocidal agent with outstanding tolerability. Numerous studies have confirmed the high virucidal and antimicrobial activity of NCT and have shown its effectiveness in the treatment of wounds [15], inflammations [16, 17], peritonitis [18], etc., with different ways of its administration in the body. Currently, the possibility of treating acute respiratory syndromes, including COVID-19, by inhalations of NCT solutions is actively studied [19]. One of the decomposition products of NCT in the body is the initial taurine, whose beneficial functions (antioxidant, reparative, osmoregulatory, immunomodulatory, etc.) accompany the administration of such drugs. Other taurine derivatives, such as N-bromotaurine, N,N-dichlorotaurine (NDCT), and N-chloro-2,2-dimethyltaurine, are also pharmacologically active [20–23].

The synthesis of solutions of N-chlorotaurines, most often in the form of sodium salts, under laboratory conditions has been widely described. The original and simplest way to obtain them is to add taurine to a solution of sodium hypochlorite in a buffer [24]. However, in this case, the quality of the initial sodium hypochlorite is highly important, because it can be excessively alkaline and contains impurities of toxic sodium chlorate, as well as salts, which are catalysts for the decomposition of chlorine-active compounds. In addition, sodium hypochlorite is unstable, especially at a slightly acidic pH, so it is necessary to preliminarily determine the concentration of active chlorine in it to correctly calculate its ratio with taurine and constantly use the freshly prepared solution. There are technologies for the electrochemical synthesis of such solutions of NCT salts, but they are not feasible without special equipment [25]. For pharmaceutical purposes, solutions obtained by dissolving crystalline NCT in high-purity water are attractive. The synthesis of these crystalline forms is possible by a heterogeneous one-step reaction of taurine with an ethanolic solution of chloramines B or T [26, 27]. A significant drawback of NCT solutions, like all other chlorine-active compounds, is their instability. The solutions obtained from crystalline forms and stored at 2–4°C are most stable. Under these conditions, a decrease in the oxidizing capacity of 10% per year is reported [26]. Solutions obtained by other methods are less stable. In addition, in the presence of organic load, or when insufficiently pure water is used, as well as in the violation of storage conditions, especially with an increase in the temperature, the stability of solutions decreases profoundly. Therefore, the *in situ* synthesis of such solutions and their immediate application seem promising. Accordingly, the search for alternative methods for obtaining high-purity NCT solutions that do not require the use of special equipment and are suitable for implementation in "field" conditions is topical.

Previously, we described the possibility of obtaining chlorine-active solutions by activating granular and fibrous polymers with immobilized N-chlorosulfonamide groups, synthesized via our special technology, with amino compounds [28]. These polymers are compact and very stable sources of active chlorine, and are suitable for multiple regeneration; therefore, they are promising for the creation of multifunctional medical products based on them, including devices for water disinfection and obtaining antiseptic solutions in zones of military conflicts and emergencies. They are polymeric analogs of chloramine B, and their main advantage over other chloramines is that when chlorine-active solutions are obtained from them, no extraneous organic molecules get into the latter, which is especially important for medical purposes. Additionally, there are ample opportunities for varying the structure and concentration of immobilized functional groups to ensure the specified physicochemical parameters of solutions and control the release of the active agent. In the present work, the processes of synthesizing solutions of NCT by this method were detailed, the properties of the resulting solutions were studied, and a comparative evaluation of their stability and antimicrobial activity was carried out.

2. Materials and Methods

2.1. Polymeric Materials with Immobilized N-Chlorosulfonamide Groups. Polymers with immobilized functional groups used as a source of active chlorine were synthesized according to the procedures described in our studies [9, 28–30]. The simplest and most stable polymers, the functional group of which is the N-chlorosulfonamide group in the sodium form -SO_2-N(Na)Cl, were used in the research. This group was immobilized, in the first case, on copolymers of styrene with divinylbenzene in the form of granules ("granules") based on industrially manufactured raw materials for the production of ion-exchange resins of Purolite C-100 and Amberlite IR 120 types, and, in the second case, on staple fiber ("fiber") of similar chemical composition based on fibrous cation exchanger FIBAN K-4 [31]. The concentration of active chlorine immobilized on the polymer was determined by our specially developed

method of iodometric titration [28]. All physicochemical properties and IR spectra of the polymer samples used corresponded to those previously described. The main characteristics of the synthesized polymer samples are summarized in Table 1, and their appearance is shown in Figure 1.

2.2. Sodium Hypochlorite Solution Used to Synthesize the Reference Solution of N-Chlorotaurine. To obtain a solution of NCT by the classical method, the commercially available preparation "SEKOBREN," which is a high-purity solution of sodium hypochlorite obtained by the special electrochemical method [32, 33], was used. This isotonic preparation has a lower pH than other industrial solutions of sodium hypochlorite and contains an extremely low concentration of sodium chlorate. It has passed many preclinical studies, including inhalation toxicology [34], and is approved by the Ministry of Health of Ukraine for use as an antiseptic; therefore, it is attractive for the synthesis of other active chlorine preparations based on it. The main characteristics of this solution are shown in Table 2.

2.3. Study of the Chemical Composition of the Synthesized N-Chlorotaurine Solutions. The concentration of NCT in the obtained solutions was determined by the standard method of iodometric titration in acetic acid [35]. The aliquot 1 mL of the solution was dissolved in 10 mL of 1 M acetic acid, and 2.5 mL of 10% potassium iodide solution was added. Then, the reaction mixture was mixed, sealed with a stopper, and incubated for 5 min in the dark, after which it was titrated with a 0.002 N solution of sodium thiosulfate with starch as an indicator. The concentration of N-chlorotaurine was calculated by the following equation:

$$\mathrm{C(TauCl)} = \frac{\left[\mathrm{V_1 \cdot K \cdot C\left(Na_2S_2O_3\right)}\right] \cdot \mathrm{M(1/2TauCl)} \cdot 10^3}{\mathrm{V_{al}}}, \quad (1)$$

in which C(TauCl) is the concentration of NCT, mg/L; V_1 is the volume of sodium thiosulfate solution used for titration, mL; $C(Na_2S_2O_3)$ is the normality of sodium thiosulfate solution, mol/L; K is the concentration correction factor for $Na_2S_2O_3$ solution; $M(1/2TauCl) = 79.83$ is the equivalent weight of NCT, g/mol; and V_{Al} is the aliquot volume, mL. Since the functional groups in the polymers used are in the sodium form, the final product is not free NCT, but its sodium salt; the same is true for solutions obtained from sodium hypochlorite. Almost all other mentioned studies were also carried out specifically for sodium salts of chlorotaurines, so the comparison of our results with those previously described is relevant. At the same time, the calculation of concentrations is further given for N-chlorotaurinate ion and not for sodium N-chlorotaurinate; in turn, the abbreviations "NCT" and "NDCT" throughout the manuscript refer to the sodium salts of the respective compounds.

For the convenience of comparing the kinetic data for different chlorine-active solutions, the concentration of active chlorine was used, calculated by the following equation:

$$\mathrm{C\left(Cl_2\right)} = \frac{\left[\mathrm{V_1 \cdot K \cdot C\left(Na_2S_2O_3\right)}\right] \cdot \mathrm{M\left(1/2Cl_2\right)} \cdot 10^3}{\mathrm{V_{al}}}, \quad (2)$$

in which $C(Cl_2)$ is the concentration of active chlorine, mg/L; V_1 is the volume of sodium thiosulfate solution used for titration, mL; K is the concentration correction factor for $Na_2S_2O_3$ solution; $C(Na_2S_2O_3)$ is the normality of sodium thiosulfate solution, mol/L; $M(1/2Cl_2) = 35.5$ is the equivalent weight of active chlorine, g/mol; and V_{Al} is the aliquot volume, mL.

The acidity level of the solutions was determined using the ADWA AD1030 pH meter. UV spectra of the solutions were recorded on the ULAB 108UV spectrophotometer using a 1 cm quartz cuvette.

2.4. Obtaining Solutions of N-chlorotaurine by Activation of Chlorine-Active "Granules". A portion of 10.0 g of "granules" was rinsed three times on the Buchner funnel with 150 mL of water purified by reverse osmosis to remove possible impurities of inorganic salts adsorbed during synthesis and to partially swell the resin. Then, the "granules" were put into a glass flask, and 200 mL of water was added and left for 30 min under stirring. Afterward, the pH of the solution was measured (pH of the aqueous extract in Table 1), and the calculated amount of commercially available taurine (Hangzhou Keying Chem Co., Ltd., P. R. China) was added. The reaction mixture was stirred until the complete dissolution of taurine and left at room temperature, stirring periodically (at the time of sampling) until the maximum concentration of NCT in the solution was reached, which was determined by periodic titration of samples taken directly from the reaction mass. Then, depending on the type of experiment, the "granules" were either filtered, separately observing the filtrate, which is a solution of NCT, or the resulting solution of NCT was observed during storage directly in the presence of a "discharged" polymer (i.e., the residual polymer that lost all immobilized active chlorine, emitting it into the solution during the current experiment) to study its effect on the stability. The filtered "granules" were analyzed for residual immobilized active chlorine. After preparation, the solutions were left overnight at room temperature to reach a stable pH.

2.5. Obtaining Solutions of N-Chlorotaurine by Activation of the Chlorine-Active "Fiber". The procedure is generally the same as that described above for the "granules" with 5.6 g of initial "fiber;" however, when sampling the NCT solution from the reaction mixture containing the "fiber," the samples were filtered each time to avoid getting polymer fibers into the aliquot.

Table 1: The main characteristics of the samples of chlorine-active polymers used in research.

Parameter	"Granules"	"Fiber"
Polymer carrier	Macroporous copolymer of styrene with divinylbenzene in granular form	Staple cation-exchange fiber FIBAN K-4
Functional group	$-SO_2-N(Na)Cl$	$-SO_2-N(Na)Cl$
The concentration of immobilized active chlorine (% w/w)	3.20	5.10
The concentration of immobilized chlorine atoms as a component of N-chlorosulfonamide fragment (% w/w)	1.6	2.55
Density (g/mL)	0.87–0.89	0.31–0.33
Humidity of air-dry product (%)	11.0	8.0
pH of the aqueous extract* (pH units)	11.3	9.8
Water absorption (%)	150	820
The content of free SO_3H-groups (mol/g)	0.2–0.3	0.5–0.7
The average size of the granules (mm)	0.5	—
Monofilament diameter (μ)	—	40–50
Fiber thickness (mm)	—	2-3

*Refers to the pH of 200 mL of water purified by reverse osmosis containing prewashed swollen polymer (10 g of "granules" or 5.6 g of "fiber") before adding taurine.

(a) (b)

Figure 1: Appearance of the samples of synthesized chlorine-active polymers: (a) "granules" and (b) "fiber."

Table 2: Main characteristics of the used sodium hypochlorite solution "SEKOBREN."

Parameter	Value
Density at 20°C (g/mL)	1.008
pH at 20°C (pH units)	9.74
Sodium chloride content (g/L)	8.32
Active chlorine content (mg/L)	1058
Sodium hypochlorite content (mol/L)	0.015

2.6. Obtaining a Solution of N-Chlorotaurine from a Solution of Sodium Hypochlorite. This was carried out by dissolving the corresponding sample of taurine in 200 mL of the described sodium hypochlorite solution "SEKOBREN." The reaction mixture was left overnight at room temperature to reach a stable pH.

2.7. Study of the Stability of the Obtained N-Chlorotaurine Solutions. Immediately after reaching the maximum concentration of NCT and establishing the equilibrium pH, the solutions obtained were poured into 100 mL sealed polypropylene containers (three samples for each solution) and divided into four groups. Solutions of the first group were thermostated at 20°C in the dark; solutions of the second group were thermostated at 40°C in the dark; solutions of the third group were stored in a refrigerator at 4°C; and solutions of the fourth group were stored at room temperature (20 ± 3°C) in the zone of periodic exposure to direct sunlight (normal day-night rhythm), that is, under conditions close to "field." Separately, by acidification with 5% hydrochloric acid, from the solutions obtained by activation of "granules" and from "SEKOBREN," solutions of NDCT were prepared with an approximate pH of 5.5, which, according to the literature [23], corresponds to the higher antimicrobial activity of such compounds against Gram-negative bacteria and, in addition, is close to the pH of the skin; these solutions were also divided into four groups and stored under the conditions described above. Some solutions were stored in the presence of "discharged" in the current experiment chlorine-active polymers. In addition, an initial "SEKOBREN" solution was observed under similar conditions. All solutions were observed for one month, the concentration of NCT/active chlorine and pH were periodically fixed, and UV spectra were periodically recorded. If the concentration of active chlorine dropped to zero before the end of the storage period, the corresponding solutions were disposed of, previously recording the UV spectrum.

2.8. Study of the Antimicrobial Activity of the Obtained N-Chlorotaurine Solutions. The antimicrobial activity of the obtained solutions was determined by the standard agar well diffusion method [36]. The tryptic soy agar in Petri dishes was inoculated by spreading a volume of the microbial inoculum over the entire surface. The museum strains of the most common microorganisms *S. aureus*, *C. albicans*, and *E. coli* were used as the test cultures. Then, holes with a diameter of 8 mm were punched aseptically in the agar layer with a sterile cork borer, and 0.1 mL of the studied solution was added into each well. The 0.9% saline solution was used as a control. After that, the Petri dishes were kept for 1 hour at room temperature and incubated for 24–48 hours at 37°C. All microbiological experiments were performed in triplicate. The diameter of the inhibition zone of the microbial growth (average of three reps) was the criterion of the antimicrobial effect of the solution.

3. Results and Discussion

3.1. Preparation and Properties of Stock Solutions of N-Chlorotaurine. The synthesis of NCT solutions using chlorine-active polymers was carried out in excess of taurine, taking into account the results of preliminary studies [28], which showed that this promotes faster diffusion of active chlorine from the polymer and, accordingly, faster achievement of its maximum concentration in the solution. Obviously, an excess of taurine provides the solution with additional buffer capacity, which will likely prevent significant changes in its pH during subsequent storage. At the same time, unlike other methods for obtaining such solutions, we did not use extraneous buffers, bringing the procedure closer to "field" conditions. Additionally, it seemed interesting to study how an excess of taurine affects the antimicrobial activity of solutions; therefore, one solution was obtained separately with an amount of taurine that was many times greater than the amount of chlorine. When synthesizing the NCT solution from the sodium hypochlorite "SEKOBREN," the same amount of taurine was added per 200 mL of the preparation, as in the case of its

synthesis from polymers. The data on components loading for obtaining various solutions (based on 200 mL of water) are shown in Table 3.

Obviously, when obtaining NCT solutions from polymers according to our method, the hydrodynamic mode of the process plays an important role as in any heterogeneous process. However, in this work, it was necessary first to estimate the rate of emission of active chlorine under conditions close to the "field," i.e., without the use of special stirrer machines. In addition, the different physical forms of the polymers used do not allow for the organization of the same mixing conditions. Therefore, in the present study, the reaction mixtures were mixed manually only before sampling, and the effect of technological parameters on the synthesis rate will be the subject of our separate study.

The kinetic curves of the growth of the active chlorine concentration in solutions obtained from polymers are shown in Figure 2. When synthesized from sodium hypochlorite, the reaction proceeded almost instantly, and the maximum concentration of 2379 mg/L of NCT (1058 mg/L of active chlorine, i.e., equal to the initial concentration of sodium hypochlorite) is reached in less than 2 minutes.

The maximum NCT concentration when using the "fiber" (F_0 solution) was 3209 mg/L (1427 mg/L active chlorine), which was reached within 40 minutes, while the concentration of 2730 mg/L (1214 mg/L of active chlorine), which is sufficient for the manifestation of pronounced antimicrobial properties when used as an antiseptic, was achieved after 3 minutes. In the case of the G_0 solution, the process proceeded much more slowly: the maximum NCT concentration of 3017 mg/L (1342 mg/L of active chlorine) was achieved only within 23 hours. This is clearly due to the higher specific surface area of the "fiber" compared to the "granules." An increase in the mass transfer rate, as can be seen, is achieved with an increase in the taurine loading: for the $GExc_0$ solution, the maximum NCT concentration of 3200 mg/L is reached within 40 minutes, which is the same time as for the "fiber;" however, its growth gradient is still lower—the concentration reaches 2538 mg/L (1129 mg/L of active chlorine) only after 15 minutes. The G_0 and $GExc_0$ solutions are transparent and can be easily decanted from the granules, while the F_0 solution contains many suspended fibers, some of which have colloidal size and remain in solution even after filtration, resulting in slight opalescence.

The analysis of the "discharged" polymers showed the absence of active chlorine immobilized on them after the preparation of $GExc_0$ and F_0 solutions; the "granules" separated from the G_0 solution contained approximately 0.2–0.3% of immobilized chlorine, the emission of which into a fresh taurine solution of the same initial concentration proceeded extremely slowly, giving a resulting increase of no more than 30–40 mg/L of active chlorine in the solution after 2 days. This explains the slightly lower maximum active chlorine concentration in solution G_0 compared to $GExc_0$ with the same load of "granules." The data on the active chlorine concentrations in the initial polymers and solutions obtained from them are in agreement and show that complete diffusion of it into the solution is ensured even without stirring. It can be assumed that an increase in the load of the polymer in the same volume of solvent will make it possible to obtain more concentrated solutions.

The acidities of the obtained solutions after reaching their stable values differed significantly: for the G_0 solutions, pH lies in the interval of 9.00–9.10, for F_0 solutions—7.35–7.45, for S_0 solutions—7.45–7.60, and for $GExc_0$ solutions—8.10–8.20. This is due to the unequal initial pH of aqueous extracts from polymers and of "SEKOBREN" (Tables 1 and 2), different concentrations of free sulfo-groups immobilized on the polymer, which can bind acidic molecules of taurine and its derivatives, as well as different CO_2 solubilities in the obtained solutions; the latter also explains why it takes some time to reach the stable pH of NCT solutions [37]. The difference in pH between aqueous extracts from "granules" and "fibers" at practically the same (taking into account loadings) concentrations of active chlorine can be due to different contents of "uncharged" sulfamide groups in the sodium form $-SO_2NHNa$, which obviously increase pH during dissociation. As shown in Table 4, when the "granules" are removed from the solutions, the pH of the latter practically does not change, and when the "fiber" is removed, the pH increases by about 0.3 units. Most likely, this is also due to the adsorption of taurine, whose solutions have an acidic pH, on the surface of the fiber.

By acidifying solutions G_0 and S_0 with hydrochloric acid, the corresponding solutions of G5.5 and S5.5 were obtained with a pH of approximately 5.5. The study of the properties of such solutions was necessary to determine the feasibility of their preparation by the taurine activation of polymers with immobilized N-chlorosulfonamide groups in the H-form without adding additional acids.

3.2. Properties of Working Solutions of N-Chlorotaurines Prepared for the Evaluation of Stability. After reaching the maximum concentration and stationary pH, and making the necessary adjustments to the composition of the initial solutions, the following working solutions of N-chlorotaurines were obtained to compare their storage stability under various conditions (Table 4):

The characteristics of working solutions at the moment of storage start time are given in Table 5.

The UV spectra of the main obtained solutions diluted 10 times with distilled water are shown in Figure 3(a). As seen, all solutions, except G5.5 and S5.5, had an absorption maximum at 251 nm, which corresponds to NCT [26]; the absence of NDCT peaks is explained by the slightly alkaline pH, as well as the presence of an excess of taurine. The difference in the spectral structure of the F_0 solution (more intense absorption in the range of 200–240 nm) may be due to the presence of colloidal impurities in the polymer fibers, which increase the scattering coefficient. Solutions G5.5 and S5.5 have two absorption maxima at 227 nm and 301 nm, which, considering the acidic pH, is expectedly consistent with NDCT. There are no extraneous peaks in all spectra, which confirms the high purity of the solutions obtained by the described methods. As can be seen, nonacidified

Table 3: Initial components loading in the synthesis of various NCT solutions.

Initial solution symbol	Source of active chlorine and its quantity	Mass of taurine (g)	Molar ratio "immobilized chlorine atom: taurine"
G_0	"Granules," 10.0 g	1.06	1 : 2.2
$GExc_0$*	"Granules," 10.0 g	3.20	1 : 6.6
F_0	"Fiber," 5.6 g	1.06	1 : 2.2
S_0	"SEKOBREN," 200 mL	1.06	1 : 2.8

*Hereinafter "Exc" means "great excess of free taurine."

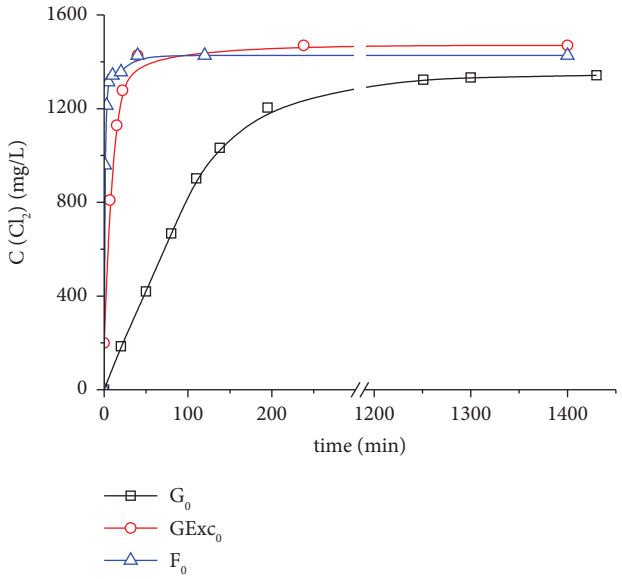

Figure 2: Kinetic curves of the increase in the active chlorine concentration in the NCT solutions obtained from the chlorine-active polymers at room temperature (20 ± 3°C).

solutions also had peaks at about 200 nm, corresponding to the taurinate-ion, the spectra of undiluted 0.53% (1.06 g of taurine in 200 mL of water with the addition of sodium hydroxide or hydrochloric acid) solutions of which at various pH are shown in Figure 3(b). Note that the absorption of free taurine is much lower than that of its chlorine derivatives, and the position, shape, and intensity of its characteristic peaks strongly depend on pH, which is associated with changes in the concentrations of various ionized forms and the zwitterion in solutions of various acidities. This, as well as the possibility of overlapping peaks of taurine and N-chlorotaurines in the working pH range, does not allow us to reliably determine free taurine in solutions using UV spectrophotometry, and, for example, the spectra of G and GExc solutions do not differ greatly, despite a significant excess of taurine in the latter.

Thus, the activation of polymers with immobilized N-chlorosulfonamide groups by taurine allows N-chlorotaurine solutions with a chemical composition satisfactory for medical use to be obtained. The rate of the process is directly proportional to the surface area of the initial polymer and the amount of taurine. From a technological point of view, it seems more rational to use polymer "granules," given their high strength, greater

Table 4: Working solutions of N-chlorotaurines obtained by various methods.

Working solution symbol	Solution description
G	Obtained from "granules" and separated from them
GG	Obtained from "granules" and observed in their presence
GExc	Obtained from the "granules" in a large excess of taurine and separated from them
GGExc	Obtained from "granules" in a large excess of taurine and observed in their presence
G5.5	Obtained by acidifying of G_0 solution with hydrochloric acid and separated from the "granules"
GG5.5	Obtained by acidifying of G_0 solution with hydrochloric acid and observed in the presence of "granules"
F	Obtained from the "fiber" and separated from it
FF	Obtained from the "fiber" and observed in its presence
S	Obtained from sodium hypochlorite "SEKOBREN"
S5.5	Obtained by acidifying of S solution with hydrochloric acid

compactness, availability of raw materials, and ease of their production and regeneration; the process rate in this case is lower, but it can probably be increased by controlling technological factors such as mixing. In addition, when "fiber" polymers are used, the final solution without additional filtration is not suitable for, for example, application to open wounds or for inhalations due to the presence of a large number of dispersed impurities that are highly likely not to be metabolized and will serve as a source of irritation and inflammation; however, this can probably be prevented by packaging chlorine-active polymer in a special container that does not prevent molecular diffusion but retains the fibers. The concentration of target solutions can be varied over a wide range by changing the loading of polymers and/or the amount of immobilized active chlorine, which, as we wrote earlier, can be increased to 15% w/w for polymeric N,N-dichlorosulfonamide [30]. To date, it has been convincingly proven that N-chlorotaurines exhibit pronounced microbicidal properties at concentrations above 0.1%. The antimicrobial and antiviral activity of a 1% NCT solution in phosphate buffer at a pH of about 7.4 is the most studied.

Table 5: Main characteristics of working solutions of N-chlorotaurines of different origin.

Parameter	Solution									
	G	GG	GExc	GGExc	G5.5	GG5.5	F	FF	S	S5.5
N-Chlorotaurine content (mg/L)	3001	3001	3161	3305	2682	2682	3209	3209	2379	2283
Active chlorine content (mg/L)	1335	1335	1406	1470	1193	1193	1427	1427	1058	1015
pH at 20°C (pH units)	9.00	8.98	8.20	8.19	5.51	5.51	7.77	7.47	7.62	5.54

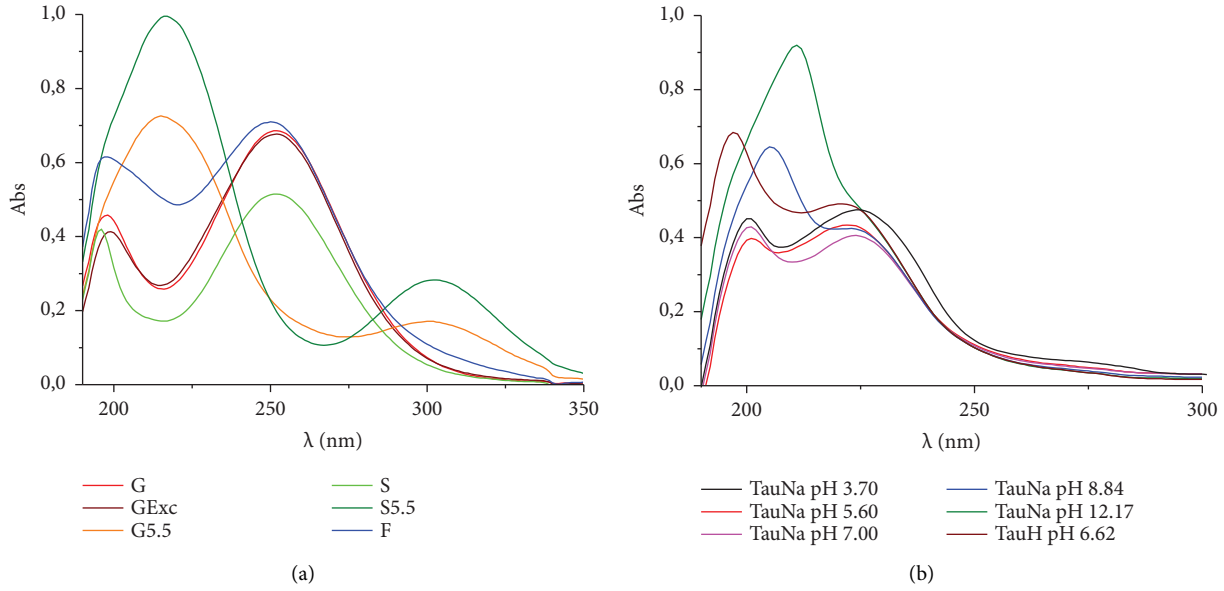

Figure 3: UV spectra of (a) obtained solutions of N-chlorotaurines with concentrations corresponding to Table 5 and (b) 0.53% taurine solutions at different pH. The spectra confirm the declared structure of chlorine-active compounds and the high purity of the solutions.

3.3. Study of the Stability of the Obtained N-Chlorotaurine Solutions at 40°C. It is known that the decomposition of NCT in aqueous solutions at pH 7.4 and above occurs by its dehydrohalogenation, under certain conditions followed by the transformation of the formed imine into sulfoacetaldehyde and ammonium chloride, and this reaction is of the first order [38]. However, these data were obtained when studying buffered solutions of NCT in the absence of excess taurine; therefore, to calculate the kinetic characteristics of our processes, it was necessary to verify this statement, as well as to compare the stability of solutions obtained from polymers and by the classical method from sodium hypochlorite. At pH below 7.0, the disproportionation of NCT to NDCT also contributes significantly [26]; however, the equilibrium constant of this process obviously also depends on the concentration of free taurine. NDCT itself can decompose by the mechanism of 1,2-elimination of hydrogen chloride or be hydrolyzed with the release of dichloramine, eventually leading to sulfoacetaldehyde anyway [39]; the rate of the decomposition process in this case is higher than that for NCT. In general, the decomposition of N-chlorotaurines at room temperature proceeds rather slowly, so the data obtained at elevated temperatures should be the most demonstrative. The kinetic curves of the decrease in the concentration of active chlorine in the synthesized solutions of N-chlorotaurines and "SEKOBREN" during thermostating at 40°C are shown in Figure 4.

As can be seen, all solutions, except for FF, G5.5, GG5.5, and S5.5, still retained some amount of active chlorine after 30 days of storage under these conditions. The obtained kinetic data are linearized in the semilogarithmic coordinates $\ln C(Cl_2) = f(\tau)$ (Figure 5), which confirms the first order of this reaction.

As seen, noticeable deviations from the straight line are observed only for the FF solution, which can be explained by the significant contribution of surface phenomena, in particular, the adsorption of solution components on the "fiber." The substitution of the kinetic data obtained for the FF solution into the reaction equations of other integer orders also did not lead to satisfactory linearization. Therefore, the decomposition rate constant of NCT in this solution can only be estimated approximately. The summary kinetic characteristics of all solutions (average value for three samples) stored at 40°C, calculated using the first-order reaction equation are shown in Table 6.

3.4. Study of the Stability of the Obtained N-Chlorotaurine Solutions under Other Conditions. The same approaches were used to analyze the stability of the solutions during storage under other conditions. It was established that the rate of N-chlorotaurine decomposition in all cases also obeys the laws of a first-order reaction, except for solutions F and FF when stored under "field" conditions and at 20°C, where

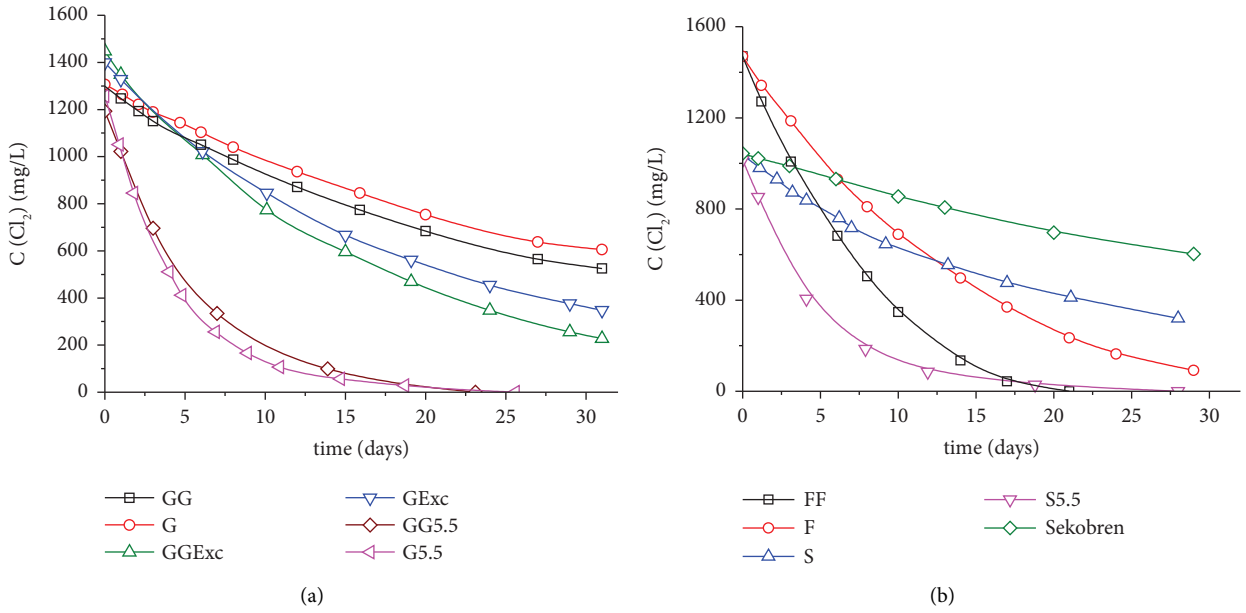

Figure 4: The decrease in the active chlorine concentration in the obtained solutions of N-chlorotaurines at 40°C: (a) solutions of different compositions obtained from "granules" and (b) other solutions. All solutions, except for FF, G5.5, GG5.5, and S5.5, retain a certain amount of active chlorine after a month of storage.

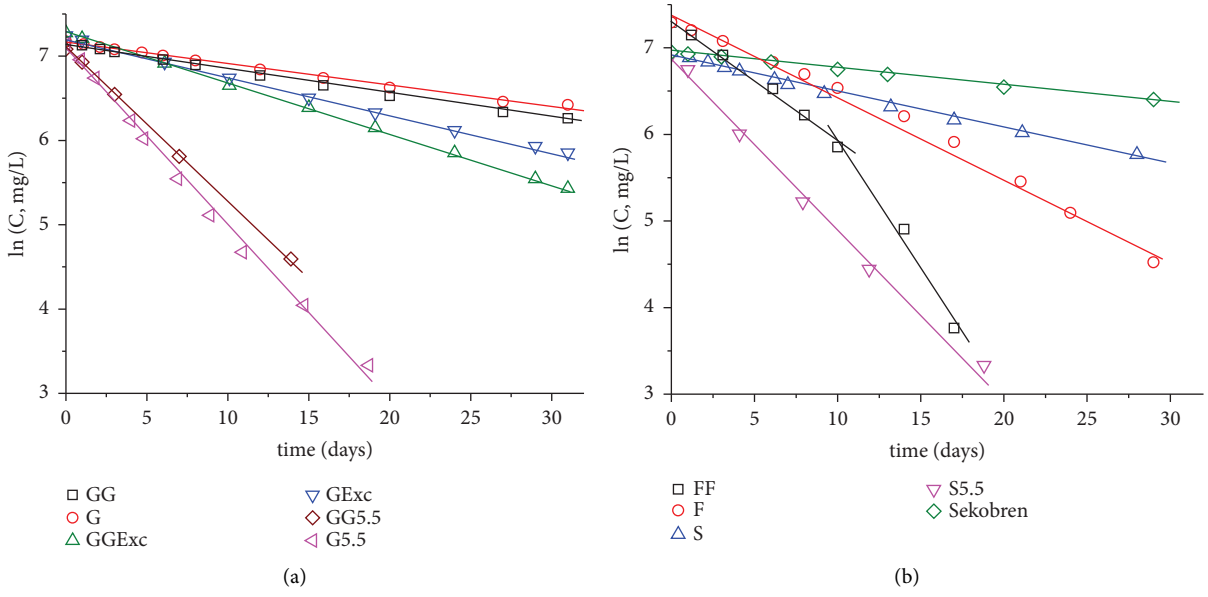

Figure 5: Kinetic curves of the decrease in the active chlorine concentration in the obtained solutions at 40°C in semilogarithmic coordinates $\ln C(Cl_2) = f(\tau)$: (a) solutions of different compositions obtained from "granules" and (b) other solutions. The coefficients of determination R^2 for all curves except FF are at least 0.989. The character of the graphs confirms the first order of the N-chlorotaurines decay reaction.

small deviations are observed again due to the presence of the dispersed phase. The kinetic curves of the decrease in the active chlorine capacity for solutions G, F, and S in semilogarithmic coordinates under various storage conditions are shown in Figure 6, and the summary kinetic characteristics for all the studied solutions are shown in Table 7. Slightly larger deviations from the first-order reaction equation than at 40°C are explained by the accumulation of errors at low degrees of conversion of the starting substances. In general, Figure 6 and further data indicate a significant acceleration of the decomposition process of all studied solutions with increasing temperature and especially during storage under field conditions, which, as shown below, is associated with exposure to sunlight.

Table 6: Kinetic characteristics of N-chlorotaurines decomposition during storage of solutions at 40°C.

Solution	Rate constant ($days^{-1}$)	Half-life (days)	The average decrease in the active chlorine concentration per day (%)
G	0.0253	27.4	2.50
GG	0.0296	23.4	2.92
GExc	0.0449	15.4	4.40
GGExc	0.0593	11.7	5.76
F	0.0949	7.3	9.07
FF	0.2067*	3.4*	18.68*
S	0.0371	18.7	3.65
G5.5	0.2072	3.3	18.72
GG5.5	0.1801	3.8	16.49
S5.5	0.1939	3.6	17.64
SEKOBREN	0.0193	35.9	1.91

*Approximately taking into account deviations from the first order.

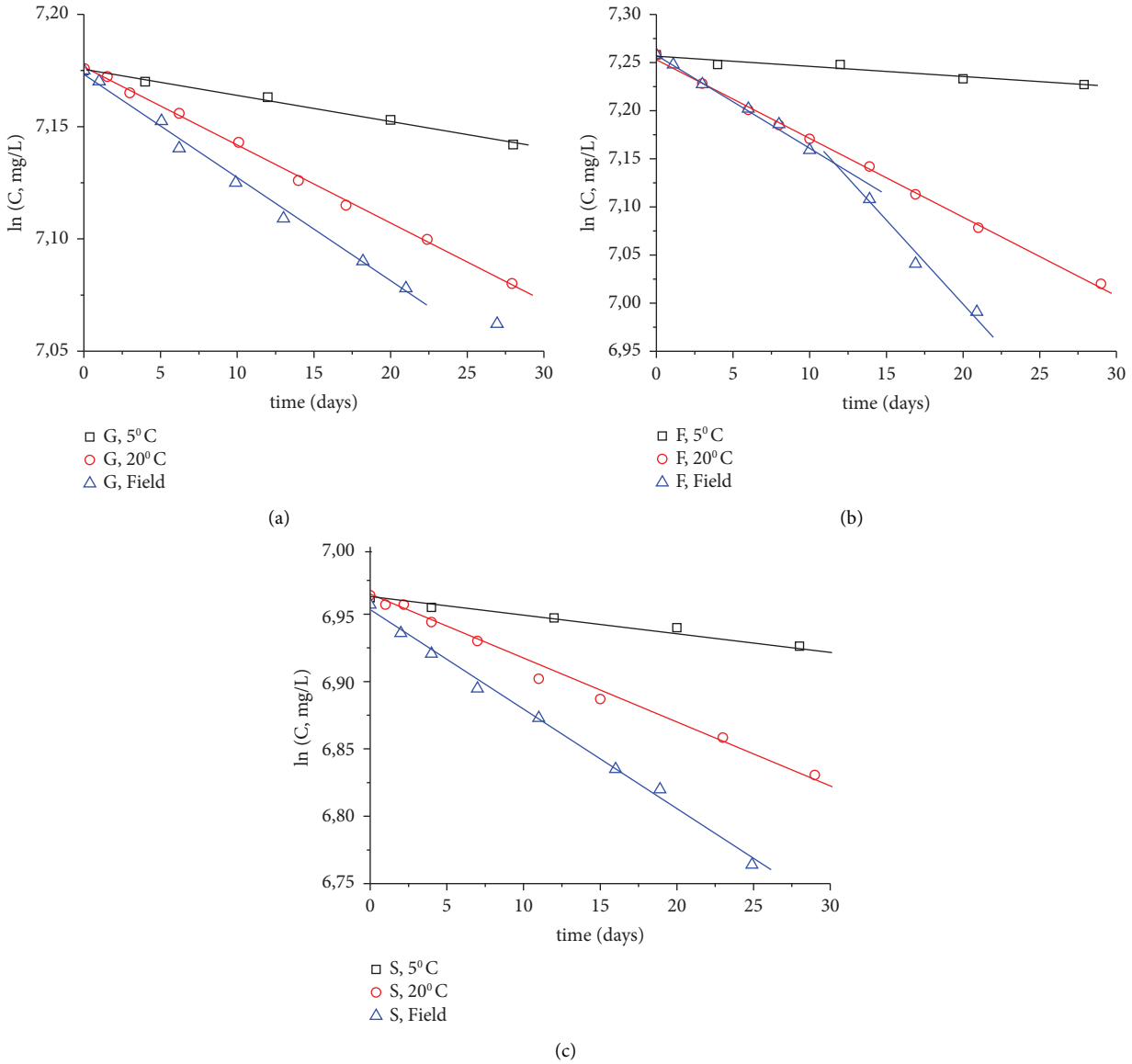

Figure 6: Kinetic curves of the decrease in the active chlorine concentration in the obtained solutions under various storage conditions in semilogarithmic coordinates: (a) solution G; (b) solution F; and (c) solution S. The coefficients of determination R^2 for all curves except for the one obtained for the F solution in field conditions are at least 0.983. The graphs confirm the first order of the N-chlorotaurines decomposition reaction in all cases.

Table 7: Kinetic characteristics of N-chlorotaurines decomposition during the storage of solutions under various conditions.

Solution	Rate constant ($days^{-1}$)			Half-life (days)			The average decrease in the active chlorine concentration per day (%)		
	5°C	20°C	"Field"	5°C	20°C	"Field"	5°C	20°C	"Field"
G	0.0012	0.0027	0.0040	578	257	173	0.12	0.28	0.40
GG	0.0013	0.0028	0.0055	533	248	126	0.13	0.27	0.55
GExc	0.0013	0.0046	0.0096	533	151	72	0.13	0.46	0.96
GGExc	0.0013	0.0096	0.0119	533	72	58	0.13	0.96	1.18
F	0.0012	0.0076*	0.0137*	578	91	51	0.12	0.76	1.36
FF	0.0023	0.0196*	0.0395*	301	35	18	0.23	1.94	3.88
S	0.0015	0.0039	0.007	462	178	99	0.15	0.39	0.70
G5.5	0.0013	0.0087	0.0291	533	80	24	0.13	0.87	2.87
GG5.5	0.0014	0.0077	0.0241	495	90	29	0.14	0.77	2.38
S5.5	0.0015	0.0089	0.0290	462	84	24	0.15	0.83	2.86
SEKOBREN	0.0006	0.0008	0.0266	1155	866	26	0.06	0.08	2.63

*Approximately taking into account deviations from the first order.

3.5. General Patterns Decrease in the Active Chlorine Concentration in the Studied Solutions during Storage. As shown in Tables 6 and 7, nonacidified solutions of N-chlorotaurines, when stored in the presence of polymers, decompose faster than the corresponding solutions separated from them. This is especially noticeable when comparing solutions F and FF, the latter of which demonstrates the least stability of all studied, regardless of the storage conditions. Most likely, the specific surface of polymers, which acts as a heterogeneous catalyst for the decomposition of chloramine, plays a key role here. In the case of the GG solution, the acceleration of NCT decomposition by "granules" was not compensated even by the diffusion of the residual immobilized active chlorine. Solutions separated from "granules" are much more stable than those obtained from "fibers," which can also be explained by the presence in the latter (even after filtration) of microscopic polymer particles that catalyzes the decomposition of NCT. Solutions G and GG show greater stability than solution S under all the conditions studied. This additionally confirms the expediency of using such polymer form as a source of active chlorine in the synthesis of NCT by this method.

Solutions GExc and GGExc outside the refrigerator decompose about two to three times faster than the corresponding solutions G and GG, which have a lower excess of taurine. This is facilitated by both the lower pH and the theoretical possibility of taurine acting as a reducing agent during oxidation with NCT.

Acidified solutions G5.5 and S5.5, as expected, are less stable, since the dehydrohalogenation of NDCT, especially in an acidic medium, proceeds more easily. At the same time, these solutions, in contrast to slightly alkaline ones, are more stable in the presence of "granules," which is due to an increase in pH as a result of ion-exchange adsorption (see below).

In the refrigerator at 5°C, all solutions of N-chlorotaurines, except for FF, have practically the same stability, which generally confirms the decisive role of the dehydrohalogenation process in decomposition kinetics.

The stability of all N-chlorotaurines solutions in the dark was lower than that of the "SEKOBREN;" however, the situation is reversed under intermittent sunlight. This is due to the greater tendency of sodium hypochlorite to undergo photolysis by a mixed chlorate-oxygen mechanism [40].

The pH level of solutions during storage obviously depends on the effect of temperature on the dissociation constants of NCT, NDCT, and free taurine, as well as on the accumulation of decomposition products: sulfoacetaldehyde, hydrochloric acid, and ammonium chloride, which should decrease the pH. The dynamics of change in this indicator is extremely important since a decrease in pH leads to a decrease in stability: thus, it was reported that at pH 5.0, the loss of active chlorine in NCT solution occurred five times faster than at pH 7.4 [41]. The level of acidity was measured by us directly at the storage temperature of the solutions using automatic temperature compensation of the pH meter. The pH values of all solutions after one day and at the end of the storage period are shown in Table 8.

As seen, at 20°C all solutions, except for those initially acidified with hydrochloric acid, despite different degrees of conversion during storage, had fairly stable pH values, the deviation does not exceed 0.15, while tending to a gradual decrease. In the case of the FF solution, the immediate decrease in the pH of 0.33 may have been due to the significant adsorption of the components of the solution by the fiber. When solutions are heated to 40°C, their pH immediately decreases by 0.4–0.6 units, which is natural for solutions of amphoteric compounds and is explained by the effect of temperature on the endothermic dissociation process and then also remains stable throughout the entire storage period with a slight tendency to decrease, except for solutions F and F5.5, for which the pH decreases significantly, which is also explained by the presence of fibers with a developed surface in them and correlates with the degree of conversion of NCT. Interestingly, in the case of the S solution, the pH at the end of the storage period turned out to be higher than at the beginning, both at 20°C and at 40°C,

Table 8: The pH level of the studied solutions at the beginning and at the end of their storage.

Solution	pH after 1 day of storage (pH units)				pH at the end of storage (pH units)			
	5°C	20°C	40°C	"Field"	5°C	20°C	40°C	"Field"
G	8.82	9.00	8.57	8.97	8.75	8.85	8.52	8.84
GG	8.84	8.98	8.45	8.79	8.80	8.84	8.42	8.68
GExc	8.40	8.20	7.82	8.17	8.46	8.11	7.77	8.03
GGExc	8.40	8.19	7.72	8.15	8.43	8.08	7.66	7.95
F	7.90	7.77	7.36	7.68	8.14	7.73	5.53	7.13
FF	7.48	7.47	7.07	7.22	7.76	7.14	5.12	6.51
S	7.43	7.62	7.23	7.59	8.05	7.75	7.50	7.45
G5.5	5.13	5.56	4.42	4.98	5.25	5.26	4.26	2.79
GG5.5	6.13	6.43	5.50	6.35	6.22	6.02	5.18	5.52
S5.5	5.06	5.45	4.55	5.23	4.81	5.23	4.40	2.98

which can be explained by the influence of the high ionic strength of this solution due to the presence of a large amount of sodium chloride.

When solutions are stored in a refrigerator, their pH increases by 0.2–0.3 units when the temperature reaches 5°C and then also remains almost constant. Note that a significant excess of taurine in the GExc and GGExc solutions did not drastically affect the stability of their pH compared to that in the G and GG solutions. Overall, the same regularities apply to solutions G5.5, GG5.5, and S5.5, although the decrease in their pH per month at all the temperatures studied is greater and amounts to 0.2–0.4 units. This is obviously due to the higher degree of conversion, which leads to the accumulation of acidic decomposition products. In general, NCT solutions obtained from "granules" demonstrate the most stable pH, the value of which is maintained, to a large extent, due to the buffer properties of excess taurine. Accordingly, when such solutions are stored for at least one month, there is no significant change in the ratio between NCT and NDCT, and, in fact, NCT remains the only active chlorine compound throughout this period. This was also confirmed by the UV spectra of the solutions, in which the characteristic peaks of NCT and NDCT (for solutions G5.5, GG5.5, and S5.5) were observed throughout the entire storage period, the intensity of which decreased proportionally to the decrease in the concentration of active chlorine. Extraneous signals were absent in all cases. The UV spectra of solution G on the first day (diluted 10 times) and at the end (diluted 5 times) of the storage period at 40°C are shown in Figure 7.

The storage of solutions under "field" conditions has several features. Although the temperature in the room did not exceed 23°C on any of the days, and the solutions themselves, despite the incident sunlight, never heated above 25°C, the decrease in pH in them for all solutions was greater than when thermostating at 20°C. This fact is especially noticeable for solutions with an initial pH of 5.5. Additionally, as evidenced by the kinetic data, when stored under such conditions, the rate constant of decomposition of NCTs is higher. Such behavior is characteristic of solutions of hypochlorous acid and sodium hypochlorite, which decompose faster in light than at elevated temperatures; however, organic chloramines are also photosensitive, absorbing UV light, and decomposing by a radical mechanism

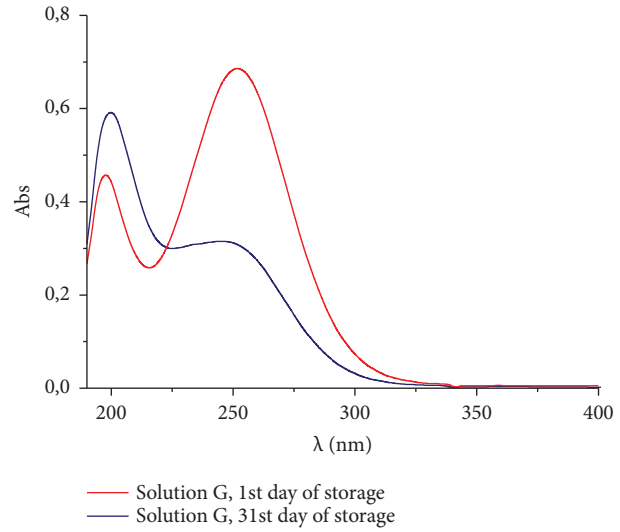

Figure 7: The UV spectra of solution G on the first day and on end of the storage period at 40°C. The spectrum confirms the absence of accumulation of foreign impurities during storage.

[42]. It was decided to conduct an additional experiment. Solutions G and S and sodium hypochlorite "SEKOBREN" in a quartz glass flask were placed under an ultraviolet lamp emitting in the range of 220–500 nm. The radiation power in the region of the flask was about 600 mW/m^2. The solutions were irradiated for 2 hours and periodically analyzed for active chlorine. The temperature of the solutions was monitored all the time and was in the range of 14–17°C. The processing of the kinetic data showed that the process of NCT decay under these conditions also obeys a first-order equation. The decomposition rate constants were as follows: for solution G—0.0040 min^{-1}, for solution S—0.0129 min^{-1}, for solution "SEKOBREN"—0.0152 min^{-1}, which is incomparably higher than when stored in the dark. In addition, a significant acidification was observed in solution S: from an initial pH of 7.58, after 45 min of irradiation, it was 3.92, and after 120 min, it was 2.75. The pH decrease in solution G was much lower: 8.96 at the beginning and 8.29 at the end of the experiment. This may be due to the lower buffer capacity of solution S due to a lower excess of taurine compared to solution G, as well as a lower initial pH. Such a decrease in pH, accordingly, leads to a shift of the

Table 9: The results of the study of the antimicrobial activity of the obtained solutions.

Solution	Active chlorine concentration (mg/L)	Growth inhibition zone (mm)		
		E. coli	*S. aureus*	*C. albicans*
F	1052	12.7 ± 0.8	15.3 ± 0.5	9.0 ± 0.8
G	1056	11.7 ± 0.5	15.7 ± 0.5	12 ± 0.8
S	1058	13.7 ± 0.5	12.0 ± 0.8	9.3 ± 0.5
GExc	1050	12.0 ± 0.8	13.3 ± 0.9	9.7 ± 0.5
G5.5	1048	9.3 ± 0.5	13.3 ± 0.9	9.0 ± 0
SEKOBREN	1058	15.7 ± 0.9	18.7 ± 0.9	32.3 ± 2.0
0.9% NaCl (control)	—	0	0	0

equilibrium toward NDCT, the decomposition rate of which in UV light is higher than that of NCT. Thus, the decrease in the stability of solutions under "field" conditions can be explained by the photolysis of NCTs under periodic exposure to direct sunlight.

3.6. Antimicrobial Activity of the Studied Solutions. To carry out a comparative assessment of the antimicrobial activity, the obtained NCT solutions were diluted with distilled water to a single concentration of approximately 1050 mg/L of active chlorine. The results of the study are shown in Table 9:

All the studied solutions exhibited an antimicrobial activity against the used microorganisms. Solutions F and G are slightly more effective than solution S, and their activity is close to that of "SEKOBREN" (with the exception of suppression of *C. albicans*, which is unusually sensitive to hypochlorite). Different, despite the same concentration of active chlorine, suppression zones are probably due to different pH levels and salinity of solutions (solution S is practically isotonic, and all other solutions are hypotonic). The G5.5 solution under these conditions turned out to be less active against all three microorganisms, although it was previously reported that in an acidic environment, the antimicrobial properties of NDCT significantly exceed those of NCT. The GExc solution also turned out to be somewhat weaker than the G solution; however, the feasibility of using an excess of taurine needs to be studied *in vivo*, because taurine itself has been reported to have wound-healing activity [41, 43]. It should be noted that a significant decrease in the antimicrobial properties of active chlorine compounds has been repeatedly reported in the presence of a large organic load, which, in our experiment, was the nutrient medium itself, the protein components of which can interact with active chlorine along with the microorganisms themselves [44]. In general, the agar diffusion test can only provide an approximate estimation of the microbiocidal activity of the compounds under study. Therefore, the zones of growth inhibition obtained, which are much smaller than, for example, those of antibiotic preparations, do not indicate a low activity of N-chlorotaurines, since they are comparable to those for 0.1% sodium hypochlorite solution, the powerful microbiocidal activity of which has been repeatedly proven by many other methods [45, 46]. At the same time, the antimicrobial activity of NCT solutions of various concentrations and compositions has been repeatedly confirmed by other methods, such as dilution testing, and is beyond doubt [16, 37]. Considering that the solutions we studied are planned to be used for treating wounds, that is, environments containing a large amount of organic impurities, it is the agar well method that is the most indicative. Our experiment, in combination with the previously described reparative properties of NCT, only confirms the promise of using such solutions for the antiseptic treatment of even heavily contaminated surfaces, such as open wounds.

In general, the study proves that the chlorine-active polymers synthesized by us can be successfully used to obtain the solutions of N-chlorotaurines. The novelty and practical value of the developed method lies in the fact that it does not imply the use of special electrical equipment or unstable raw materials, and the resulting solutions are suitable for immediate medical use. In addition, this method is simple and safe and, therefore, can be implemented by nonprofessionals in the field conditions, for example, in the zones of military conflicts and emergency situations. All facts indicate that granular forms of polymers are more suitable for these purposes, even though the process rate of NCT formation in the solution, in this case, is less than if using "fiber." The miscellaneous structure of N-chlorosulfonamide groups immobilized on the polymer, as well as the possibility of further functionalization of these materials (e.g., the introduction of ion-exchange groups), will make it possible to obtain such solutions with the desired properties (active chlorine concentration, pH, salinity, etc.) depending on the purpose of the application, which will be the subject of our separate study. The antimicrobial [9], virucidal [47], and reparative [29] properties of the polymers themselves, and their microbial impermeability [48], together with the data obtained in this study, open up broad prospects for the manufacture of multifunctional medical devices using such materials.

4. Conclusions

Thus, it was shown that the activation of fibrous and granular forms of styrene-divinylbenzene polymers with immobilized N-chlorosulfonamide groups by taurine makes it possible to obtain high-purity solutions of N-chlorotaurines, which are more stable than those obtained by the classical method from electrochemically generated sodium hypochlorite and are not inferior to the latter in antimicrobial activity. Given the compactness, high stability, variability of the structure of the functional group, and the

possibility of regeneration of the studied chlorine-active polymers themselves, this approach is promising for the development of technologies and devices for the synthesis of multifunctional solutions of medical N-chlorotaurine with the desirable physical and chemical properties.

Data Availability

All the data used to confirm the results obtained in this study are included within the manuscript. Any additional explanations and materials, including the results of the titrimetry of the solutions studied, can be received upon e-mail request to the corresponding author.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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