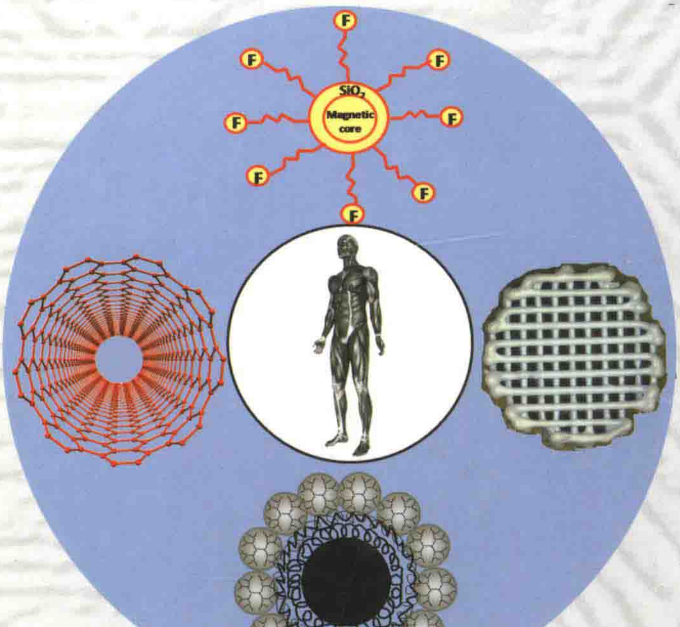
Advanced Bioceramics in Nanomedicine and Tissue Engineering



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M. Vallet-Regí and M. Vila

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Advanced Bioceramics in Nanomedicine and Tissue Engineering

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Advanced Bioceramics in Nanomedicine and Tissue Engineering

Preface

Challenges in nanomedicine and tissue engineering

Nanoscience is revolutionizing the design of medical devices, scaffolds and drug delivery systems. The scientific community, for approaching the still actual unsolved critical problems in tissue regeneration and disease treatment, has proposed to use new methods based on nanotechnology.

The new discoveries on nano systems for other research areas have opened the possibility of using them in biomedicine. But this nanoscience and these highlight ideas bordering the science fiction, have to be kept in perspective for not loosing the ground in terms of possibilities, fabrication, safety and applications inside the limits that the biology of the human body requires.

In modern society our needs of nanomedicine focus nowadays in the treatment of cancer, tissue regeneration, diagnosis and imaging. These needs, blossom as a huge effort for diminishing the secondary effects of aggressive treatments or to see what until now was unimaginable to observe or to regenerate tissue where it has been lost.

The main goal of this book is to join together some of the new advanced trends in biomedicine that involves potential nano candidates for the future disease treatments, diagnosis and control of biological systems and regenerative medicine.

One of the main requirements on these nanosystems is that they react with an intelligent response under certain stimuli, to do what we design them for, so we can call them "smart materials". These intelligent materials will perform certain activities inside the human body and will be activated by internal or external stimuli.

With this book, we tried to make a review in three parts, of the leading advances in biomedicine related to nanoceramics and nanosystems. These three Parts are dedicated to:

Part I. Carbon nanotubes. Heights of science fashion and under the critical eyes of the community, are giving rise to a vast field of applications in nanomedicine. Their possible use as nanocarriers of several substances such as DNA, proteins, drugs, etc…, for imaging or drug delivery, or the simple use of their exceptional properties by applying an external stimuli of infrared light, acoustic waves or electrical impulses, as well as their mechanical resistance, open a new window, carefully and deeply explored.

Moreover, we have included in this section a chapter showing the important role that the electron transmission microscopy techniques display on the nanotube characterization. This technique is and efficient method for characterizing nanomaterials.

Part II. Scaffolds for tissue engineering. Implants and prostheses as we imagined and classified as 1st and 2nd generation biomaterials are being substituted by materials that induce and accelerate bone regeneration processes. The aim of these materials in the form of scaffolds is to "disappear" as the new tissue is being formed. The new technologies for designing them are already combining in situ drug delivery and promotion of cell interactions envisaging total bone healing and reconstruction.

Part III. Nanoparticles. The promises for cancer treatment; Will they win the battle against this disease? The aim is to develop safer and more effective therapeutic or diagnostic modalities to avoid the aggression to the body of the actual treatments. There have been already huge advances in gene/drug delivery as well as in molecular imaging using targeted multi-functionalized nanoparticles.

As all the new emergent ways of technology in their earlier stages, there is always a question to make, is this nanotechnology harmful? Toxicity in nano-dimensional systems has been studied since the early beginning of their boom. For example, the main problem of using carbon nanotubes on medicine was the toxicity they presented in certain applications. Nowadays, these multilevel complex nanosystems are able to be finely engineer and manipulated to be designed to fulfil our requirements. Their surfaces are functionalized, their structures are modified and the barrier of toxicity is being knocked down. Carbon nanotubes are already well known, and are the example of how a response can be transformed. This fact opens the door to more recently proposed nanoparticles that maybe today find limits on their application, but in a few years could be the new Trojan horses against disease.

There are still many challenges remaining to be overcame, as the efficiency of encapsulation and targeting or the toxicity, but the better understanding of these systems envisages wide clinical improvements.

Because of all these reasons we have joined together specialized scientists in the three areas to give an overview and a reference of what nowadays are the hot topics of nanomedicine.

M. Vallet-Regí and M.Vila

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Part 1:
Carbon Nanotubes

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Carbon Nanotubes: a solution for processing smart biomaterials.

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1. Introduction

1.1 Smart materials

In the recent years the driving force for technological change in many respects has shifted towards the design and process of materials that offer a set of responses to external stimuli or environmental conditions. These materials are called "smart materials". Such responses are designed to fulfil the range of scenarios to which a material or structure may be exposed providing them with a particular functionality.

These materials are not only useful because of their structural, chemical, physical or mechanical properties; they can also perform an action within a process.

It has been described[1] that smart structures exhibit one or more of the following features; they can act as sensors or actuators within a structural material or bonded in the surface; or they have controllable capabilities that permit to respond to the stimuli according to a prescribed function. These materials become intelligent when they have the ability to respond intelligently and autonomously to changing conditions.

There are lots of possibilities within the term functional "smart materials" but in all of them, the term is used to describe systems which respond to a stimulus in a useful and predictable manner. Nowadays it is widely known the useful capability of, piezoelectric, electro-optic, magnetic, electro-mechanic materials, etc…that respond to stimuli such as, electric or magnetic fields, stress, temperature, moisture or pH. These multifunctional character and capability of biomaterials makes them suitable for a big number of applications in every order of human activity, from photochromic lenses for sunglasses to military and aerospace uses. They are already a big part of the market in the engineering industry.

In the biomedical research area, it is being a giant effort of engineering and designing materials copying concepts from biological structures with the purpose of processing synthetic materials that will mimic the natural structures. The 'smart' or intelligent response, will allow the structure to adapt and interact with the media inducing biological responses.

Nowadays, the solutions for repairing tissues or treating diseases based on biomaterials applications have developed highly successful solutions. For example, neural networks, systems which respond to temperature and pH, stimuli-responsive polymer systems, shape memory materials, biomaterials designed to act as an "on-off" switch for drug delivery technologies, gene therapy, affinity separations, chromatography, diagnostics, imaging etc..; or moveable magnetic nanoparticles that can carry anticancer agents to the cancer or tumour cell, etc... such smart biomaterials are revolutionizing the design of medical devices and drug delivery systems.

Also, biomaterials structuring scaffolds for tissue engineering play a very important role in regenerative medicine. The nature and structure of these biomaterials affect the long-term success and the wound healing process. Nevertheless, although nowadays they are already widely applied in implant surgery, there are still limitations in their use as all the medical implants metallic, ceramic or polymeric have secondary reactions that are not still avoided, such as the formation of undesiderable fibrous tissue around the implant or its wear and tear leading to the implant failure and subsequent removing.

An approach for improving their performance has been, for example, introducing nanosized particles and carbon nanofibers into implant materials or functionalizing their surfaces with biologically active molecules for enhancing osteoblastic cells adhesion. Therefore, controlling the biomaterial surface by the combination of several materials, one could take advantage of the different physical and chemical properties of the combination, and use them with a specific purpose. For example, as it will be commented later, using the electroactive properties of carbon nanotubes (CNTs) blended into a biomaterial, enhanced cell behaviours could be obtained.

The already well established research in nanomaterials is opening new strategies in the design of biomaterials. As the main feature of this chapter, CNTs are part of a growing new class of functional smart biomaterials.

1.2 Carbon nanotubes

Carbon nanotubes are one of the allotropes (elements that can exist in two or more different forms) of carbon, with a cylindrical nanostructure. The fact that carbon could form stable, ordered structures other than graphite and diamond, inspired researchers to search for other new forms of carbon. After the discovery of the C60 Buckminsterfullerene[2], the exploration was given new motion when it was shown in 1990 that these C60 could be produced in an arc-evaporation apparatus readily available in the laboratories. The work specifically on carbon nanotubes was boosted by the publication made by Iijima that reported fullerene-related carbon nanotubes in 1991.[3] The tubes contained at least two layers, and ranged in outer diameter from about 3 nm to 30 nm. Those were called multiwalled carbon nanotubes (MWCNTs). Later in 1993, a new class of carbon nanotube with just a single layer was discovered.[4,5,6] (see Figure 1).

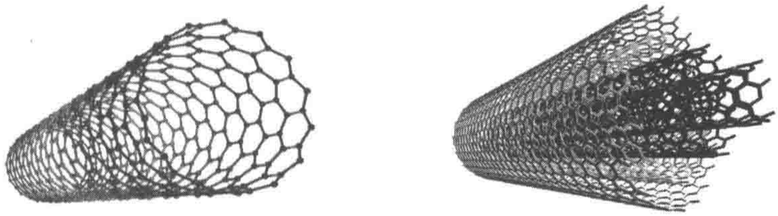

Fig.1. Single walled (left) and Multiwalled (right) carbon nanotube structures.

1.2.1 Structure and properties

In carbon structures, carbon atom bonds to each other covalently by the sharing of electron pairs and these covalent bonds present directional properties. This gives carbon the ability to adapt into various molecular and crystalline structures. The bonding in carbon nanotubes is sp^2, with each atom joined to three neighbours, as in graphite. The tubes can therefore be considered as rolled-up graphene sheets (graphene is an individual graphite layer, a single sheet of a honeycomb network of carbon atoms) and when is coiled, the carbon arrangement becomes very strong (see Figure 1). The three distinct ways in which a graphene sheet can be rolled into a tube are described by the chiral vector (n, m) that represents the "twist" of the nanotube.[7] With a slight difference in these parameters, the character of the nanotubes could be changed from metallic to semiconductor. The tube diameter and wrapping angle, by means of their chirality, affect its conductance, density, lattice structure, and other properties.

Depending on the number of rolled layers (concentric tubes) of graphite, carbon nanotubes are defined as Multi-walled nanotubes (MWNTs) or Single-walled nanotubes (SWNTs). Most SWNTs present a diameter close to 1 nanometer, while for the MWNTs the diamenter ranges from 4 to 50 nm approximately.

In graphite, there is a stacking of layers parallel with respect to each other and the chemical bonding in the layers is sp^2 hybridisation while the layers are held together by Van der Waals forces. In these carbon tubes, the fact that all the basal planes run parallel coaxial to the tube axis, makes them one of the strongest materials known. In this structure the weakness of graphite due to the interplanar bonding (see figure 2) is avoided and the sp^2 carbon-carbon bond in the basal plane, as the strongest of all chemical bonds, is the only bond dominating the structure.[8]

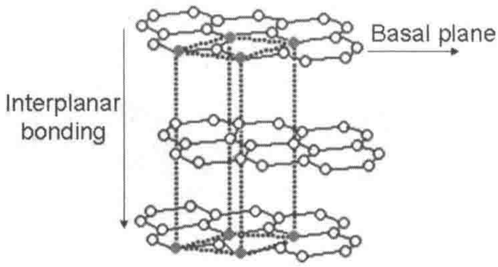

Fig.2. Planar sheets of graphite stack in hexagonal arrangement.

Also, their large elastic modulus and breaking strength makes them suitable candidates as reinforcement elements in ceramic, metal and polymer matrix composites.[8]

As it has been mentioned before, properties in electronic conduction of these nanotubes are directly dependent on the tubular structure, diameter and degree of helical arrangement. They have been classified into three classes: metallic tubes, semiconducting tubes with very narrow band gaps and semiconductive ones with moderate band gaps. [9,10]

Moreover, taking into account that monocrystalline diamond is one of the best thermal conductors due to its stiff sp^3 bonds, it was expected that carbon nanotubes had an unusual high thermal conductance. Atoms in this structure are held together by sp^2 bonding (even stronger than sp^3) and are consisted on atomically perfect graphitic cylinders with a few nanometers of diameter. Named high values are associated with large phonon mean free paths in these systems, with the rigidity and with the absence of atomic defects or coupling to soft phonon modes of the medium.[11]

More studies have been made analyzing CNTs properties finding that their field emission of electrons from individually mounted carbon nanotubes is enhanced when the nanotube tips are opened;[12] Additionally it has been found that they can adsorb large quantities of gases suggesting that they might be effective as a hydrogen-storage material.[13]

In terms of their optical properties, their light-emitting properties[14]and photo-conductivity[15] have been reported showing a narrow selectivity in the wavelength of emission and detection of light and the possibility of its fine tuning through the nanotube structure interesting for the development of light sensors.

In relation with their biocompatibility, CNTs have been under discussion as at the beginning of this nanotechnology boom, it was believed that they were toxic however recent studies on CNTs surface functionalization have demonstrated that their biocompatibility is dependent on the cell type exposed to, and it is assured by a proper surface treatment and functionalization.[16,17] Consequently, they have attracted a great interest in nanomedicine.[18]

Another fact to point out is the influence that the structural defects have in the CNTs properties. CNTs structural defects are atomic vacancies corresponding to deficiencies of carbon atoms in the network (incomplete bonding defects, vacancies, dislocations...) or topologic defects deviated from the hexagonal rings (introduction of ring types other than hexagons) also, the ability of the carbon atoms to hybridize between sp^2 and sp^3, etc...[19] The most common defects are called Stone-Wales (SW) defects that are created by a rotation of one of the C-C bonds from its initial site forming two heptagons or two pentagons in local structure.[20]

The single vacancies in the tubes, as they are active chemically, prefer to interact with adsorbates nearby, of which the interaction of the defects with hydrogen atom, hydrogen molecule and some small hydrocarbon radicals ($-CH$, $-CH_2$ and $-CH_3$).

Deffects influence the electronic structure of the systems as well as affecting their vibrational properties and the tensile strength of the tubes.

1.2.2 CNTs growth

Carbon nanotube synthesis is commonly carried out by using three techniques: Carbon arc-Discharge, Chemical vapor Deposition (CVD) and Laser Ablation. [21] These are vacuum techniques where the process is carried out in an inert gas pressure atmosphere which is one of the parameter that controls the processes.

In almost all cases carbon nanotubes are produced only when some catalyst particles are previously grown in the substrate, usually nanometer size metal particles (Fe, Co, Ni...). In the case of CVD, these particles catalyze the breaking of the gas molecules (common gases used are methane, ethylene and acethylene), liberating the carbon atoms, while the tube grows with the particle at the tip at certain temperatures. The size of the metal particles will influence on the final tube diameter.

On the laser ablation technique, where a laser is used to ablate a carbon target, graphite powder is dispersed on the substrate and CNTs are grown selectively as a function of the temperature.

In the case of arc discharge, a potential is set up between two electrodes and when the inert gas is introduced on to the chamber and at a certain distance between electrodes, an arc is striked and the plasma is formed. CNTs deposits in the anode when the arc is stabilized.

1.2.3 CNTs functionalization

Chemical surface modification (grafting chemical functional groups to a surface) and solubilization of CNTs are under research as functionalization is required to add new properties to the CNTs. Prominent examples can be found in semiconductor industry and biomaterial research.

Although CNTs electronic structure is conserved after non-covalent interactions with the surfaces as well as with the CNTs filling, thus preventing disruption of the sp^2 structure, the most common CNTs treatments are by covalent chemical modification strategies, which have the highest potential of giving them adaptable properties.[22]Also, covalent modifications are the most efficient approach to obtain a soluble material in a wide range of solvents.

The as-prepared CNTs always contain large amounts of impurities, such as amorphous carbon and catalytic metal particles and it was reported that treatments with nitric or nitric/sulfuric acid mixtures are the most common purification methods.[23,24] Treating CNTs with these acids, apart from purifying them from metal particles and opening the end caps of the tubes or shorting the length, creates defect sites. In general, intrinsic defects are supplemented by oxidative damage to the CNT network by strong acids which leave holes functionalized with oxygenated functional groups such as carboxylic acid, alcohol or ester groups.[22,25,26]

There are two most common routes to solubilizing (in water, or common organic solvents) CNTs and to achieve specific activities by binding molecules to the functionalized surfaces. One is the generation of an amide bond formation with the oxygenated functional groups and also, is widely used the attachment of surfactants as poly(ethylene glycol)(PEG) [27,28]and polymers or dendrimers.

This range of functionalized CNTs are seen like a high potential material for the development of innovative vectors for drugs,[29] DNA or vaccine delivery as it has been reported to be possible to link covalently to the surfaces bioactive peptides,[30] proteins fluorescent probes or series of aminoacids. [31]

2. Applications of CNTs in Biomedicine

Carbon nanotubes, because of their properties and tuneability, play an integral role as a unique biomaterial for biomedical applications, especially when it was discovered that their potential citotoxic effect can be mitigated by chemical surface functionalization. [32,33]

As it has been commented in the previous section, and deeply studied recently by Zhao et al.[33], CNTs can be functionalized with different functional groups to carry simultaneous moieties for targeting, sensing, imaging and delivery therapy.[34] Also, their mechanical and electrical