Preparation and characterization of stable water soluble hybrid nanostructures of hydrophobic compounds by encapsulation into nanoparticles of amphiphilic N-vinylpyrrolidone copolymers of new generation

S V Kurmaz¹, D V Konev¹, V D Sen¹, V A Kurmaz¹, * and A V Kulikov¹, ²

¹Institute of Problems of Chemical Physics, Russian Academy of Sciences, 1 prosp. akad. Semenova, 142432 Chernogolovka, Moscow Region, Russian Federation.
²Lomonosov Moscow State University, Department of Fundamental Physical and Chemical Engineering, 1 Leninskiie Gory, 119991 Moscow, Russian Federation

*E-mail: kurmaz@icp.ac.ru

Abstract. The conditions for obtaining stable aqueous solutions of prospective pharmaceutical: a lipophilic aminonitroxyl platinum complex, namely, e-amine-d-(4-amino-2,2,6,6-tetramethylpiperidine 1-oxyl)-a,fbis(octanoato)-b,c-dichloroplatinum(IV) (PNC), and a dye zinc tetraphenylporphyrinate (ZnTPP) by means of their solubilization with polymer particles of N-vinylpyrrolidone with dimethacrylate. Aqueous solutions of PNC and ZnTPP encapsulated into polymer particles were investigated by dynamic light scattering, and the temperature dependence of nanostructure sizes was studied. According to transmission electron microscopy, the hybrid nanostructures are core—shell particles, in which the Pt⁴⁺ complex forms small clusters (~4 nm). It was established by ESR and voltammetric measurements that the free radical fragment of the aminonitroxyl Pt⁴⁺ complex kept its mobility and the same ESR and redox characteristics as the 4-acetylamino-2,2,6,6-tetramethylpiperidine 1-oxyl radical. The obtained results indicate that biocompatible copolymers of N-vinylpyrrolidone are of interests as carriers and delivery tools for ZnTPP and organic Pt⁴⁺ complexes. Hybrid structures of given dimensions and properties can be created on their basis necessary for biomedical applications.

1. Introduction
Poor solubility of many organic and inorganic compounds in aqueous media produces many problems in their practical use and scientific investigations. In part, efficiency of many pharmaceuticals increases sufficiently at lipoficity growth. However, their water solubility is decreased considerably in the same time that may retard seriously their targeting delivery. Meanwhile, up to 70% of the synthesized active pharmaceutical ingredients are sparingly soluble in water [1]. Many approaches can be used to solve this problem, partially, chemical modification (e.g., covalent grafting of hydrophilic groups to a substrate, coordination / coordinating binding) or encapsulation in water-soluble matrix, partially polymer one [2-9]. This immobilization is important for practical biomedical applications as a kind of target delivery of lipophilic drugs into a living cell.

Synthetic amphiphilic polymers with a complex architecture can be promising objects for these purposes. However, the difficulty of synthesizing dendrimers and highly branched polymers with a regular structure prevents their widespread use for these purposes [10]. Therefore, polymer nanostructure materials based on less regular amphiphilic copolymers with a branched structure were developed. They are characterized by rich architectural diversity and a wide range of physicochemical properties.

These materials include amphiphilic copolymers of N-vinylpyrrolidone with triethylene glycol dimethacrylate (VP-TEGDM), synthesized by radical copolymerization in toluene [11]. The advantages of these copolymers include the simplicity of their preparation in combination with wide
possibilities to control their composition, molecular weight, content of branches, dimensions of nanoparticles, as well as their low cytotoxicity for cells. These copolymers have proven themselves as potential agents for the delivery of various hydrophobic compounds of pharmaceutical activity, namely, fullerene $C_{60}$ [12-14], and also have been tested as NO-carrying systems of binuclear iron tetrarnitrosyl complexes with antitumor activity [15].

Interest toward branched VP-copolymers is due to modern advances in the use of linear polymers consisting of a hydrophilic polyvinylpyrrolidone (PVP) fragment of various molecular weights and a hydrophobic alkyl fragment of various lengths as carriers of hydrophobic biologically active (antitumor) substances [16, 17]. They exhibited low toxicity and high safety in vitro and in vivo conditions, and also had the ability to efficiently deliver the active agent into the cell and increase the bioavailability of hydrophobic drugs.

In this connection, the goal of the study is to obtain water-soluble forms of $e$-amine-$d$-(4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl)-$a,f$-bis(octanoato)-$b,c$-dichloroplatinum(IV) (PNC, 1) of antitumor activity, and 5, 10, 15, 20-Tetraphenyl-21$H,23H$, porphine zinc (ZnTPP, 3) as a prospective diagnostics remedy based on VP-TEGDM copolymers and their characterization. PNC choose to study was determined with its efficacy against cisplatin-resistant tumor cell lines in vitro and in vivo [18]. The stable radical 4-acetylamino-2,2,6,6-tetramethylpiperidine 1-oxyl (2) was used for a comparative electrochemical and ESR identification and study of the radical fragment with a free valence in PNC. Metalloporphyrins are of interest for various radiological and magnetic resonance diagnostic methods due to their high optical absorption and fluorescence in red area of spectrum, relatively high quantum yields of the triplet state, and fluorescence, along with the paramagnetism [19, 20, 21]. Biomedical application of water-insoluble ZnTPP is seriously limited, and to increase it is an important task. Figure 1 presents chemical structures of 1-3.

![Figure 1. Chemical structures of 1-3.](image)

2. Materials and Methods

2.1 Materials, reagents and preparation of hybrid nanostructures

The copolymers VP-TEGDM were prepared via radical copolymerization [19] in toluene at a molar ratio of the reagents, VP : TEGDM, of 100 : 5, initiated by 2,2'-azo-bis-isobutyronitrile. F1 and F2 were fractions of VP-TEGDM copolymer, and F3 was non-fractionated copolymer. After the polymerization of active dimethacrylates, a polymer structure is formed containing side double bonds, to which the growing PVP chains are predominantly added. As a result, a 3D-structure is formed with a core consisting of methacrylate fragments and a shell formed by polymer chains of VP units. F1 and F2 differing in composition and ratio of VP and TEGDM units: copolymer F1 consists mainly of VP units, while F2 contains four times as many TEGDM units. NMR data evidenced a difference in monomer composition of copolymers F1 and F2 (Figure 2a). The absolute average molecular mass $M_w$ of copolymer F2 enriched with TEGDM (196.0 kDa) was sufficiently higher with respect to F1 (26.0 kDa) due to a globular nature of its branched macromolecules, and for F3 $M_w = 56.4$ kDa.

The compound PNC ($M = 740.68$) appears as yellow crystals, m.p. 169—170 °C (decomp.) (from an ethyl acetate—hexane mixture). The complex structure is consistent with the results of elemental analysis, UV, IR spectroscopy, ESR, and electrospray ionization mass spectrometry [18].

The aqueous solutions were prepared based on bidistillate, DMSO (Lab-Scan, Poland) was purified by freezing, propan-2-ol ($i$-PrOH) (reagent grade Khimmed, Russia) was distilled. MeCN (Lab-
Scan, Poland), components of buffer solutions (reagent grade Khimmed, Russia), TBAPF$_6$ and radical 2 (all from Aldrich, USA) were used without additional purification. The water content in DMSO (less than 0.05%) was controlled by IR spectroscopy according to the previously described procedure [22].

Encapsulation of PNC into polymer particles was carried out according to the following procedure. Solutions of F1 and F2 in $i$-PrOH (3.5 and 3.7 mg ml$^{-1}$, respectively) and of the complex in DMSO (8.2 mg mL$^{-1}$) were prepared. Various volumes of the Pt$^{IV}$ complex solution were added dropwise to the alcohol solution of the copolymer (4 ml) with continuous magnetic stirring. Calculating on the copolymer, solution of F1 contained 2, 3, 4, 5, 9, and 18 wt.% of Pt$^{IV}$ complex, and in the solution of copolymer F2 these values were equal to 2, 3, 4, and 18 wt.% respectively. Organic solvents were then removed in air and in vacuo. An aqueous phosphate buffer solutions (PBS) with pH 6.8—7.0 (8 ml, 137 mmol l$^{-1}$ of NaCl, 2.68 mmol l$^{-1}$ of KCl, 4.29 mmol l$^{-1}$ of Na$_2$HPO$_4$, 1.47 mmol l$^{-1}$ of KH$_2$PO$_4$) was added to the dry residues to obtain solutions of encapsulated into polymer particles complexes PNC$_n$F1 (the complex content $n$ = 2—5, 9, 18%) and PNC$_n$F2 ($n$ = 2—4, 18%). Solutions of PNC$_n$F1 were slightly opalescent and had a bluish tint typical of micellar solutions and good stability, if $n$ = 2 or 3 but where $n$ = 4, 9, and 18 they were opalescent noticeably.

Hybrid macromolecular structures of the ZnTPPF3 were prepared using solutions of copolymer F3 with different concentrations (from 0.007 to 1 mg/ml) in $i$-PrOH and a solution of ZnTPP in freshly distilled toluene (0.07 mg/ml). The content of ZnTPP per the copolymer varied from 25 to 0.19%, and the next stages of the procedure were like for PNC$_n$F structures. Optical transparency of ZnTPP macromolecular structures depended on the dye content in a solution: it decreased at ZnTPP content increasing as a result of opalescence appearance, and a solution color was changed from yellowish to lilac one.

2.2 GPC-analysis of VP-TEGDM copolymers, absorbance and IR-spectroscopy, TEM

The absolute molecular weights $M_w$ of copolymers were measured using a Waters GPCV 2000 liquid chromatograph (USA) (two PS-gel columns, 5 μm, MIXED-C, 300 × 7.5 mm) equipped with a refractometric detector and a WYATT DAWN HELOS II light scattering detector ($λ$ = 658 nm) in N-methylpyrrolidone in the presence 1% LiCl to prevent macromolecules aggregation.

The absorption spectra of the solutions in $i$-PrOH and buffer solutions were measured on Specord M40 (Germany) and PerkinElmer EZ-210 spectrophotometers in 1 cm cells. IR spectra of the initial PNC, copolymer powders, and PNCF after drying in vacuo were recorded in the disturbed total internal reflection (FTIR) regime, using a Bruker a Fourier-transform IR spectrometer (Bruker, Germany) in the range of 400—4000 cm$^{-1}$, the number of scans was 16.

The aqueous solution of polymer particles loaded with PNC was deposited on the substrate, a solvent was quickly evaporated, and images of hybrid nanostructures were obtained by Leo 912 AB equipment.

2.3 Dynamic light scattering

Solutions of the copolymer and hybrid structures in PBS were studied by dynamic light scattering (DLS) at a detection angle of 90° using a Photocor Compact installation (Photocor Instruments Inc., USA) equipped with a diode laser operating at a wavelength of 654 nm. The aqueous solutions were filtered through a microporous filter (0.45 mm). Before measurements, the vials with solutions were thermostated for ~20 min. The experimental data were processed using DynaLS v. 2.8.3 software by means of regularization (distribution analysis). The values of hydrodynamic radii $R_h$ of particles was calculated using Einstein–Stokes equation $D = kT/6πηR_h$, where $D$ is the coefficient of diffusion, $k$ is the Boltzmann constant, $T$ is the absolute temperature, and $η$ is the viscosity of the medium in which hybrid nanostructures were suspended. The experimental results were presented in the form of distribution of the intensity of scattered light $I$ by the sizes of the particles (hydrodynamic radii $R_h$).

2.4 ESR-spectroscopy

ESR spectra of aqueous solutions of encapsulated PNC were recorded on an Elexsys II E500 instrument (Bruker, Germany) at room temperature. The concentration and the $g$-factor were
determined using the Xepr software package. A solution of nitroxyl in DMSO with a known concentration, CuSO₄•5H₂O powder, and a sample of diphenylpicrylhydrazyl (DPPH) with a g-factor of 2.0036 were used to verify these procedures. ESR spectra of the initial complex in DMSO and in a water—DMSO mixture (4.4•10⁻⁵ mol l⁻¹) and of radical 2 in DMSO (10⁻⁵—10⁻³ mol L⁻¹) were recorded for comparison.

2.5 Cyclic, differential pulse and square-wave voltammetry
A cycle of electrochemical studies of the depolarisers 1-3 was carried out via cyclic (CVA), differential pulse (DPVA) and square-wave voltammetry (SWVA) in aqueous neutral PBS (pH 6.86), non-aqueous solvents (DMSO, MeCN) and in their admixtures with H₂O. It was used an Autolab/PGSTAT302N universal high-speed potentiostat/galvanostat (ECOCHMIE, Netherlands) and an IPC-ProL potentiostat (IPCE of RAS, Russia), and a three-electrode quartz or glass cells; the volume of the working solution was ~10 cm³. The range of sweep rates v in CVA was 0.02 - 5 V s⁻¹; in SWVA, the potential step was 5 mV, the amplitude was 20 mV, and the frequency was 25 Hz. The working electrode were Au, Pt (Menica, Poland) and glassy carbon (GC) (HTW Segradur-G, Germany) disc electrodes soldered into glass with a diameter of ~1 cm², and in ZnTTP case an Au wire electrode (visible area is ~0.1 cm²) and a carbon paper (Sigraset 39AA, Germany) as well. The auxiliary electrode was always a Pt wire, and the reference electrode was a silver/silver chloride electrode (Ag/AgCl) in aqueous solutions. The measurements in non-aqueous solutions were carried out relative to the Ag/Ag⁺-reference electrode (10 mmol ¹⁻ of AgNO₃, 100 mmol⁻¹ of Bu₄NPF₆ in the used solvent, i.e., MeCN or DMSO), separated from the working compartment of the cell by a double porous glass diaphragm. Its potential was +300 mV vs Ag/AgCl. Before the start of the experiment, the electrodes were polished with a diamond suspension (particle diameter ~1 mm), then cleaned by ultrasonic treatment in the medium in which the studies were carried out (water or a respective non-aqueous solvent). The experimental procedure is described in more detail in [20, 23, 24].

3. Results and Discussion

3.1 Composition and physical chemical properties of hybrid nanostructures of PNC
Solubilization of PNC by polymer particles results in the formation of the "guest—host" type nanostructures, in which the "guest" molecules retained through non-covalent interactions (van der Waals, hydrophobic, as well as hydrogen bonding). Chemical analysis of solid PNCF indicated the presence of Pt and Cl in them. Thus the content of Pt and Cl in PNC₄F₁ (from an i-PrOH—DMSO mixture) was ~1.3 and 0.6%, which is in good agreement with the calculated values and indirectly indicated that the encapsulated complex is stable.

IR spectra of powders of copolymers PNCF₁ and PNCF₂ containing 2—3% of the Pt⁴⁺ complex are practically the same. Due to the low Pt⁴⁺ content, its characteristic absorption bands do not appear in the spectrum. Absorption bands characteristic of PNC are clearly visible in the IR spectrum of the insoluble product isolated from an aqueous solution of PNC₁₈F₁ (Figure 2b). The IR spectrum in the region of 1800—1500 cm⁻¹ has a complex pattern; absorption bands with a maximum at 1725 cm⁻¹ can be distinguished (stretching vibrations of the C=O bond in the TEGDM units); a shoulder at 1681 cm⁻¹; a maximum at 1652 cm⁻¹, which is characteristic of stretching vibrations of hydrogen bonded C=O groups of VP units. The absorption maxima at 1629 cm⁻¹ and 1576 cm⁻¹ should be attributed to the aminonitroxyl complex. The absorption band at 1580 cm⁻¹ is apparently related to the bending vibrations of the N—H bond. It is shifted toward lower frequencies, from 1597 to 1580 cm⁻¹, as compared to the band in the spectrum of the initial complex. It can be assumed that a hydrogen bond is formed between copolymer F₁ and the complex involving its NH₂ groups. The band belonging to C=O groups of the carboxylate ligand is also shifted toward lower frequencies from 1638 to 1630 cm⁻¹, which can also be related to its bonding to the copolymer.

According to TEM (Figure 3a), PNC₄F₁ and PNC₄F₂ are a core—shell-type particles. The contrast core can be ~30 nm with a total size of ~70 nm. PNC₄F₂ particles are less than 50 nm. Dark inclusions
of small aggregates, apparently consisting of platinum complex molecules, can be distinguished within particles of both types.

Figure 2. $^1$H NMR spectra of the copolymers F1 (1) and F2 (2) recorded in CDCl$_3$ (a) and IR-spectra of PNC (1), copolymer F1 (2), and insoluble in water fraction of PNC$_{18}$F1 (3) (b).

Aqueous solutions of PNC$_3$F1 and PNC$_3$F2 were studied by DLS. The intensity of light scattering increased almost linearly with temperature (Figure 3b), while the sizes of scattering centers decreased. In the temperature range of 28—40 °C, the principal contribution to light scattering was made by particles with $R_h$ ~50 nm. The same linear dependence $I(T)$ was observed for F2 polymer particles. In this case, the size of the predominant type of particles did not change and was lower than that of the polymer particles encapsulated with the Pt$^{IV}$ complex. Thus, the behavior of hybrid structures in a PBS was determined by the polymer component. The changing temperature of the aqueous solution of the encapsulated complex PNC$_3$F2 also was accompanied by aggregation, which was reversible, as opposed to the case of PNC$_3$F1.

Figure 3. TEM image of the nanostructures of PNC$_4$F2 (a) temperature dependences of light scattering intensity ($I$) and hydrodynamic radius ($R_h$) for an aqueous solution of PNC$_3$F2. For comparison, the dotted lines show similar dependences for F2 polymer particles in an aqueous PBS (3, 4) (b).

The ESR spectra of aqueous dispersions of the encapsulated complex (Figure 4) contained three lines of approximately the same intensity, which is characteristic of its free form in a water—DMSO mixture, and DMSO. Apparently, the same local environment, namely water molecules, is the reason for the absence of considerable differences in the ESR spectra of the free Pt$^{IV}$ complex and of the one encapsulated into polymer particles of various types. It was demonstrated by recording of ESR spectra of aqueous dispersions of PNC$_3$F1 and PNC$_3$F2, the free PNC complex in DMSO and in a water—DMSO mixture, and spectra of radical 2 in DMSO and MeCN, respectively (Figure 4) for comparison that the encapsulated aminonitroxyl fragment of radical nature retained its structure and mobility in polymer particles (Table 1). Measurements performed after four months showed that aqueous solutions of PNC encapsulated into polymer nanoparticles remained stable during storage, and the concentrations of radicals in aqueous solutions and the ESR spectra parameters did not undergo considerable changes.
Figure 4. (a) - ESR spectra of aqueous solutions of PNC$_3$F1 (1) and PNC$_3$F2 (2), and of the free PNC in DMSO (3) and in a water—DMSO (4) mixture. The experimental conditions and numbers of spectra respect to that of in Table 1. (b) - ESR spectra of radical 2 (1 mmol l$^{-1}$) in DMSO and MeCN.

Table 1. Concentrations of nitroxyls and radical 2, and parameters of ESR spectra of aqueous PBS of PNC$_3$F1 (sample 1), PNC$_3$F2 (sample 2), the free Pt$^{IV}$ complex in DMSO (sample 3) and in a water—DMSO mixture (sample 4), as well as the radical 2 in DMSO (sample 5).

| Sample | C $\cdot$ 10$^5$, mol L$^{-1}$ (±15%) | g- factor (± 0.0002) | $a_N$, G (±0.1) | $A_0/A_1$ (±0.02) |
|--------|---------------------------------|-----------------|----------------|-----------------|
| 1      | 4/3.8$^a$                      | 2.0054          | 16.8           | 1.16            |
| 2      | 6.5/7.5$^a$                   | 2.0054          | 16.8           | 1.14            |
| 3      | 6.3                            | 2.0058          | 15.8           | 1.41            |
| 4      | 3.0                            | 2.0054          | 16.8           | 1.19            |
| 5      | 100                            | 2.0062          | 15.7           | 1.13            |

$^a$The numerator shows the values for freshly prepared aqueous dispersions of the complex encapsulated into polymer nanoparticles, the denominator indicates those values after four months of storage.

It was sufficiently similar also the potentials of anodic and cathodic peaks for reversible one-electron oxidation/reduction or radical 2 being in good agreement with literature [25], and that of the radical moiety of PNC (Figure 5). The difference in several tenth of mV were apparently due to the influence of central Pt atom and the ligand environment in PNC, and with substituents in para-positions of radicals.

Figure 5. Anodic branches of CVA curves of the radical 2 (1) and the Pt$^{IV}$ complex (2) on Pt (a) and GC (b) electrodes in MeCN + 0.1 mol L$^{-1}$ of TBAPF$_6$. $v$ is 100 mV s$^{-1}$.

3.2. Composition and physical chemical properties of hybrid nanostructures of ZnTPPF3

Water soluble ZnTPP forms were prepared by its solubilization with a copolymer F3 micellar particles [19, 23]. In electron absorption spectra of PBS of hybrid nanostructures, absorption in the region of 350–700 nm is associated only with the water-soluble form of ZnTPPF3, since the solution of copolymer F3 is optically transparent in the range of wavelengths above 250 nm, and the
hydrophobic dye is almost insoluble in water. With an increase in the concentration of ZnTPP in the hybrid structures, the $A$ value of the Soret absorption band of the dye grows nonlinearly. With excitation using light with $\lambda = 422$ nm, aqueous solutions of encapsulated ZnTPP fluoresced in the red spectral region, and two emission bands were observed at the wavelengths with the maxima at 603 and 643 nm.

It follows from DLS that the structure of F3, the sizes and size distribution of aggregates depended on the concentration of the copolymer. In the highly diluted solutions of the copolymer, the distribution curves were wide (Figure 6a, curve 1). The solutions were apparently dispersions of monomolecular micelles [26] with different sizes. Upon an increase in the concentration of the copolymer in the solutions, intense narrow peaks caused by the stable polymer aggregates making the major contribution to the intensity of light scattering were observed in the curves. In concentrated solutions, the distribution of the intensity of light scattering according to the sizes of the particles was virtually unimodal (Figure 6b), and the $R_h$ of ZnTPPF3 nanoparticles was $\sim 106$ nm at the peak maximum. In PBS, hybrid nanostructures respond to the change in the temperature. Upon an increase in temperature, the intensity of light scattering grows sharply, and $R_h$ drops intermittently to reach 50–60 nm in the 30–60°C range of temperatures.

The aqueous PBS of high concentration ZnTPPF3 hybrid nanostructures were taken for electrochemical investigations. The anodic branch of CVA curve of PBS contained a small oxidation signal at $E = +1.22 \pm 0.02$ V (Figure. 7a) It was absent on the CVA curves of the background, and in the saturated solutions (suspensions) of the insoluble dye in water. According to the literature [27-30] and our ones, it corresponded roughly to the second oxidation–reduction peak in the anode branch of ZnTPP in nonaqueous solutions, and was located at the potentials which are 100–150 mV more positive than the oxidation (decomposition) peak of water on an Au electrode with the formation of gold oxide in the background solutions. In the cathodic branch of the CVA curve, the peak of its reduction was retained at about the same potentials (around 0.4–0.5 V, the insert on Figure 7a) as in the solutions of the background. Since the total concentration of ZnTPP in the solution was low, this peak was adsorption and not diffusion in nature. Polarization curves of ZnTPP in non-aqueous solutions (e.g., in MeCN, Figure 7b) contained two pairs of reversible cathodic and anodic diffusion peaks. We proposed a model of electrochemical transformations of nanoparticles ZnTPPF3 [20] considered for non-adiabatic electron transfer probability. For nanoparticles "core-shell" structure, the probability to realize of the mechanism have to depended first of all on their hydrodynamic radius $R_h$. Because of the maximum length of electron tunneling generally does not exceed several tens of ångströms [31], this mechanism may be realized only in individual cases where $R_h$ values are equal or
less of this length. It is a consequence of non-unimodal distribution of particles on $R_h$ (Figure 6).

Figure 7. (a) - Anodic branches of CVA curves of the background (aqueous PBS): (1); (2–5) PBS containing ZnTPPF3. The times of potentiostating at $E = 0.2 \text{ V}$ are 2 (2, 3, and 5) and 30 s (4). Insert - CVA curve of Au-electrode in aqueous PBS. $v$ is 100 mV/s. (b) – DPVA-curves of of Pt- and GC-electrodes in MeCN + 0.1 mol L$^{-1}$ of TBAPF$_6$. $v$ is 100 mV s$^{-1}$.

A dynamics of polymer micelles destruction in MeCN and H$_2$O – MeCN mixtures (10-50%) was also studied spectroscopically (Figure 8a) on the Soret absorption band at $\lambda = 425 \text{ nm}$, and electrochemically (Figure 8b), on its redox reactions. The polymer micelles ZnTPPF3 were destroyed sufficiently fast, for several seconds. The Soret band was absent in an aqueous PBS but was sufficiently large in MeCN and to increase with the non-aqueous solvent content increasing in the admixture proportionally. It was practically absent in 90% PBS, was getting visible in 70% ones and clearly visible at 50%. The band near 325 nm was changed oppositely. An uniform increasing of the absorbance after his band pointed on a colloid character of PBS with hybrid nanostructures of ZnTPP.

Figure 8. (a) – Absorbance spectra of ZnTPPF3 in MeCN, PBS and MeCN-PBS mixtures. (b) - CVA curves of ZnTPPF3 on Au-electrode in MeCN, PBS and MeCN-PBS mixtures. $v$ is 100 mV/s. 1$\text{st}$ scan.

Note that such a fast destruction we observed earlier for nanostructures of Pt$^{IV}$ complex in DMSO that it followed from a comparison of CVA curves of polymer particles loaded with the complex in an aqueous PBS and DMSO [23, 24].

4. Summary

Thus, it was shown for a lipophilic aminonitroxyl Pt$^{IV}$-complex and zinc tetraphenyl porphyrinate dye that water-soluble forms of functional materials for various biomedical applications can be obtained through the solubilization of poorly and insoluble component by amphiphilic branched copolymers of N-vinylpyrrolidone with triethylene glycol dimethacrylate of different monomer composition and the topology presented in solutions as individual macromolecules and their aggregates (nanoscale polymer particles). As a result, new possibilities are opened to control not only...
their solubility but also bioavailability, prolonged action, distribution in the body, duration of circulation in the blood and accumulation in tumors, toxicity, etc.

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