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Biomedical Applications of Promising Nanomaterials with Carbon Nanotubes

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Some medical applications of composite nanomaterials containing carbon nanotubes are described. Particular applications are bone and cartilage tissue implants, biological solders for laser welding, artificial muscles, and highly conductive layers for electrodes of medical devices (defibrillators, cardiographs, encephalographs, etc.). Additionally, safety of composite nanomaterials with carbon nanotubes is discussed.

Introduction

Composite materials based on carbon nanotubes (CNT, single-wall CNT (SWCNT) and multi-wall CNT (MWCNT)) are of considerable interest for a variety of biomedical applications. Some of the unique physical parameters of CNT, such as the tensile strength ≥ 50 GPa, Young's modulus ≥ 1 TPa, conductivity $\sigma_{in} \geq 10^7$ S/m, maximum current transmittance $J_{in} \geq 100$ MA/cm^2, density $\rho \leq 1600$ kg/m^3, are important for development of modern advanced composite materials, including biocompatible materials [1]. For example, CNTs containing materials have hardness $H_V \geq 60$ GPa, tensile strength $S_T \sim 10$ GPa, and conductivity $\sigma_e \sim 800$ kS/m [2]. Their mechanical properties are better than those of special hardened steel, but their σ_e values are several times less than those of copper or aluminum wire and film coating. However, the value of the derived parameter $S_T\sigma_{in}/\rho$ of CNT is an order of magnitude higher than that of known strong metals and highly conductive materials (steel, titanium, copper, aluminum, various alloys of precious metals) that are often used in engineering, microelectronics, and medicine [3].

This article discusses some aspects of medical applications of composite nanomaterials with CNTs and addresses their safety. In particular, such biocompatible nanomaterials are implanted bone and cartilage tissue, solders for laser welding of biological tissue, artificial muscles, and others.

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Implants

A variety of CNT-containing composite nanomaterials is manufactured. These materials use polymers as matrix and various types of carbon nanotubes as filler. Polymeric matrix reinforced with CNT can be used as a structural material for bone cement, as well as a structural material in skin tissue engineering. Polyurethane and CNT-containing composites with pronounced electrical and mechanical properties can be used for stimulation of growth of bone and nervous tissues [4, 5].

Biocompatible materials based on hydroxyapatite (HA, medical cement) are similar in composition to bone tissue, and they have been used in medical practice for a long time (about a quarter of a century), but they have drawbacks: low resorption rate, slight stimulating effect on tissue growth, low fatigue strength under physiological conditions, etc. [6]. Hence studies are carried out to improve the functional characteristics of the HA by the addition of MWCNT, thus increasing S_T and E severalfold [7]. However, their absolute values are substantially (several orders of magnitude) lower than the corresponding parameters of human bone tissue – $S_T \leq 50$ MPa, $E \approx 150$ MPa, $H_V \approx 500$ MPa [8].

Most of the materials (metals, ceramics, polymers, etc.) used in implantation or endoprosthetics do not contain natural biological matrices, so in some cases the degree of biocompatibility is not high. Thus, biological materials, which are often characterized by complete or high degree of biocompatibility, are preferred for the aforementioned applications. Natural protein albumin is particularly applicable as it is completely biocompatible, easily available,

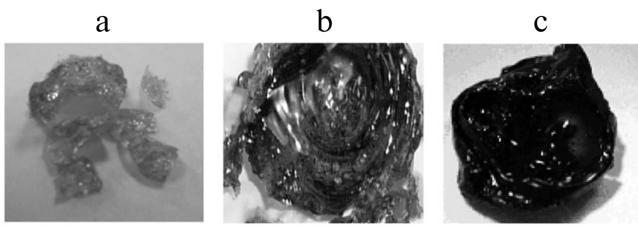

Fig. 1. Appearance of some samples: a) dried BSA; b) CNM, $C \approx 0.003\%$ w/w MWCNT; c) CNM, $C \approx 0.003\%$ w/w $MWCNT_f$ [10].

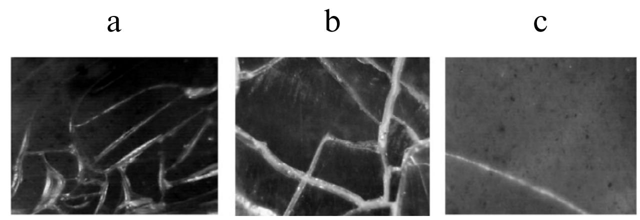

Fig. 2. Cracks in the polished surfaces of BCNM for different concentrations of MWCNT [12] (wt. %): a) 0.1; b) 0.2; c) 0.4.

widely used in biomedical practice, and has stable characteristic parameters. However, pure albumin is a powder, so formation of 3D-implants is not possible.

The authors of [9-12] described in detail the method of manufacturing of bulk composite nanomaterials (BCNM, 3D) consisting of bovine serum albumin (BSA) and CNT, i.e. BSA + CNT created using cumulative laser technology and nanotechnology. The final BCNM product had black color and polymer (plastic)-like appearance, the consistency varying from gelatinous to solid material. Selection of BSA as a BCNM matrix was justified due to its high degree of biocompatibility and stability, wide application in biomedical practice, and relatively low cost compared to human serum albumin.

Studies were conducted with BCNM consisting of BSA and CNTs (functionalized with carboxylic groups $MWCNT_f$ or non-functionalized MWCNT). BCNM were produced from aqueous dispersions containing 25% w/w BSA and 0.0015-0.04% w/w $MWCNT_f$ or MWCNT. The appearance of BCNM samples is shown in Fig. 1. It is seen that samples with MWCNT (Fig. 1b) have a lighter appearance than $MWCNT_f$ samples (Fig. 1c) that corresponds to the color of the dispersions.

Note that all BCNM or BSA samples obtained without laser radiation (LR), as well as samples of BSA without CNT decomposed after drying or after ~24 h of storage. However, LR-treated BCNM retain their shape and mechanical properties throughout the entire observation time – more than 7 years. H_V hardness value of BCNM with $MWCNT_f$ was ~250 MPa, and in the case of BCNM with MWCNT H_V was ~300 MPa, which is 5-6 times higher than in the control samples of pure BSA and composite material BSA + K-354 carbon-black (H_V ~ 45-50 MPa). Tensile strength of BCNM was approximately one order of magnitude lower (S_T ~ 30 MPa) than their hardness. BCNM density for any CNTs was ~ 1200 kg/m^3 and insignificantly superior to ρ of BSA (~1030 kg/m^3) but was significantly less than that of natural bone (~1950 kg/m^3). Maximum values of specific hardness H_V/ρ ~ 0.24 MPa/(kg/m^3) and specific strength σ/ρ ~ 0.024 MPa/(kg/m^3) for BCNM were almost identical to the corresponding values for human porous bone tissue: σ/ρ ~ 0.026 MPa/(kg/m^3) [10].

Cracks develop gradually within a sample of dried BSA (Fig. 2a) until it is destroyed and transformed to powder. With increasing concentration of the MWCNT in the range of 0.1-0.4% w/w, the number of cracks abruptly decreases (Fig. 2c) [12].

Application. Preliminary studies on rabbits of BCNM BSA + MWCNTs as cartilage tissue showed that osteoblast regeneration rate increased several-fold, while toxic or allergic reactions were not observed [11]. It can be expected that layers of BCNM BSA + MWCNT serving as coating for various implants such as metal or ceramic will increase their biocompatibility, including reducing likelihood of blood clotting.

Compounds of Biological Tissues

Laser welding (LW) is a new direction that can significantly improve traditional methods of connection and restoration of biological tissue (BT). The resulting seam, the so-called laser seam (LS), has virtually no rough or particularly visible scars.

LW is performed by coating the surface of the future joint with special biological solder (BS, biosolder) that absorbs LR intensely. Recent studies have shown that as BS for LW most suitable are aqueous colloidal dispersions of albumin. LW using BS made of BSA was performed on various tissues (e.g. brain membrane [13], ureter [14]). Achieved tensile strength $S_T < 0.1$ MPa for LS was relatively low compared to traditional methods, such as sewing or medical adhesives (e.g. sulfacrylate: S_T ~ 0.5 MPa [15]).

A large effect of increasing strength of the connecting tissue seam was observed when BS based on BSA and carbon nanotubes (CNTs) [10-18] were used. The BS was an aqueous ultradispersion: matrix – 25% w/w BSA and

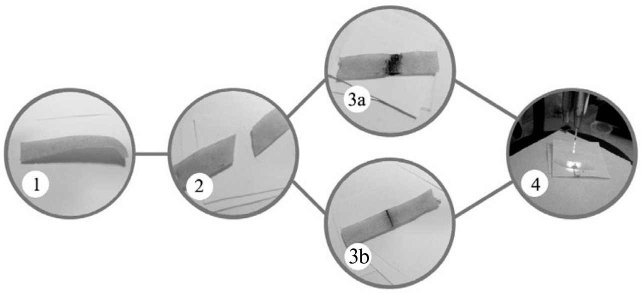

Fig. 3. Scheme of steps in LW of BT (porcine skin): 1) solid sample; 2) cut sample; 3a) LS obtained by LW in case when BS and surgical mesh Prolene were used; 3b) LS obtained without surgical mesh; 4) LW process (green color of pilot laser beam). The black color of the laser seam is due to the natural color of the solder [18].

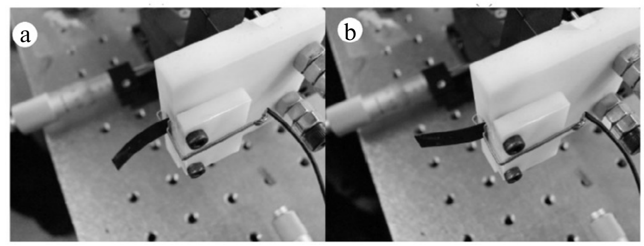

Fig. 4. Mechanical response of actuator with MWCNTs when voltage is applied: a) 2 V; b) –2 V [19].

filler – nanoparticles in the form of CNT. At concentrations C ~ 0.1-0.2% w/w of CNT (SWCNT or MWCNT), increased S_T value was achieved. Particularly, at the optimal temperature (t ~ 60-65°C) of the welded BT area maximum values of relative strength S_T/S_{Tm} ~ 23-32% for bovine cartilage and 10-15% for pigskin were reached, where S_{Tm} – strength of continuous tissue. To enhance the BT connection, in some samples the seam was reinforced by surgical mesh of Prolene type, which additionally increased the strength by 10-25%. The experiments were conducted *in vitro* on strips of bovine tracheal cartilage and of porcine skin with length of 25-30 mm, width of 4-8 mm, and thickness of 0.5-1.5 mm (Fig. 3). In the case of BS made of pure BSA (without CNT additives), S_T/S_{Tm} ~ 0.15-0.3% was obtained. As control samples, BS-based LS were taken that contained carbon black or activated charcoal and CNT-containing BS obtained under identical conditions. For them there was a 30-50% decrease in values of S_T/S_{Tm} relative to BS made of pure BSA.

Positive results were obtained *in vitro*, but it can be assumed that similar *in vivo* experiments with BS containing CNT nanoparticles will also increase the strength of LS.

Application. The results of recent studies [16-18] demonstrate the potential application of biological solder based on an aqueous dispersion of BSA + CNT for laser welding. Strength of the laser seam is comparable to that obtained by conventional methods, while by the degree of minimal injury rate, sterility, and the complexity of the connecting process is better.

Artificial Muscle

Electric actuators can be used as muscles for humanoid robots or biocompatible implants for humans, as well as for innovative surgical instruments.

In medical applications, three-layered ion–metal–polymer composite (IMPC) actuator is most suitable. Its properties were improved by replacing platinum or gold electrode with a MWCNT-based electrode [19]. MWCNT solvent was applied on both sides of ionic polymer membranes (e.g. Nafion film). After annealing, the electrodes were formed and the structure was impregnated with ionic liquid. Surface resistance R_S ~ 100 Ω/m was achieved for the actuator. Actuators with MWCNT show 20% greater displacement compared to traditional platinum-based IMPC, and they are much less expensive than the latter (Fig. 4).

The authors of [20] described an actuator that is manufactured by hot pressing SWCNT films (electrodes) and semidried electrolyte layer of chitosan/ionic liquid (1-ethyl-3-methylimidazolium). They suggest that in general the proposed actuator is biocompatible, as its main part, the electrolyte, has a high degree of biocompatibility.

Further improvement of actuator parameters is possible with decreasing R_S. Therefore, SWCNTs with high conductivity 200 kS/m were used [21, 22]. Benefits of SWCNTs compared to MWCNTs in elastomer structures disappear given the complexity of their production, high cost, and relatively high degree of toxicity relative to MWCNTs. Therefore, the creation of flexible electrodes with a minimum content of MWCNTs is particularly interesting. For example, in a matrix of carboxymethylcellulose (CMC), percolation threshold at level C = 0.1-0.25% w/w MWCNTs was achieved [23]. Under optimal conditions for heat treatment in various environments (air, hydrogen), more than two order of magnitude increase in value σ_e was achieved for nanomaterial layers of aqueous ultradispersion with 4% w/w CMC and 5% w/w MWCNTs [24-26]. In these nanomaterials, specific conductivity values σ_e ~ 40 kS/m are of the same order as that achieved in layers consisting almost exclusively of MWCNTs [5]. In [27], it is reported that laser radiation increases conductivity of the layers of the composite nanomaterial CMC + CNT (SWCNT or MWCNT) up to 300%. Additionally, further annealing at t ~ 190 ± 10°C leads to a multifold increase in conductivity with respect to the initial state, i.e. to the state in the absence of laser radiation and annealing.

Obviously, the CNT-based actuator is considered as the artificial muscle prototype. For the case of SWCNT-based actuator, specific mechanical power per unit P_m ~ 244 W/kg mass was achieved, which is within an order of magnitude of the value P_m of typical mammalian muscle tissue [22].

Higher values of P_m were obtained based on a MWCNT-containing composite [27]. MWCNT bundles were twisted into yarn and filled with paraffin wax, which wetted the nanotube. By applying current and thermal heating, MWCNT filaments stretched, which made the artificial muscle deform (work). In this case P_m ~ 30 kW/kg was achieved, which is approximately two orders of magnitude higher than that of human muscle tissue.

Application. Conductive nanomaterials of the system CMC + CNT have prospects for use as electrodes in various medical devices: defibrillator cardiography, encephalography, and others.

CNT-containing actuators develop specific order or power many times greater than that of human muscle tissue. Accumulated experimental data on CNT-containing nanomaterials are sufficient for the development and creation of artificial muscles. However, their implementation in clinical practice should be expected only after careful study of their safety for human health and the environment.

Some Safety Aspects of CNT-Containing Nanomaterials

Numerous studies have been published on the safety for human health and the environment of carbon nanotubes and nanomaterials based on them [28-32]. From these, the following conclusions can be made.

1) SWCNTs are more toxic than MWCNTs.

2) Purified SWCNTs are more toxic than crude (technical), while functionalized SWCNTs are much less toxic. Blood functionalizes CNT.

3) LDL_o (lowest dose causing the death of the animal) in mice is greater than 1 g/kg body weight for all tested CNT types for intraperitoneal administration.

4) When CNT is implanted, the presence of fluid in tissues of animals and inflammatory signs are expressed most strongly for SWCNTs, but toxic effects of CNT are lower than the toxicity of the same dose of asbestos particles introduced under the skin of mice.

5) MWCNTs do not cause the formation of free radicals; on the contrary, they quench them.

6) MWCNTs with the structure of nested cups are less toxic than MWCNTs with open ends.

7) Citrullination within cells, i.e. activation of cellular mechanism that is not associated with inflammation, may be an indicator of CNT cytotoxicity in early stages.

8) Oxidative enzymatic cleavage of CNT occurs in the biological environment within eight weeks.

Conclusion

Systems obtained from aqueous dispersions of BSA and carbon nanotubes using laser technology and nanotechnology are preferred of all biocompatible CNT-containing composite nanomaterials considered. These nanomaterials can be deemed functional as on their basis different products can be constructed, such as 3D-products, coatings for metallic, ceramic, or other implants to enhance their biocompatibility (for example, the degree of reduction of blood clotting) and biosolder for laser welding.

Composite nanomaterial of carboxymethylcellulose and carbon nanotube systems also has high potential. Aqueous dispersions of this system are used for production of layers with high conductivity of about 40 kS/m with low concentration of carbon nanotubes (≤10% w/w). Based on such system, electrically conductive elements of various medical devices, such as electrodes, electric actuators, etc., can be produced. Achieved mechanical power density in artificial muscles based on composite materials with CNTs is of the same order or many times higher than the power density of human muscle tissue.

Accumulated research experience on the safety of nanomaterials with carbon nanotubes to human health and the environment allows considering them less dangerous than asbestos.

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