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Novel water-soluble vehicle based on iron-containing nanospecies and hydroxypropyl-β-cyclodextrin

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The novel class of capacious hydrophilic water-soluble vehicles for the delivery of water-insoluble compounds was prepared by the interaction of $FeSO_4{\cdot}(NH_4)_2SO_4{\cdot}6H_2O$ with $NaH_2PO_2{\cdot}H_2O$ in the presence of highly substituted hydroxypropyl-β-cyclodextrin in an alkaline aerated solution.

Cyclodextrins (CDs) are cyclic oligosaccharides with a hydrophilic outer surface and relatively hydrophobic central toroidal cavity structures, and their derivatives represent a modern class of drug delivery systems.[1,2] Due to their structure, they allow one to solubilize poor water soluble/insoluble drugs and increase their bioavailability and stability. The key application of construction of CDs-based drug delivery systems is targeted delivery.[1,2] CDs and their derivatives exhibit a strong affinity for metal/metal oxide particles to give water-soluble metal-containing species.[3,4] It is proposed that β-CD with multiple hydroxyl groups can chelate ferric oxide or hydroxide and adsorb onto certain crystal planes as a coating agent to provide steric hindrances.[5]

It is known that the β-CD forms columnar structures,[6] *i.e.*, CD-containing covalent nanotubes (CDNTs). CDNTs can form adducts with iron-containing particles in which inorganic moieties are not incorporated in the cavities of CD molecules, but organic and inorganic moieties form separate phases and are arranged perpendicular to each other.[7,8] Another type of nanocomposites may be produced using small organic molecules instead of macromolecular structures. Here, we focus on the system based on hydroxypropyl-β-cyclodextrin (HPCD) and iron. Note that HPCDs are the products of statistical replacement of both primary and secondary OH groups in β-CD molecules.

The structure of these molecules with a number of free-pendent hydroxypropyl groups [Figure 1(*a*)] is close to the structure of the end part of nanotube [Figure 1(*b*)]. The high solubility of HPCDs in water (50% w/v) is another attractive feature of these compounds.[9] It was of interest to clarify the possibility of formation of water-soluble organo-inorganic ferriferous adducts based on HPCD.

The reduction of $(NH_4)_2Fe(SO_4)_2$ with NaH_2PO_2 in the presence of HPCD occurs in aqueous basic solution at room temperature. The simplest method of adduct separation from unreacted low-molecular-weight reagents and products is membrane dialysis. The dialysis of adducts was performed using MWCO 15000 against pure water during three days. The reaction product was isolated by lyophilization. In our experiments, the generation of large particles retained by the membrane provides conclusive evidence for adduct formation. The formation of high-molecular-weight product occurs only in the presence of HPCD with MM = 1540 (the degree of substitution DS = 6.8).

The adduct composition was determined by the quantitation of all components involved in it. For this purpose, we used both the isolated adduct and the adduct previously decomposed by treatment with NaOH.

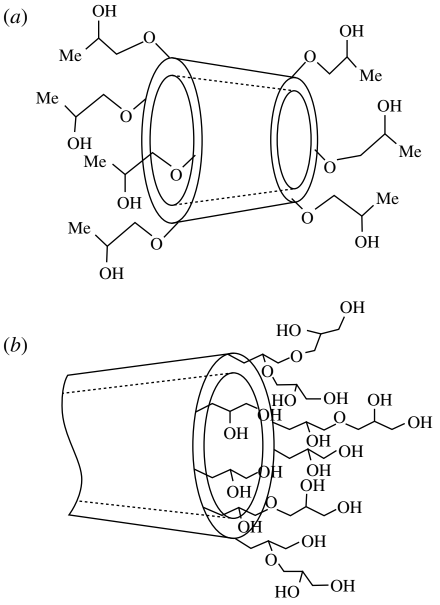

Figure 1 Structures of (*a*) HPCD and (*b*) the end part of a covalent nanotube based on β-CD.

The quantification of the iron content in adducts was performed using complexation with 2-hydroxy-5-sulfobenzoic acid. The adduct contained 4% oxidized iron, which is substantially higher compared to the adduct based on CDNT produced by the same method.[8]

The analysis of adduct also revealed that it contains the inorganic ions Na^+, SO_4^{2-} and PO_4^{3-}. The Na^+ content was determined by conductivity, and the amounts of the anions were found by ion-exchange chromatography and gravimetry. The gravimetric analysis was based on a reaction between the adduct and $BaCl_2$ with the formation of insoluble $BaSO_4$. The same reaction performed with the adduct previously decomposed by treatment with NaOH gave the total amount of SO_4^{2-} arranged inside the adduct and at its outer surface.

The addition of aqueous solution of $AgNO_3$ to the solutions of adduct resulted in the formation of metallic silver, which indicates that the oxidation–reduction reaction between Ag^+ and included in adduct Fe^{2+} mainly occurs. However, the quantification of metallic silver demonstrated only traces of Fe^{2+} in adduct.

For the determination of the phase composition of synthesized products in a solid state, X-ray diffraction analysis (XRD) was

Table 1 Weight ratios of iron and inorganic ions included in 1 g of the adduct based on the HPCD.

Species	Fe^{III} (wt%)	SO_4^{2-} (wt%)	Cl^-	Na^+ (wt%)	PO_4^{3-} (wt%)
Adduct	4	22	–	11	1

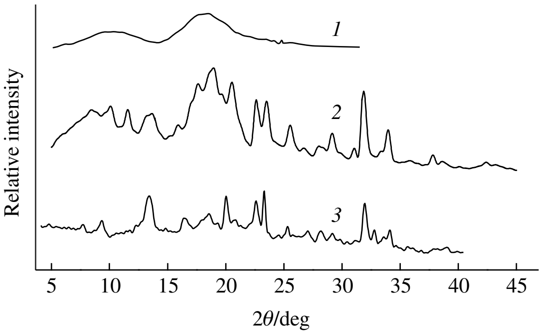

Figure 2 Powder XRD patterns of (*1*) HPCD, (*2*) HPCD–iron adduct and (*3*) $Na_2SO_4 \cdot 10H_2O$ salt.

used. The powder XRD pattern of HPCD is displayed in Figure 2 (curve *1*). The presence of two wide haloes with maxima at 2θ of 9.6 and 18.4° gave evidence for the amorphous structure of this sample.

The diffraction pattern of the adduct exhibited a set of well-defined reflections and two amorphous haloes (Figure 2, curve *2*). The powder XRD pattern of $Na_2SO_4 \cdot 10H_2O$ is shown (curve *3*) for comparison. The size of the ordered domains adduct estimated from the half-width of the corresponding peaks constitutes was ~30 nm. Thus, the results of X-ray analysis led to the conclusion that the adduct of HPCD with iron species possesses a heterophase structure with the amorphous phase of modified CD and the crystal phase of inorganic salts.

The behavior of the nanosized reaction product in aqueous solution was studied by dynamic light scattering (DLS). The distribution function of translational diffusion coefficients has shown that, at concentrations from 0.125 to 1 wt%, adducts formed large particles with the hydrodynamic radius $R_h \sim 200$ nm. It was demonstrated that the peak of distribution is sufficiently narrow. It was established that the adduct particles were colloidal-stable over long periods of time. In contrast, the initial HPCD did not form large particles in solution under the same conditions. For the specification of the process occurring under the action of the alkali we used MALDI-MS method. For this purpose, we analyzed the resulting adducts and adducts previously decomposed by the treatment with a concentrated solution of NaOH. In both cases, the MALDI-MS spectra exhibited the presence of only the initial HPCD. Thus, the non-covalent character of bonds between the components in the adduct was demonstrated.

The interaction of β-CD and its derivatives with phenolphthalein is typical of the determination of free holes inside the compounds.[10] Figure 3 shows the titration curve of HPCD aqueous solution by phenolphthalein (curve *1*), indicating the binding of the dye molecules by the macrocycle.

Another type of titration curve was observed in case of the adduct (curve *2*), which testifies to the decrease in dye absorbance pronounced less than in case of HPCD solution. Solution of individual HPCDs absorbs more dye at the same concentrations but coupling per particle for adduct is much higher. Thus, the partial dye binding proceeds in the adduct solution due to steric factors, *i.e.*, HPCD shields the cavities of adjacent molecules in nanospecies. As a result, the formation of inclusion complexes with phenolphthalein occurs only on the surface of adduct.

The participation of HPCD in the formation of adducts with the products of the Fe^{2+} reduction due to HPCD self-organization around the inorganic nuclei was supported by analysis of the adduct composition and properties including the decrease in the adduct solubility compared to the pure HPCD. It was found that the adduct solubility in water at room temperature decreased up to 1 wt%.

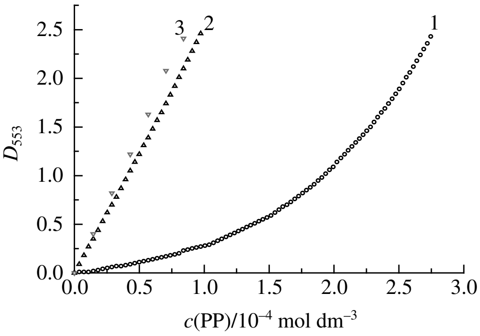

Figure 3 Titration curves of HPCD and adduct with phenolphthalein (PP). (*1*) HPCD–iron adduct, $c = 1.5 \times 10^{-3}$ mol dm^{-3}; (*1*) HPCD, $c = 1.5 \times 10^{-3}$ mol dm^{-3} and (*2*) pure phenolphthalein.

The comparison of the self-assembly modes between the systems based on HPCD and iron nanoparticles and CDNT–Fe has shown a striking difference. CDNTs form large associates in the solution in the absence of iron. The latter served as cross-linking agent combining the stacks of CDNT oligomers. At the same concentrations, HPCD does not form organized structures in the solution in the absence of iron nanoparticles. These particles play a role of seeding agents favoring the formation of structures containing HPCD as a stabilizing layer. Thus, the self-assembly of both constituents in HPCD–iron adduct occurred synergetically, *i.e.*, one level of self-assembly (the formation of metal nanoparticles) guided the next level (the formation of organic layer from HPCD molecules).

In conclusion, we found that the interaction of $(NH_4)_2Fe(SO_4)_2$ with NaH_2PO_2 in the presence of HPCD gives the HPCD–iron adduct. HPCD with smaller degree of substitution DS = 3.5 and the parent β-CD do not form adducts with iron-containing nanospecies under the same conditions. The oxidized iron content of the adduct was 4%. The adduct contains HPCD as an organic component, sodium ions, SO_4^{2-}, PO_4^{3-} in a small quantity. The non-covalent character of bonds between components in the adduct has been estimated. In aqueous solution, the adduct forms large particles with a hydrodynamic radius of ~200 nm. The existence of superparamagnetic components corresponding to iron and iron oxide in adduct might be assumed on the basis of the obtained results.

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