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Sulfur nanoparticles stabilized in the presence of water-soluble polymers

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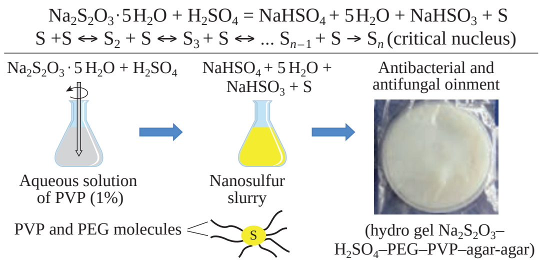
A method was developed to prepare sulfur nanoparticles (nanosulfur) *via* reaction between sodium thiosulfate and sulfuric acid in the presence of water-soluble poly-*N*-vinylpyrrolidone (PVP) with different molecular weights. Polymeric hydrogel ointments were prepared from agar-agar, PVP, poly(ethylene glycol) solutions with virable concentrations of sodium thiosulfate and sulfuric acid. The ointment samples showed antibacterial and antifungal activities against *Staphylococcus aureus*, *Escherichia coli* and *Candida guilliermondii*.



Sulfur is widely used in chemical industry.[1] Application of nanodispersed sulfur (nanosulfur[2]) in biotechnology and medicine is based on its unique properties such as bactericidal, antiviral and antitumor activities.[3–5] Due to pesticidal[3,6] and fungicidal[3,7] activities as well as hydrophobicity,[3,8] sulfur can be employed in agriculture and construction industry. In addition, its electrochemical properties are useful in power engineering,[9–16] catalysis[17–22] and analytical chemistry.[23–25] There are numerous allotropic modifications of sulfur with wide range of applications.[3–8,26,27]

The main methods for nanosulfur preparation in spherical (α-S) or cylindrical (β-S) forms were fully described elsewhere.[3] However, it may be also obtained in the form of tubes, wires and rods. Note that the size varies from nanometers to microns for sulfur particles and preparation phases,[3] *viz.*, nanosulfur in its free form, suspensions in water and other solvents, specially prepared liquids and materials for stabilization of the nanoparticles and composites.

Monodisperse spherical sulfur particles were first prepared *via* acidification of sodium thiosulfate solutions.[27] This process [reactions (1)] was studied in detail.[29–31]

$$Na_2S_2O_3\cdot 5H_2O + H_2SO_4 = NaHSO_4 + NaHSO_3 + 5H_2O + S^0;$$
$$S + S \leftrightarrow S_2 + S \leftrightarrow S_3 + S \leftrightarrow \ldots \leftrightarrow S_{n-1} + S \leftrightarrow S_n \text{ (critical nucleus)} \quad (1)$$

Poly-*N*-vinylpyrrolidone (PVP)[32,33] and poly(ethylene glycol) (PEG)[34,35] are of practical importance, especially in medicine[36,37] and nanotechnology.[38–40] These polymers are used as components of drug delivery systems due to their solubility in water and many organic solvents, ability to form complexes with different compounds and high biocompatibility. In particular, it is a blood substitute component carrier of various drugs.[41]

In this study, the method has been elaborated to prepare ointments based on nanosulfur with antiseptic (antibacterial and antifungal) properties.

Synthesis of nanosulfur was carried out according to reactions (1) in acidic media.[†] Two methods of ointment preparation were developed: (1) radiation cross-linking of ointments obtained from acidified and non-acidified solutions, and (2) acidification of the solution mixture without further radiation.

The antibacterial and antifungal activities of prepared ointment materials with different concentrations of sodium thiosulfate and sulfuric acid were studied using diffusion into nutrient media based on agar-agar. Assays were proceeded with nutrient agar using

[†] The following reagents and materials were used in the experiments: $Na_2S_2O_3\cdot 5H_2O$ and H_2SO_4, standard titers for the preparation of solutions with known concentrations (usually of 0.2 N);[29] PVP with molecular weights M_W = 10 000 and M_W = 360 000 (Fluka Chemika), M_W = 44000–54 000 (BioChemica), and M_W = 1 000 000 (BASF Kollidon); PEG (M_W = = 6000, Fluka Chemika) and microbiological agar (Aldrich).

Sodium thiosulfate solution (0.4 N) was mixed with sulfuric acid solution (0.4 N) in a ratio of 1 : 1. To prevent aggregation of sulfur particles, PVP and PEG were used as stabilizing agents. The obtained yellow precipitate was filtered, dried at 70 °C and analyzed by X-ray diffraction (XRD) analysis on a Bruker D8 ADVANCE diffractometer (CuKα radiation).

Sulfur particle size distributions were measured by dynamic light scattering (DLS) method using Zetasizer Nano ZS90 (Malvern Company). PVP solution (0.5 ml), $Na_2S_2O_3$ solution (0.2 N, 0.1 ml), bidistilled water (0.3 ml) and H_2SO_4 (0.2 N, 0.1 ml) were sequentially added into the measuring cuvette (1 ml).

The kinetics of swelling was studied by the gravimetric method with accuracy of 0.0001 g. The equilibrium-swelling ratio for the polymeric hydrogels was determined as $\alpha = (m - m_0)/m_0$, where m is the mass of swollen hydrogel and m_0 is the dry weight of the gel.

Ointment materials were prepared using a polymeric matrix containing $Na_2S_2O_3\cdot 5H_2O$, PVP, PEG, agar, and H_2SO_4. To obtain a polymer composite ointment containing 5.24 wt% of $Na_2S_2O_3$ or 1.06 wt% of sulfur in a beaker, the solution of $Na_2S_2O_3\cdot 5H_2O$ (2.5 g), PVP (2.1 g) and PEG (0.45 g) in bidistilled water (10 ml) was prepared at room temperature, while in the another beaker, agar (0.3 g) was dissolved in water (12.5 ml) at 60–70 °C. Then both solutions were mixed with each other and H_2SO_4 (0.2 N, 2.5 ml, 0.0807 wt% or protons 0.00166 wt%) was added using a magnetic stir bar. Note that the sulfuric acid was always added last.

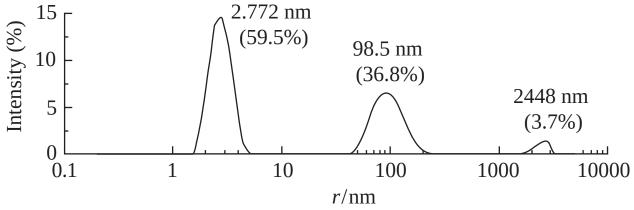


Figure 1 The typical particle size distribution of sulfur by DLS measurements (see Table S1, line 2, column 2, M_W = 10000, C = 1%, t = 0 min).

gram-positive bacteria *Staphylococcus aureus*, gram-negative bacteria *Escherichia coli*, and yeasts (yeast-like fungi) *Candida guilliermondii* as test organisms.[‡]

XRD study showed that the test sample was sulfur phase α-S, which is in agreement with previously reported[3] size of coherent-scattering regions at ~70 nm. The DLS measurement was carried out for ~80 min (Table S1, Online Supplementary Materials). The typical polymodal size distribution of nanosulfur particles is shown in Figure 1.

In addition, the kinetics of nanosulfur stabilization in PVP solutions was studied. Figure 1 demonstrates that the distribution function of the hydrodynamic diameter r of sulfur particles[3] has a polymodal form, which depends on measuring time, M_W and the concentration of PVP. In a number of cases, the number of peaks on the DLS curve reaches four and the size values range from ~1 nm to ~2500 nm. Stabilization of nanosulfur in the prepared samples occurs in 30 min after the start of measurement, leading to the disappearance of micrometer-sized particles. The nanosulfur size distribution was in the range ~180–400 nm and was presented by small fractions of ~3–60 nm. Note that the size of nanosulfur increases if M_W as well as concentration of PVP are raised, while no significant effect on nanosulfur size distribution was observed upon the addition of PEG to PVP.

Ointment samples were prepared according to the patent data,[42] where radiation-cross-linked polymeric composite was proposed to be used as a host material for medicine applications. In our study, the obtained hydrogel-polymer ointment samples with nanosulfur [reaction (1)] were homogeneous without impurities and defects. Selected ointment samples were exposed to radiation at 175 kGy for complete cross-linking, and the kinetics of their swelling was studied. Figure 2 shows that increase in $Na_2S_2O_3$ content in initial composite (clearly, the products of its decomposition such as $NaHSO_4$, $NaHSO_3$ and S^0) leads to increase in the swelling capacity of the prepared ointments. As a consequence, the number of cross-linking sites in the polymer matrix is reduced. Note that ointments are soluble in water if have not been exposed to radiation cross-linking. Since the ointments subjected to cross-linking did not show antimicrobial and antifungal activities, further studies were conducted with the samples of ointments that were not exposed to radiation.

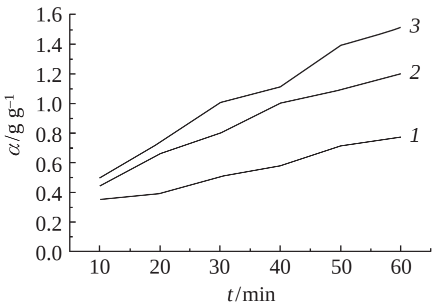
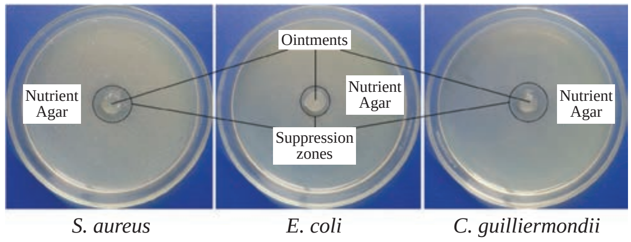


Figure 2 Kinetics of swelling for the hydrogel ointments (acidified and irradiated samples). The initial concentration of $Na_2S_2O_3$ (%): (*1*) 0.5, (*2*) 1, (*3*) 2.

Table 1 Antibacterial and antifungal activities of the ointment samples depending on the concentration of sodium thiosulfate and sulfuric acid.

Entry	c (wt%)		$c \times 10^2$ (wt%)		Diameter of the suppression zone of test organism growth[a]/mm		
	$Na_2S_2O_3$	S	H_2SO_4	$2H^+$	*S. aureus*	*E. coli*	*C. guilliermondii*
1	0.566	0.115	8.72	0.176	18 / bs	14 / bs	20 / fs
2	1.12	0.228	8.64	0.174	18 / bs	14 / bs	20 / fs
3	2.73	0.554	8.42	0.173	18 / bs	15 / bs	16 / fs
4	5.24	1.060	8.07	0.166	16 / bs	18 / bs	18 / fs
5	7.55	1.530	7.75	0.159	16 / bs	18 / bs	18 / fs
6	1.19	0.240	3.65	0.075	19 / bs	12 / bs	19 / fs
7	2.83	0.574	5.23	0.107	24 / bs	24 / bs	22 / fs
8	2.62	0.531	12.1	0.249	24 / bs	24 / bs	22 / fs

[a] bs is a bacteriostatic effect, fs is a fungistatic one.



S. aureus *E. coli* *C. guilliermondii*

Figure 3 Illustration for measuring the inhibition of microorganism growth by a composite polymer-gel ointment sample.

We have found (Table 1 and Figure 3) that the degree of growth inhibition for studied organisms depends on concentration of $Na_2S_2O_3$ in ointment samples. For instance, the samples with low concentration of sodium thiosulfate (1–2%) exhibited bacteriostatic and fungistatic activities, partly inhibiting the growth of the test organisms. The ointment samples with sodium thiosulfate concentration of 5% showed the highest inhibition of the growth for all test organisms and, unlike other examined samples, resulted in a transparent lysis zone. No changes of inhibition effect on the studied organisms were observed for the ointment samples containing up to 10–15% of $Na_2S_2O_3$ and up to 0.127% of H_2SO_4. Thus, the optimal combinations of sodium thiosulfate and sulfuric acid additives were $Na_2S_2O_3$ (5%), H_2SO_4 (0.047%) and $Na_2S_2O_3$ (5%), H_2SO_4 (0.127%). These samples demonstrated the highest level of growth inhibition of opportunistic microorganisms, *viz.*, 24 mm (*S. aureus* and *E. coli*) and 22 mm for yeast-like fungi *C. guilliermondii*.

In conclusion, composite polymeric ointments based on sulfur nanoparticles exhibited high antibacterial and antifungal activities, and potentially may be used in medicine.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.03.017.

[‡] The following composition of the nutrient medium (pH 7.4–7.6) was used: meat extract (0.15 wt%), yeast extract (0.15 wt%), peptone (0.5 wt%), NaCl (0.5 wt%), agar (20 wt%), and water (78.7 wt%). Incubation of test organisms (seeding rate ~10^5 cells or spores per 1 ml of given medium) with samples of ointments applied onto the surface of medium was carried out in the thermostat at 37 °C for 24 h for bacterial microorganisms (*S. aureus* and *E. coli*) or 48 h for yeasts (*C. guilliermondii*). The antibacterial and antifungal activities of samples with different initial concentrations of $Na_2S_2O_3 \cdot 5H_2O$ and H_2SO_4 (or nanosulfur) were studied by measuring the area of suppression of organism growth (in mm).

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