Synthesis and physico-chemical properties of poly(*N*-vinyl pyrrolidone)-based hydrogels with titania nanoparticles

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ABSTRACT

Poly(*N*-vinyl pyrrolidone) (PVP)-based hydrogels with titania nanoparticles (TN) were synthesized by the sol–gel method for the first time and were characterized in different states (native, freeze-dried, air-dried to constant weight and ground to powder, or swollen to constant weight in H₂O or D₂O) by various methods such as wide-angle and small-angle X-ray and neutron scattering, neutron spin-echo (NSE) spectroscopy, and scanning electron microscopy. The static (static polymer–polymer correlation length (mesh size), associates of cross-links and PVP microchains) and dynamic (polymer chain relaxation rate, hydrodynamic polymer–polymer correlation length) structural elements were determined. The incorporation of titania nanoparticles into PVP hydrogel slightly increases the size of structural inhomogeneities (an increase in the static and dynamic polymer–polymer correlation length, the formation of associates of cross-links and PVP chains). Titania nanoparticles have an impact on the microstructure of the composite hydrogel and form associates with sizes from 0.5 to 2 μm attached to PVP hydrogel pore walls. The PVP and TN/PVP hydrogels show a high degree of water swelling. Moreover, the presence of titania nanoparticles in TN/PVP increases the number of water adsorption cycles compared to PVP hydrogel. The high swelling degree, bacteria-resistant and antimicrobial properties against *Staphylococcus aureus* allow considering NT/PVP hydrogels for medical applications as wound coatings.

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Introduction

Hydrogels are cross-linked hydrophilic polymers capable of inhibiting large volumes of water, and yet are insoluble because of their network structures, crystalline regions, or entanglements. The hydrophilicity of these materials is due to the presence of hydrophilic functional groups such as $-\text{OH}$, $-\text{COOH}$, $-\text{COHN}_2$, $-\text{COHN}$, and $-\text{SO}_3\text{H}$ along the polymer chains [1]. Hydrogels are used as scaffolds for tissue engineering, temporary supports for cell growth, vehicles for drug delivery systems, and wound healing [2–6].

Wound dressings based on polymer hydrogels were first invented by Rosiak's group [7]. This hydrogel system was prepared by simultaneous cross-linking and radiation sterilization of a mixture of medical grade poly(*N*-vinyl pyrrolidone) (PVP), poly(ethylene glycol) (PEG), and agar polymers [8] and can be used as artificial cartilage replacement [9, 10].

Poly(*N*-vinyl pyrrolidone) ($\text{C}_6\text{H}_9\text{NO}$)_{*n*} has a hydrophilic amide carbonyl group $\text{N}-\text{C}=\text{O}$ and a hydrophobic polymer $\text{C}-\text{C}$ chain [11]. Due to its specific molecular structure, PVP is soluble in water and most organic solvents. It has an excellent chelating ability to be used as a chelating agent in the medicine and food industry [12]. The toxicity of organic compounds and their solubility and diffusion in body tissues increase with the decrease in molar weight [8]. The materials obtained by ionizing irradiation of PVP and PEG [8] did not present a toxic effect. Therefore, the *in vitro* and *in vivo* evaluations suggested that these biomaterials could be safely used in contact with the skin for wound dressing management in the form of advanced bandages or for drug immobilization as transdermal therapeutic systems. PVP-based hydrogels have excellent transparency, biocompatibility, swelling capacity, ability to disperse different active compounds and have been applied as dressings for the treatment of wounds such as burns and skin ulceration [13], drug delivery systems [14], in protein release [15], atopic dermatitis [16], and skin regeneration [17, 18].

Composite hydrogel wound dressings with antimicrobial activity and/or those serving as barriers to microbes have attracted considerable interest. Such dressings will help both to protect wounds from infections from the external environment (to prevent contamination) and eradicate the infection from the wound (absorb exudates, provide an ideal moisture balance at the wound surface, and kill bacteria or

inhibit their growth if the hydrogel exhibits bactericidal activity). The prevention of the further spread of pathogenic microorganisms is important not only for composite hydrogel dressings (wound bandages, contact lenses, artificial skin materials, and targeted drug delivery systems) but also for cosmetic and pharmaceutical applications. In this aspect, composite hydrogels based on PVP and functional titanium dioxide TiO_2 nanoparticles hold promise.

The aim of this work is to prepare and characterize new PVP-based composite hydrogels with nanosized titania particles. The fabrication of composite hydrogels based on PVP and functional TiO_2 nanoparticles with bactericidal properties [19] along with other useful properties (photocatalytic and adsorption activity, high chemical stability, nontoxicity, low cost) can be exploited to design new materials for medical applications. In most works on polymer composites with antimicrobial activity under UV irradiation, TiO_2 nanoparticles with anatase structure or a mixture of anatase and rutile (polypropylene/ TiO_2 composites with antimicrobial activity against microorganisms—*Escherichia coli* [20]; low-density polyethylene films with TiO_2 —against *Pseudomonas* spp. and *Rhodotorula mucilaginosa* [21]) are used.

Studies concerning hydrogels involving PVP and TiO_2 nanoparticles are scarce. Cao et al. [22] showed that TiO_2 particles in polyvinyl alcohol/PVP- TiO_2 hydrogel increase its antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli*. Archana et al. [23] reported the preparation of nanocomposite mixtures based on chitosan, PVP, and TiO_2 as wound dressing materials with high antimicrobial efficacy and good biocompatibility against NIH3T3 and L929 fibroblast cells. But, there are no data about the bacteria-resistant properties of such hydrogels. In the present study, we report new results of the evaluation of PVP-titania nanoparticles composite hydrogels. These hydrogels were prepared by sol-gel technology with nanosized titania with anatase structure (no literature data) and were evaluated as a bacteria-resistant material.

Materials and methods

Preparation

PVP-based hydrogels were prepared by the sol-gel method from PVP, tetraethoxysilane (TEOS), and

nanosized TiO_2 (TN, commercial Hombifine N, Sachtleben Chemie GmbH). A mixture of 10 wt% aqueous PVP solution, lactic acid (catalyst), TEOS (cross-linking agent), and polyethylene glycol (PEG-8, surfactant) in a TEOS:PEG:lactic acid ratio of 77.7:1.1:1 was stirred at room temperature ($\sim 23^\circ\text{C}$) for 30 min at a rate of 3000 rpm and then poured into a mold. The thickness of the mixtures in the mold was 4–6 mm. For the preparation of composite hydrogels, TiO_2 (commercial sample Hombifine N, Sachtleben Chemie GmbH, with nano-anatase structure with the average size of primary particles of 10–15 nm (some particles have a size of ≤ 5 nm) and their associates ~ 20 –80 nm) was added in amounts of 0.25, 0.50, and 1.00 wt% before the introduction of TEOS; these hybrid samples are, respectively, referred to as 0.25, 0.5, or 1.0TN/PVP. The synthesis conditions of hydrogels PVP and TN/PVP are the same. Pure PVP hydrogel is transparent, in contrast to the composite hydrogels TN/PVP, which have a white opaque appearance due to multiple light scattering by titania nanoparticles.

Wide-angle X-ray scattering (WAXS)

The following two types of PVP and TN/PVP hydrogels were investigated: native state (N) and a powder state. (The initial samples were dried in air at $\sim 23^\circ\text{C}$ to constant weight and ground in a porcelain mortar to a finely dispersed state) (DG) (Fig. 1.) X-ray diffraction (XRD) patterns were measured by the rotation method on a HZG-4 diffractometer (graphite monochromator); CuK_α radiation; and a step-scan mode. (The count time was 10 s per step, the step size was 0.02° , and the 2θ angle range was 2° to 50° .) The XRD patterns were processed and the parameters of the substructure were calculated

using the « Program for processing XRD patterns of nanoscale and amorphous substances and calculations of substructure characteristics » [24]. The average sizes of coherent regions (crystallites) of TN in the synthesized hydrogels were evaluated by the formula

$$D = K\lambda/\beta \cos \theta \quad (1)$$

for the 101 reflection at $2\theta \sim 25^\circ$, where $\lambda(\text{CuK}_\alpha) = 1.54051 \text{ \AA}$ is the wavelength, β is the integral peak width, and $K=0.9$ is the empirical coefficient. The standard deviation was $\pm 5\%$.

Figure 1 summarizes different types of samples and methods used for their characterization.

Small-angle X-ray scattering (SAXS)

Scattering intensities ($I(q)$) were measured at the DICS1 synchrotron beamline (National Research Centre « Kurchatov Institute », Moscow, Russia) [25] at $\lambda = 0.162 \text{ nm}$. For these experiments, air-dried gels were swollen in H_2O (SW) (Fig. 1). The samples of $\sim 2 \text{ mm}$ nominal thickness and $5 \times 5 \text{ cm}$ cross section were deposited on a Kapton foil perpendicular to the synchrotron beam. The X-ray spectra were recorded using a DECTRIS Pilatus3 1 M area detector. (The sample-to-detector distance was 500 mm, and the exposure time was 180 s.) The beam was collimated using a three-pinhole collimator system and was focused to a beam size of $0.4 \times 0.6 \text{ mm}$ at the sample position using a bent monochromator and a bent mirror. The angular scale was calibrated by processing the XRD pattern of polycrystalline silver behenate powder [26].

Two-dimensional X-ray scattering patterns were integrated and processed with the Fit2D software [27]. The scattering of the empty Kapton cell was subtracted from the scattering curve of the sample using the PRIMUS program [28] implemented in the ATSAS program package [29]. The experimental SAXS intensities ($I(q)$) were calculated as a function of the magnitude of the scattering vector

$$q = 4\pi \sin \theta / \lambda, \quad (2)$$

where 2θ is the scattering angle, and λ is the wavelength; the scattering angle range was $0.35 < q < 6.5 \text{ nm}^{-1}$. Then, the experimental SAXS curves were processed with the GNOM program [30] using the indirect Fourier transformation technique assuming a polydisperse spherical particle model.

Figure 1 Samples and methods of their characterization.

The maximum radius of the scattering particle ($R_{\max}$, nm) was determined from the functions of the volume particle size distribution

$$D_v(R) = \frac{4\pi}{3} R^2 N(R) \quad (3)$$

and the intensity

$$I(q) = I(0) \exp\left(-\frac{qR_g^2}{3}\right) \quad (4)$$

where R is the maximum radius of the sphere, $N(R)$ is the relative number of particles of this radius in the system, $I(0)$ is the scattering intensity at $2\theta = 0^\circ$, and R_g is the mean radius of gyration averaged over all particles taken with the corresponding weights (contributions) to the size distribution functions [31]. The standard deviation was 2–3%.

Small-angle neutron scattering (SANS)

Small-angle neutron scattering (SANS) data [32] were acquired on a D11 diffractometer at the Laue–Langevin Institute (Grenoble, France). For these experiments, gel disks were swollen in D₂O (SD) (Fig. 1). Samples of ~ 2 mm nominal thickness and 10 mm in diameter were placed in 1.5 mm path length sandwich-type cells. Three configurations were used, with a constant wavelength $\lambda = 0.50$ nm and sample-to-detector distances of 1.4, 8, and 39 m, with collimation at 5.5, 8, and 40.5 m, respectively, leading to a q range of 0.0016 – $0.53 \text{ \AA}^{-1}$, where q is the magnitude of the wavevector q ; θ is the scattering angle. The scattering data were reduced using the Lamp program [33] with a flat field, taking into account transmission and thickness and subtracting the background composed of a D₂O cell of the same thickness as the samples. The SANS data were acquired in 256×256 pixel mode. The absolute scale was obtained from the attenuated transmitted beam. The data were fitted with SASfit software [34].

Neutron spin-echo (NSE) measurements

NSE measurements were performed on an IN11 spectrometer equipped with an IN11A high-resolution setup at the Laue–Langevin Institute (Grenoble, France). For these experiments, gel films of 4 mm nominal thickness and 3×4 cm cross section were used. Prior to the measurements, the gel samples were dried and then reswollen in excess D₂O for at least 3 days at $22.0 \pm 0.1^\circ\text{C}$ (SD) (Fig. 1). The

swollen samples were placed in 4-mm-thick sandwich-type cells with quartz windows. The remaining space in the sample holder was filled with D₂O to exclude air and avoid deswelling. Measurements were performed at $22.0 \pm 0.1^\circ\text{C}$ in the transfer vector q range $0.042 \text{ \AA}^{-1} \leq q \leq 0.219 \text{ \AA}^{-1}$, where q is the wavevector, λ is the incident neutron wavelength ($\lambda = 0.6$ nm), and θ is the scattering angle. The Fourier time range was from 0.1 to 30 ns. The resolution functions of the instrument were determined for different experimental conditions using the elastic scattering of graphite. The NSE method directly measures the intermediate scattering function $I(q, \tau)$ as a function of q and the Fourier time τ , i.e., it directly yields the time dependence of the density–density autocorrelation function [35]. The resulting intermediate scattering functions were corrected for the D₂O background dynamics.

Scanning electron microscopy (SEM)

The morphology of PVP and 0.25TN/PVP hydrogels was studied using a JSM 7500F ultra-high-vacuum high-resolution field emission scanning electron microscope equipped with a cold autoemission cathode (JEOL, Japan). Prior to the measurements, two types of samples (native samples (N) and native samples air-dried with subsequent swelling in H₂O (SW)) were freeze-dried (L) (Fig. 1) [36]. Images were obtained using low-energy secondary electrons because this mode ensures the highest resolution (at an incident beam energy of 5 keV, the resolution was 1.5 nm); the accelerating voltage was 5 kV, the electron probe current was $\sim 5 \times 10^{-12}$ A, which was provided by a cold autoemission cathode with cold field emission.

Equilibrium swelling degree

The equilibrium swelling degree (ESD) of the samples was measured using air-dried 2-mm-thick gel disks of 9 mm in diameter. Once the swelling equilibrium in distilled water at $25.0 \pm 0.2^\circ\text{C}$ was reached, the ESD was determined as

$$\frac{m - m_0}{m_0} \times 100\%, \quad (5)$$

where m and m_0 are the weights of the swollen and dry samples, respectively.

Water adsorption–desorption

The fatigue resistance is one of the main criteria of hydrogel quality. We studied the dynamics of water adsorption–desorption of hydrogels dried to constant weight during three cycles. The procedure for water adsorption was identical to that used in studies of swelling of hydrogels in water (see the swelling kinetics). Each water adsorption cycle was followed by the water desorption cycle. Measurements of water desorption from PVP and 0.25TN/PVP hydrogels, which were characterized by the equilibrium swelling degree, were carried out in air at 20 ± 1 °C. Hydrogel samples were weighed at regular time intervals until the samples were completely dried. The degree of drying (desorption) (degree of deswelling) was calculated by the formula

$$DD = 100 - \frac{m_s - m}{m_s} \times 100\%, \quad (6)$$

where DD is the degree of desorption, %; m is the weight of PVP or 0.25TN/PVP hydrogel at a certain time during the water desorption, g; and m_s is the weight of the hydrogel sample swollen to constant weight, g. The relative weight difference for desorption kinetics was calculated as the relative initial weight of the hydrogel (100%) minus the relative equilibrium hydrogel weight (%).

Bacterial penetration test

To test the ability of bacteria to penetrate native PVP(N) and 0.25TN/PVP(N) hydrogels, we performed microbiological assays in two variants.

The first variant « agar-hydrogels-microorganisms » : PVP and 0.25TN/PVP hydrogels as 45 mm diameter $\times$ 3 mm thick disks were placed in Petri dishes filled with Mueller–Hinton agar. A culture of the microorganism *Staphylococcus aureus* ATCC 25923 (10^6 CFU mL $^{-1}$) was deposited on the hydrogel surface.

Second variant « agar-microorganisms-hydrogels » : PVP and 0.25TN/PVP hydrogels as 5- and 3-mm-thick disks 45 mm in diameter were placed in Petri dishes filled with Mueller–Hinton agar, which was pre-inoculated with a lawn of 2 mL of *Staphylococcus aureus* ATCC 25923 (10^6 CFU mL $^{-1}$).

In both cases, the Petri dishes containing the hydrogels were incubated at 37 °C overnight. After the incubation, the following washings were taken: in

the first case, the washing from the agar surface under the sample; in the second case, the washing from the hydrogel surface. The smears were placed in a nutrient broth and incubated at 37 °C overnight. Then, the growth of *Staphylococcus aureus* or its absence was detected in the test tubes.

Results

Powder X-ray diffraction

Figure 2 shows powder XRD patterns of initial PVP(I) and TN (Hombifine N) powders (Fig. 2a, b) and PVP and 0.25TN/PVP hydrogels in the native (N) and powder states (DG) (Fig. 2c, d).

A physical interpretation of the first and second diffuse peaks at $2\theta \sim 11^\circ$ (interplanar spacing $d = 7.9$ Å) and $2\theta \sim 22^\circ$ ($d = 4.05$ Å) in the powder XRD pattern of initial powder PVP(I) used for synthesis of PVP-based hydrogels (Fig. 2a) can be made taking into account the data on PVP published previously [37, 38]. Thus, the first peak of PVP is responsible for intermolecular interactions of C–C polymer chains, while the second peak is attributed to inter- and intramolecular interactions between the pyrrolidone (substituent) rings.

The powder XRD pattern of native PVP hydrogel (N) (Fig. 2c) shows an amorphous halo at $2\theta \sim 26.88^\circ$ ($d = 3.31$ Å) assigned to **free water** (it fills the spaces between the polymer chains and

Figure 2 Powder X-ray diffraction patterns of: **a** PVP(I) and **b** TN (Hombifine N) powders, **c** hydrogel in the native state PVP(N) and powder state PVP(DG), and **d** composite hydrogel in the native state 0.25TN/PVP(N) and powder state 0.25TN/PVP(DG).

pores), **bound water** (attached to hydrophilic functional groups N–C=O of the substituents via N–C=O...H–O...H hydrogen bonds), and **half-bound water** (in our view, this water is located in ordered regions of the polymer chain) and a diffuse peak at $2\theta = 40.46^\circ$ ($d = 2.227 \text{ \AA}$) belonging to **interstitial water** (it is not attached to a hydrogel network but is physically entrapped between polymer chains, that is, cluster water apparently associated with hydrophobic interactions) [37, 39, 40].

In the XRD pattern of PVP(DG) hydrogel, which was dried to constant weight and ground to powder (Fig. 2c), the first peak is split into peaks at $2\theta = 9.50^\circ$ ($d = 9.302 \text{ \AA}$) and $2\theta = 11.58^\circ$ ($d = 7.635 \text{ \AA}$) due to the presence of **half-bound water** (ordered PVP chains with different water content give rise to different interplanar spacings) and the broadened second peak at $2\theta = 20.64^\circ$ ($d = 4.299 \text{ \AA}$), which attests to the water that remained in the system, primarily **bound water**.

In the powder XRD pattern of native 0.25TN/PVP(N) composite hydrogel (Fig. 2d), the first peak ($2\theta = 10.43^\circ$, $d = 8.47 \text{ \AA}$) and the second peak ($2\theta = 21.34^\circ$, $d = 4.16 \text{ \AA}$) are identical to the corresponding peaks for the initial PVP(I) (Fig. 2a) with changed intensities: 100% and 63% for PVP(I) and 7% and 100% for native 0.25TN/PVP(N) composite hydrogel. Hence, the **free and bound water** content in 0.25TN/PVP(N) is lower than that in PVP(N) but is higher compared to PVP(I). The third diffuse peak assigned to **interstitial (cluster water)** (Fig. 2d) consists of two components at $2\theta = 37.74^\circ$ ($d = 2.382 \text{ \AA}$) and $2\theta = 42.26^\circ$ ($d = 2.137 \text{ \AA}$), i.e., it attests to the presence of different clusters. The narrow diffraction peak at $2\theta = 48.14^\circ$ ($d = 1.888 \text{ \AA}$) with $D = 70(3) \text{ \AA}$ is assigned to nanosized titania.

The powder XRD pattern of 0.25TN/PVP(DG) hydrogel (Fig. 2d) displays diffraction peaks assigned to the polymer and titania. The first diffuse peak of PVP (Fig. 2a) is split into two peaks ($2\theta = 9.60^\circ$, $d = 9.87 \text{ \AA}$ and $2\theta = 11.90^\circ$, $d = 7.43 \text{ \AA}$) (half-bound water), and the second peak of PVP is asymmetric with a center of gravity at $2\theta = 18.68^\circ$ ($d = 4.75 \text{ \AA}$). Three diffraction peaks at $2\theta = 25.24^\circ$ ($d = 3.525 \text{ \AA}$), $2\theta = 37.77^\circ$ ($d = 2.379 \text{ \AA}$), and $2\theta = 47.89^\circ$ ($d = 1.897 \text{ \AA}$) belong to nanosized titania with anatase structure (JCPDS No 89-4921) with an average crystallite size $D = 65(3) \text{ \AA}$ smaller compared to the initial Hombifine N ($D = 82(4) \text{ \AA}$).

According to the study [41], the powder XRD pattern of TiO_2 /PVP gels, which were prepared by hydrolysis and polycondensation of tetrabutyl titanate in a PVP acid solution and then annealed at 250°C , displays two amorphous halos at $2\theta \sim 25^\circ$ and $\sim 38^\circ$ belonging to anatase-phase TiO_2 and a peak in the angle range of 8° – 10° assigned to a coordination compound that was formed by the reaction between TiO_2 and PVP. The powder X-ray diffraction data are indicative of amorphization of nanosized anatase and the absence of its interaction with PVP in 0.25TN/PVP composite hydrogel.

Scanning electron microscopy

Figure 3 shows SEM images of cross sections of freeze-dried native PVP hydrogel (NL), which has a disordered structure.

Despite the fact that freeze-drying, according to the study [36], completely removes residual solvent from the sample, while leaving the structure of the material intact, no pores were observed in the SEM images of the hydrogels cross sections (Fig. 3a, b). It is associated with the conditions of particular freeze-drying (probably, the drying of the hydrogel is accompanied by its shrinkage, and the final structure is not completely identical to that of the initial native hydrogel) and (or) with the composition of the sample (primarily, with the water content). The storage of freeze-dried PVP hydrogel in a refrigerator at 11°C for one month led to the formation of spherical particles with an average size of 30–40 nm in the chip of the hydrogel (Fig. 3d).

The freeze-dried native sample 0.25TN/PVP(LN) has a smooth surface (Fig. 4a) with irregularly arranged TN with a size of 40–60 nm (Fig. 5a). On the contrary, freeze-dried water-swollen 0.25TN/PVP(LSW) has pores on the surface (Fig. 4d).

The cross sections of freeze-dried native 0.25TN/PVP(LN) (Fig. 4b) and water-swollen 0.25TN/PVP(LSW) (Fig. 4e, f) are characterized by the same pore size distribution (Fig. 5c, d). The pores in swollen 0.25TN/PVP(LSW) point in the same direction (Fig. 4e), i.e., water swelling lead to the ordering of the hydrogel structure. In the cross section of freeze-dried native 0.25TN/PVP hydrogel, titania nanoparticles form associates with sizes of 30–60 nm (the nanoparticle size in initial Hombifine N is 10–15 nm; some particles have a size of 5 nm and less) (Fig. 5b) located in 3–11 μm pores of PVP hydrogel (Fig. 5c).

Figure 3 SEM images of a cross section of **a** PVP(NL) hydrogel after freeze-drying and **b, c** after storage of freeze-dried PVP hydrogel for one month at 11 °C; **d** the particle size distribution for the SEM image **c**.

Figure 4 SEM images of **a** the surface and **b, c** the cross sections of freeze-dried native 0.25TN/PVP(NL) hydrogel and of **d** the surface and **e, f** the cross sections of freeze-dried 0.25TN/PVP(SWL) hydrogel swollen to constant weight.

Figure 5 Size distribution of TN particles **a** over the surface and **b** in the cross section of freeze-dried native 0.25TN/PVP hydrogel: distribution of micropores in **c** cross section of freeze-dried native

0.25TN/PVP hydrogel and **d** the same hydrogel water-swollen to constant weight.

In the cross section of freeze-dried water-swollen 0.25TN/PVP(LSW) hydrogel (Fig. 4f), TiO₂ nanoparticles form associates with sizes of 2–5 μm.

Differential scanning calorimetry (DSC)

The PVP(N) and 0.25TN/PVP(N) hydrogels contain three types of water according to DSC (Fig. 6, Table 1).

The 0.25TN/PVP(N) hydrogel contains less water of all types. It is consistent with the WAXS data. The presence of titania nanoparticles has an effect on the temperature of endothermic peaks.

Small-angle X-ray scattering

Figure 7 shows SAXS curves and the volume particle size distribution functions for TN powder (Hombifine N) and native PVP and TN/PVP hydrogels water-swollen after air-drying to constant weight.

The lack of linearity in the region $qR_g \leq 1.3$ for all samples (q is the final point in the Guinier region) is attributed to their polydispersity. The scattering profiles differ in low scattering vector ranges ($q < 0.4$ nm⁻¹). Since the scattering power of titania

particles is higher than that of PVP polymer, the scattering intensity of TN/PVP increases at $q = 0$ (I_0).

The TN sample (commercial Hombifine N) is characterized by a broad size distribution of structural inhomogeneities (particles) up to $R_{\max} = 30$ nm with a maximum at $R_1 = 6$ nm (consistent with the crystallite sizes determined by WAXS) (Table 2, Fig. 7f) and the presence of a flat plateau in the range of 10–20 nm (region R_2) (consistent with the sizes in Fig. 5a, b). Some differences between the theoretical curves and experimental data for TN in the q range 1.5–2.0 nm⁻¹ (Fig. 7) may be attributed to a nonuniform density of TN particles and the possible deviation of these particles from ideal spherical symmetry.

The addition of titania nanoparticles to PVP hydrogel leads to a change in the small-angle scattering pattern. Thus, PVP hydrogel has $R_{\max} = 15$ nm, while the addition of TN increases $R_{\max}$ to 20 nm (Fig. 7b, d). The SAXS patterns of PVP and 0.25TN/PVP hydrogels show two pronounced peaks in the region of scattering inhomogeneities with sizes $R_1 = 1.2$ nm, $R_2 = 4.8$ nm for PVP and $R_1 = 1.1$ nm, $R_2 = 5.8$ nm for TN/PVP (Table 2, Fig. 7b, d), i.e., the presence of TN in TN/PVP has an effect on R_2 , resulting in its increase.

Figure 6 DSC curves for **a** PVP(N) **a** and **b** 0.25TN/PVP(N).

Table 1 Assignment of the peaks to possible types of water in native PVP(N) and 0.25TN/PVP(N) hydrogels

PVP		0.25TN/PVP		Peak assignment
T (°C)	H (J/g)	T (°C)	H (J/g)	
9.5	− 231.1	10.7	− 284.8	Cluster water
88.3	− 676.9	80.1	− 867.9	Bound water
119.5	− 1411.6	107.6	− 1625.4	Free water
434.5	105.4	427.5	91.7	Polymer decomposition

According to the study [31], this SAXS experiment provides information on scattering inhomogeneities with sizes of $\sim 2\text{--}40$ nm, i.e., the sizes of submicron particles are beyond the scope of SAXS.

Table 2 Sizes of structural inhomogeneities (SAXS data)

Sample	$R_{\max}$ (nm)	R_1 (nm)	R_2 (nm)	R_g (nm)
PVP	15.00	1.20	4.80	7.11
0.25TN/PVP	20.00	1.10	5.80	11.00
NA	30.00	6.00	10.00–20.00	16.47

Small-angle neutron scattering

The nanostructure of PVP-based hydrogels was studied by small-angle neutron scattering. The SANS curves for PVP, 0.25TN/PVP, 0.50TN/PVP, and 1.0TN/PVP samples are slightly different (Fig. 8).

Figure 7 **a** SAXS curves for native PVP and 0.25TN/PVP hydrogels water-swollen after air-drying to constant weight and TN powder (1—the theoretical scattering curve for TN; 2—the experimental scattering curve for TN; 3—the experimental

scattering curves for TN/PVP and PVP; 4—the theoretical scattering curves for TN/PVP and PVP); **b** the particle size distribution functions for PVP, 0.25TN/PVP, and TN.

Figure 8 **a** SANS curves for PVP, 0.25TN/PVP, 0.50TN/PVP, and 1.0TN/PVP (empty polygons). The curves are described by the modified Ornstein–Zernike equation (black curves) in the range $0.0069 \text{ Å}^{-1} \leq q \leq 0.1317 \text{ Å}^{-1}$. The q range studied by neutron

spin-echo spectroscopy is shown in gray; **b** the plot of the correlation length ξ and ξ_H (Å) versus the TN concentration; **c** the Kratky plot.

The region $0.0069 \text{ Å}^{-1} \leq q \leq 0.1317 \text{ Å}^{-1}$ was described by the modified Ornstein–Zernike (OZ) equation

$$I(q) = \frac{I_{OZ}}{(1 + (q\xi)^2)^{\frac{p}{2}}} \quad (7)$$

where I_{OZ} is the scattering intensity at $q = 0.0069 \text{ Å}^{-1}$, ξ is the static polymer–polymer correlation length (mesh size or the distance between two cross-links) [42], $2p$ is the fractal dimension of polymer coils consisting of PVP chains. Equation 7 characterizes polymer/solvent interactions. The neutron scattering length density of the PVP matrix differs from that of the D₂O solvent (swelling medium) (Table 3), giving rise to a strong scattering peak.

Table 3 Neutron scattering length density for components of hydrogels

Component	SLD (Å ²)
PVP (C ₆ H ₉ NO) _n	0.939×10^{-6}
TiO ₂	2.628×10^{-6}
D ₂ O	6.335×10^{-6}

The introduction of titania nanoparticles into PVP hydrogels changes the scattering in the range $0.0018 \text{ Å}^{-1} \leq q \leq 0.0068 \text{ Å}^{-1}$ (Fig. 8a). The hydrogels are characterized by the power-law slope of the scattering curves $I(q) \sim q^{-\alpha}$, where α is a non-integer value of the exponent. For PVP hydrogel,

Table 4 Parameters of samples determined from SANS (ζ , α) and NSE spectroscopy (D_{diff} , ζ_H)

Sample	α	ζ (Å)	Size of the object from the Kratky plot (nm)	$D_{\text{diff}} \times 10^{11}$ (m ² /s)	ζ_H (Å)
PVP	0.84 ± 0.04	34.98 ± 0.04	20.9	6.63 ± 0.50	29.78 ± 0.50
0.25TN/PVP	2.58 ± 0.07	38.23 ± 0.05	23.2	7.15 ± 0.11	27.61 ± 0.01
0.50TN/PVP	2.90 ± 0.06	43.40 ± 0.02	23.2	— ^a	—
1.0TN/PVP	3.35 ± 0.04	46.14 ± 0.01	27.3	5.55 ± 0.01	35.57 ± 0.01

^aNSE spectroscopy was not performed

$\alpha = 0.84 \pm 0.04$ (Table 4), i.e., the scattering object is a mass fractal and has a globular shape [42]. An increase in the TN concentration in TN/PVP hydrogels leads to an increase in α , which is indicative of the presence of diffusion-limited aggregates [43] of titania with a size of 2–5 μm in the gel structure.

Figure 8b and Table 4 present changes in the polymer/polymer correlation length ζ (Å) versus the TN concentration. The ζ increases with the increase in TN content in the system. All samples are characterized by the exponent $p \sim 5/3$ in Eq. 7, which is in agreement with the theory of interactions between polymer chains in good solvent (for fully swollen coils) [44].

The distances between single cross-links (mesh size) vary from 35 to 46 Å (Fig. 8b), i.e., TN nanoparticles even with the minimum sizes of ~ 5 nm cannot be present in the hydrogel network.

The Kratky plot $I(q) \times q^2$ versus q (Fig. 8c) has a peak at $q \sim 0.024 \text{ Å}^{-1}$ followed by the asymptote for each hydrogel sample, which attests to the presence of partially folded (sphere-random coil) structural domains in the gel [37] with sizes from ~ 200 to $\sim 270 \text{ Å}$ (Table 4). The position of this peak is inversely proportional to the size of globular objects [33, 39]. An increase in the TN concentration in hydrogels leads to an increase in the size of the objects with local ordering (Table 4). At the boundary between two q regions ($0.0018 \text{ Å}^{-1} \leq q \leq 0.0068 \text{ Å}^{-1}$ and $0.0069 \text{ Å}^{-1} \leq q \leq 0.1317 \text{ Å}^{-1}$), the characteristic length between structural domains with local ordering $L = \frac{2\pi}{q^*} \sim 92 \text{ nm}$ was determined for all samples. The structural domains (Table 4), and the sizes of titania nanoparticles (10–15 nm) suggest that the domains are nanosized associates consisting of cross-links and PVP microchains.

Neutron spin-echo spectroscopy

The dynamic structure of PVP and TN/PVP hydrogels was studied by NSE spectroscopy [35]. The curves $I(q, t)$ for PVP and TN/PVP hydrogels normalized to the signal ($I(q, 0)$) for completely elastic scattering are shown in Fig. 9 for $q = 0.042, 0.110, 0.137, 0.165$, and 0.192 Å^{-1} .

The curves $I(q, \tau)/I(q, 0)$ can be described by the function

$$\frac{I(q, \tau)}{I(q, 0)} \propto \exp(-\Gamma\tau), \quad (8)$$

where $\Gamma = 1/\tau$ is the relaxation rate, τ is the relaxation time or the decay time of the normalized intermediate scattering function, and β is the parameter characterizing diffusion in the system (equal to unity for collective diffusion) [45].

In a low q range (0.042 – 0.137 Å^{-1}), the Fourier time is too short to observe complete decay of the function $I(q, \tau)/I(q, 0)$, but the functions fall to zero at $q = 0.192 \text{ Å}^{-1}$ (Fig. 9). For the PVP, 0.25TN/PVP, and 1.0TN/PVP gels, the scattering functions decay to zero in the infinite time limit, which is indicative of pseudo-ergodic behavior, i.e., there are no frozen structural inhomogeneities in the system [46, 47]. The hydrogels contain inhomogeneities according to SANS data, but SANS and NSE spectroscopy operate in different q ranges.

The measured relaxation rates ($\Gamma = 1/\tau$) are proportional to q^2 (Fig. 10), which is characteristic of diffusion motion. The diffusion coefficient (D_{diff}) can be obtained from the equation

$$\Gamma = D_{\text{diff}} \cdot q^2 \quad (9)$$

The hydrodynamic correlation length (ζ_H) can be determined from the Stokes–Einstein equation

$$D_{\text{diff}} = \frac{k_B T}{6\pi\eta\zeta_H}, \quad (10)$$

Figure 9 Experimental scattering functions with the corresponding exponential approximations for **a** pure PVP hydrogel, **b** 0.25TN/PVP and **c** 1.0TN/PVP composite hydrogels measured at 22 °C.

Figure 10 Plot of the relaxation rate (Γ) versus q^2 for PVP, 0.25TN/PVP, and 1.0TN/PVP hydrogels. The line represents the approximation.

where k_B is the Boltzmann constant, T is the absolute temperature (K), and η is the viscosity of the medium ($\eta_{D_2O, 22^\circ C} = 1.175 \times 10^{-3} \text{Ns/m}^2$; the interpolation of the data reported in [48]) (Table 4). The ζ_H value for pure PVP hydrogel is smaller compared to 0.25TN/PVP and 1.0TN/PVP composite hydrogels.

Titanium dioxide nanoparticles at concentrations of 0.25 and 1.00 wt% have only a slight effect on the overall motion of polymer chains in PVP-based hydrogels. Therefore, titania nanoparticles insignificantly decrease the diffusion coefficient and increase

the ζ_H value compared to pure PVP gel. Table 5 presents static and dynamic characteristics of the hydrogels under study.

Swelling kinetics

PVP and 0.25TN/PVP hydrogels are characterized by a high swelling degree (ESD, %) in water (Fig. 11, Table 5), but the introduction of titania nanoparticles in PVP leads to a $\sim 15\%$ decrease in the water swelling degree of hydrogels compared to the PVP.

During the swelling of the dried composite hydrogel, titania was not washed off from the PVP microstructure, which was monitored by spectrophotometry based on the color of the solution and by the absence of a precipitate.

The swelling of PVP(SW) and 0.25TN/PVP(SW) hydrogels follows second-order kinetics:

$$\frac{dSD}{dt} = K(ESD - SD)^2, \quad (11)$$

where ESD is the equilibrium swelling degree (%) and SD is the swelling degree (%) at a certain time t . The experimental data in the $t/SD-t$ coordinates are described by a linear dependence

$$\frac{t}{SD} = \frac{1}{K \cdot ESD} + \frac{t}{ESD} \quad (12)$$

from which the swelling rate constant (K , $\text{g} \times \text{g}^{-1} \times \text{min}^{-1}$) was evaluated (Table 5).

Table 5 Characteristics of hydrogels

Characteristics	Method	State of hydrogels	PVP	0.25TN/PVP	0.50TN/PVP	1.0TN/PVP
<i>Elements of static structure</i>						
Pore size (μm)	SEM	Freeze-drying of native gel	— ^a	3–11	— ^b	
		Freeze-drying of swollen gel		7–13		
Fractal dimension	SANS	Swelling in D_2O	0.84 ± 0.04	2.58 ± 0.07	2.90 ± 0.06	3.35 ± 0.04
ξ ($\text{\AA}$)			34.98 ± 0.04	38.23 ± 0.05	43.40 ± 0.02	46.14 ± 0.01
Size of the object from the Kratky plot (nm)			20.9	23.2	23.2	27.3
Equilibrium swelling degree (ESD) (%)	First cycle	Swelling kinetics in H_2O	3757	3530	— ^b	
	Second cycle		11020	7052		
	Third cycle		— ^c	11108		
<i>Elements of dynamics</i>						
ξ_H ($\text{\AA}$)	NSE	Swelling in D_2O	29.78 ± 0.50	27.61 ± 0.01	— ^b	35.57 ± 0.01
$D_{\text{diff}} \times 10^{11}$ (m^2/s)			6.63 ± 0.50	7.15 ± 0.11		5.55 ± 0.01

^aPores were not detected; ^bnot studied; ^cthe third cycle for PVP hydrogels is absent

Figure 11 Swelling curves for PVP(SW) and 0.25TN/PVP(SW) hydrogels.

Water adsorption–desorption

PVP hydrogel is stable in two water adsorption–desorption cycles (Fig. 12a, c); 0.25TN/PVP hydrogel is stable in three water adsorption cycles and two water desorption cycles. Then, both hydrogels degrade (Fig. 12b, d), which is evidence that the presence of titania nanoparticles in 0.25TN/PVP increases the operating life of hydrogel by one more cycle of water adsorption.

As mentioned above, the water adsorption for PVP and 0.25TN/PVP hydrogels during the first cycle follows second-order kinetics. Table 6 presents the

swelling rate constants (K), the equilibrium swelling degrees (ESD, %), ranges of applicability of the second-order kinetic model (P), and correlation coefficients (R) for the first cycle. The water adsorption kinetics during the second cycle for PVP and 0.25TN/PVP hydrogels does not obey the second-order model. Thus, the experimental data in the $t/\text{SD}-t$ coordinates are not described by a linear dependence.

We attempted to describe the corresponding data by the first-order kinetics. The swelling kinetics can be described by the first-order kinetic reaction and the following equation can be applied:

$$\ln \frac{\text{ESD}}{\text{ESD} - \text{SD}} = Kt, \quad (13)$$

where ESD is the equilibrium swelling degree (%), SD is the swelling degree (%) at a certain time t , and K is the swelling rate constant ($\text{g} \times \text{g}^{-1} \times \text{min}^{-1}$).

The plots of $\ln \frac{\text{ESD}}{\text{ESD} - \text{SD}}$ versus the time (t) give straight lines [49]. The plots of $\ln \frac{\text{ESD}}{\text{ESD} - \text{SD}}$ as a function of time (t) give straight lines only at the beginning of the swelling process for a limited swelling extent, which is the range of applicability (P). The changes in P for the first-order kinetics, the corresponding correlation coefficients (R), and the swelling rate constants (K) calculated from the slopes of the curves for PVP and 0.25TN/PVP hydrogels in two cycles are given in Table 6.

The dependence of $\frac{t}{\text{SD}}$ as a function of t gives straight lines in different stages of the swelling

Figure 12 Adsorption curves for **a** PVP and **b** 0.25TN/PVP hydrogels and desorption curves for **c** PVP and **d** 0.25TN/PVP hydrogels.

Table 6 Ranges of applicability (P), swelling rate constants (K), equilibrium swelling degrees (W_{∞}), and correlation coefficients (R) for different orders of swelling kinetics for PVP and 0.25TN/PVP hydrogels

Adsorption cycles	Sample	Order of kinetics	Swelling rate constant K ($\text{g} \times \text{g}^{-1} \times \text{min}^{-1}$)	P (%)	R	Equilibrium swelling degree (ESD) (%)
First cycle	PVP	2	3.13×10^{-7}	100	0.9964	3757
	0.25TN/PVP	2	3.83×10^{-7}	100	0.9977	3530
Second cycle	PVP	1	1.15×10^{-3}	0–18	0.9793	11020
		1	1.18×10^{-3}	19–59	0.9801	
		1	2.15×10^{-4}	60–100	0.9866	
	0.25TN/PVP	1	7.46×10^{-4}	0–24	0.8883	7052
		1	1.69×10^{-4}	25–82	0.9873	
		1	4.70×10^{-4}	83–100	0.9562	
Third cycle	PVP	—	—	—	—	—
	0.25TN/PVP	1	23.5×10^{-4}	0–15	0.8779	11108
		1	2.83×10^{-4}	16–82	0.9889	
		1	22.2×10^{-4}	83–100	0.8883	

process. Evidently, the kinetics of the second water adsorption cycle is more complex and can be described by the first-order kinetic model with different rate constants of water adsorption (swelling). Table 6 gives the ranges of applicability of the second-order kinetic equations and the rates constants. After the second adsorption cycle, PVP hydrogel has a higher equilibrium swelling degree compared to the first cycle (Fig. 12a, Table 6), a longer time being required to reach the equilibrium swelling degree in

the second adsorption cycle (~ 219 h). After the first water adsorption (swelling) cycle, the equilibrium swelling degree for PVP hydrogel was 3757%; after the second cycle, 11020% (Fig. 12a, b).

An increase in the number of water adsorption cycles for 0.25TN/PVP hydrogel results in an increase in the equilibrium swelling degree (Fig. 12b, Table 6): 3530% for the first cycle, 7052% for the second cycle, and 11108% for the third cycle. During

the third water adsorption cycle, 0.25TN/PVP hydrogel degrades in ~ 150 h.

During the second water desorption cycle, the drying of PVP hydrogel at room temperature occurs faster than in the first cycle (Fig. 12c) because the water content in the latter was ~ 3 times higher (Fig. 12a). The maximum possible three-dimensional hydrogel network expansion was achieved due to an increase in the pore size as a result of a decrease in its rigidity. Apparently, there are changes in the polymer chain relaxation, which makes a certain contribution to the overall water adsorption kinetics, thereby resulting in the faster water desorption. It worth noting that during the first and second water desorption cycles, PVP hydrogels were dried to a smaller final weight compared to the weight of the initial gels (m_0) (Table 6) and during different times (~ 146 h for the first cycle and ~ 47 h for the second cycle). This is also associated with the changes in the polymer chain relaxation in the hydrogel. After the second water desorption cycle, PVP hydrogel completely degraded.

Similar behavior was observed for 0.25TN/PVP hydrogel (Fig. 12d). Thus, the final weight of the dried hydrogel was smaller than that of the initial gels (Table 6), and the drying was achieved during different times (~ 173 h for the first cycle and ~ 47 h for the second cycle). The curve for the first water desorption cycle has a complex shape (Fig. 12d), which is indicative of the uneven release of water with time.

Bacterial penetration test

The first variant « agar-hydrogels-microorganisms » . After the completion of the incubation period, the thickness of PVP and 0.25TN/PVP hydrogels decreased from 5 to ~ 3 mm due to the release of water from the hydrogels at 37 °C. During that time, the culture of the microorganism *Staphylococcus aureus* deposited on top of PVP and 0.25TN/PVP hydrogels did not diffuse through their full depth, which is evidence that the hydrogels adsorbed the microorganism. The microorganism penetration depth into hydrogels cannot be visually evaluated.

In the next stage, we performed the microbiological assay for the same hydrogels but with the smaller thickness (3 mm). The 3 mm thickness of hydrogels proved to be inefficient for using samples as wound dressings. Thus, the culture of the microorganism

deposited on top of the hydrogels diffused through their full depth, and the growth of bacteria was observed under hydrogels.

The second variant « agar-microorganisms-hydrogels » proved to be more efficient. The microorganism did not penetrate through 3-mm-thick hydrogels. (Bacterial growth was not observed on the hydrogel surface.) There is an inhibition zone of microorganism growth with a thickness of 2–3 mm in 0.25TN/PVP hydrogel. Apparently, hydrogels exhibit **antimicrobial properties**, although the inhibition zone of *Staphylococcus aureus* growth has not been observed previously for the initial components of PVP and TN powders and also for PVP and 0.25TN/PVP hydrogels with a thickness of 5 mm. The **antimicrobial properties** were evaluated by the phenomenon of the growth delay of microorganisms around the disks; the diameter of growth delay of microbes around the disks was determined using a ruler including the diameter of the disk itself [50]. Microbiological investigations were performed in a second class microbiological protection box equipped with an UV lamp and with a laminar air flow.

Conclusions

New composite hydrogels in the PVP–titania nanoparticles (TN) system were studied by a combination of different methods, which revealed the influence of titania nanoparticles on the static structure and dynamics of hydrogels. The content of all types of water (free, bound, half-bound, and interstitial) in TN/PVP was found to decrease and the size of structural inhomogeneities was shown to increase compared to PVP. The polymer/polymer correlation length and the fractal dimension increase with the increase in concentration of titania nanoparticles in gels. The introduction of titania nanoparticles in PVP leads to a decrease in the water swelling degree of hydrogels air-dried to constant weight compared to the corresponding PVP; however, it leads to an increase in the operating life of hydrogel by one water adsorption cycle. The presence of titania nanoparticles in hydrogel imparts bacteria-resistant properties to the hydrogel (prevent the penetration of bacteria) and antimicrobial properties (the presence of the 2–3 mm inhibition zone) against *Staphylococcus aureus*, which can be used for the development of wound dressing materials.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest regarding the publication of this article.

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