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Prologue: Thin-Film Synthesis and Application for Medical and Biological Use

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1. Introduction

With the advent of nanotechnology, researchers started almost simultaneously the use of nanophysics in medical industry and life sciences. The extreme and device-specific physicochemical properties and comparable molecular size scales of ‘nanoproducts’ had initiated a wide range of efforts searching useful applications and utilizations of the whole objects of macromolecules, systems and organisms. On the other hand, very rapid development in the field of fabrication technologies is introduced into the area of manufacturing with tailored properties. Different thin-film technologies enable the growth of coherent mono- or multilayer composite films with quite large surface areas. The possible utilizations and applications of different kind of thin-film structures in life sciences will be shortly discussed.

Nanotechnology is the study of extremely small structures, having size of 0.1–100 nm. The prefix ‘nano’ is a Greek word which means ‘dwarf’. The word ‘nano’ means very small or miniature size in real life. These materials should show/represent different properties, e.g. chemical reactivity, magnetic and optoelectronic effects, conductance, mechanical and plastic properties, etc. As a result of their small size, the **bulk** and **surface** properties are strictly different. But the most important property for us is their **biocompatibility**.

2. Historical background

‘There’s Plenty of Room at the Bottom: An Invitation to Enter a New Field of Physics’ was a lecture given by physicist Richard Feynman at the annual American Physical Society meeting at Caltech on December 29, 1959. Feynman considered the possibility of direct manipulation of individual atoms as a more powerful form of synthetic chemistry. Feynman also suggested that it should be possible, in principle, to make nanoscale machines that ‘arrange the atoms the way we want’ and do chemical synthesis by mechanical manipulation. These sentences can be seen as the birth of the ‘nanoworld’ [1].

Norio Taniguchi has introduced the term of nanotechnology in order to describe some physical processes running on the scale of nanometres. These phenomena are related to processing of separation, deformation and consolidation on the basis of some atoms and molecules [2]. Some important milestones in nanotechnology are the following:

- 1981, IBM: development of the scanning tunnelling microscope (STM) [3, 4].
- 1985: invention of Bucky Ball by Kroto [5]. A buckyball is a molecule called Buckminsterfullerene. Consisted of 60 carbon atoms arranged in the shape of a hollow ball, buckyballs have, as yet, little practical use, although they do make up nanotubes, which have some uses.
- 1986: the first book about nanotechnology [6].
- 1991: Iijima discovered carbon nanotubes (CNT) for the first time [7].
- 1999: first nanomedicine book by Freitas was published [8].
- 2011: the era of molecular nanotechnology started.

3. Classification of nanomaterials

A plenty of experimental methods are available for the fabrication of nano-sized structures, but each of them can be put into one of the two main classes. Nanomaterials and nanostructures can be fabricated by removing some part of a bulk material to sculpture the desired shape that can be constructed from much smaller parts. These two main classes are termed as 'top-down' and 'bottom-up' approaches [9, 10].

3.1 Top-down methods

Top-down manufacturing method deals with mechanical operations, for example, cutting, moulding and carving. Because of size limitations, we will get highly specialised nanostructures. Some manufacturing methods involve laser-based ones like ablation, deposition and milling; some of them use hydrothermal techniques like liquid- or gas-phase deposition. Electromechanical and electro-chemical methods are also widely used (electroplating, etching, etc.).

Most top-down nanofabrication methods are for surface patterning. By patterning local surface regions of a solid substrate with nanoscale features, the substrate has the ability to recognise specific nanostructures. For instance, when the substrate is placed in a solution, millions of nanostructures can self-assemble in parallel. Some patterning methods are developed to write nanoscale features, others are to replicate.

3.2 Bottom-up approach

Bottom-up methods represent a wide range of component-construction techniques. The building blocks are probably simple molecules held together by their covalent bonds. The resulted macroscale components are strong enough and stable. Many different techniques like atomic force microscopy (AFM), liquid- and gas-phase techniques, consisting sol-gel processes, and inverse micelles are involved. One of the most important characteristics is the molecular self-assembly.

3.3 Deposition techniques

Thin-film deposition involves processing above the substrate surface (typically a silicon wafer with a thickness of 300–700 μm), where different materials are

added to substrates in form of simple or structured layers (thin films or composed aggregates with discrete spacers later to be removed). Deposition techniques fall into two categories, depending on whether the process is primarily chemical or physical.

Chemical deposition means deposition of layers via chemical reactions. The deposition rate on the substrate is governed by the properties of materials like pressure, temperature, etc. Based on the precursor phase, deposition processes can be classified as plating, spin coating, low-pressure deposition, plasma-enhanced deposition or layer-by-layer (atomic) deposition.

In the process of **physical deposition**, the material (solid, liquid or vapour) is physically transferred to the substrate (heated). These processes are thermal deposition, sputtering, ion plating, etc. The main operating factors are the substrate structure and temperature. The rate of deposition describes the volume/mass of the deposited material in unit time.

These layers are deposited and subsequently patterned using photolithographic (induced by laser or electron beam) techniques and then etched or washed away to release the final structure. We should also mention the electrophoretic deposition (EPD) that is a wet electrolytic deposition technology for thin films. EPD employs the mechanism of electrophoresis. Electric field is applied between two electrodes and charged particles dispersed or suspended in a liquid medium moving towards the oppositely charged electrode (electrophoresis), followed by the accumulation of particles on the deposition electrode in an ordered manner, producing a relatively compact and homogeneous film.

4. Some advantages and limitation of thin films: Drug delivery

Thin-film drug delivery stands as an alternative method to the traditional pills and capsules. Thin films and strips of a few centimetres in size might be subjected to oral or under tongue administrations. As the strip dissolves, the drug enters the bloodstream (buccally or sublingually). These drug delivery options allow the bypass of the metabolic pathway; therefore, this medication method is more bioavailable.

Polymeric thin films can also be beneficial for bedridden and non-cooperative patients. Thin films are useful in cases where rapid onset of action is required, such as in motion sickness, sudden episodes of allergic attack or coughing, bronchitis or asthma.

The use of thin films is sometimes limited due to low drug loading capacity compared to a less potent drug given at high dose. Thin films are usually very hygroscopic in nature, and sometimes it is difficult to obtain them in high degree of accuracy.

The most important polymeric films used in pharmaceutical and medical applications are hydroxypropyl methylcellulose (HPMC), carboxymethyl cellulose (CMC), hydroxypropyl cellulose (HPC), poly(vinyl pyrrolidone) (PVP), poly(ethylene oxide) (PEO), pullulan, pectin, chitosan, carrageenan and gelatin.

5. Biocompatibility

Biocompatibility is related to the behaviour of biomaterials in various contexts. It means that the biomaterial is able to get prompt and exact response from the host/tissue materials in different and specific situations. The most important common definitions related to the term of biocompatibility are the following:

1. The quality of not having toxic or injurious effects on biological systems.
2. The ability of a material to perform with an appropriate host response in a specific application.
3. The tissue response to the implanted/added material should be recognized as suitable with control materials.
4. The biomaterial should carry out its prescribed function by medical therapy. No other eliciting and undesirable effects are allowed. From the part of recipient, the most desirable tissue response should be realized.
5. In the case of a prosthetic implant, the harmonic tissue reflectance is of first-order importance. No any deleterious change is allowed.

6. Nanotechnology in life sciences

The major problems like cancer, Parkinson's disease and Alzheimer's disease are subject to nanoparticle utilizations for surgery and therapy. Also some other diseases like cardiovascular ones, multiple sclerosis and inflammatory or other infectious diseases are subjects for nanotechnology interference. This field is called nanomedicine. Different researches are conducted on nanocomposites or doped nanocomposites for use as interventions involving bones, cartilages, muscles, etc.

Molecules can be absorbed on the surface of single-walled carbon nanotubes. They could greatly influence the electrical properties or could serve as sensors with very high sensitivity and selectivity.

Advanced biosensors with novel features can be developed with the help of carbon nanotubes (CNT). This technology is also being used to develop sensors for cancer diagnostics. Though CNT is inert, it can be functionalized at the tip with a probe molecule. Their study uses atomic force microscopy (AFM) as an experimental platform.

Some of the researches in biomedicine have shown that carbon nanotubes can also be used for drug delivery. Magnetic nanoparticles are used to isolate and group stem cells. They also can be used in digital imaging methods of cells. Because of their very small size, nanoparticles represent a good candidate to be used in oncology imaging studies. Due to the quantum confinement properties, they can be used in imaging of tumour sites. Compared to organic dyes, nanoparticles have higher brightness and more efficient fluorescence efficiency leading to higher contrast in image reconstructions. Due to their high surface-area-to-volume ratio, it is possible to bind them to tumour cells. Because of their small size, they can accumulate on tumour sites with high probability.

6.1 Cancer research

Due to the small size of nanoparticles, they can be of great use in oncology, particularly in imaging. Nanoparticles, such as quantum dots with quantum confinement properties, such as size-tunable light emission, can be used in conjunction with magnetic resonance imaging, to produce exceptional images of tumour sites. As compared to organic dyes, nanoparticles are much brighter and need only one light source for excitation. Thus, the fluorescent quantum dots could produce a higher contrast image at a lower cost than organic dyes used as contrast media. But quantum dots are usually made of quite toxic elements.

Nanoparticles have a special property of high surface-area-to-volume ratio, which allows various functional groups to get attached to a nanoparticle and thus bind to certain tumour cells. Furthermore, the 10–100 nm size of nanoparticles allows them to preferentially accumulate at tumour sites as tumours lack an effective lymphatic drainage system. Multifunctional nanoparticles can be manufactured that would detect, image and then treat a tumour in future cancer. Nanowires are used to prepare sensor chips, which can detect proteins and other biomarkers left behind by cancer cells and detect and make diagnosis of cancer possible in the early stages from a single drop of a patient's blood.

The possible applications of various nanosystems in cancer therapy [12]:

- Carbon nanotubes, with 0.5–3 nm in diameter and length of 20–1000 nm, are used for detection of DNA mutation and for detection of disease protein biomarker.
- Dendrimers, less than 10 nm in size, are useful for controlled release in drug delivery and as image contrast agents.
- Nanocrystals, with a size of 2–10 nm, could serve as breast cancer markers.
- Nanoparticles are of 10–1000 nm in size and can be used in MRI and as contrast agents in ultrasound image formation.
- Nanoshells find application in tumour-specific imaging and deep tissue thermal ablation.
- Nanowires are useful for disease protein biomarker detection.
- Quantum dots with size of 2–10 nm can help in optical visualisation of genes tumour and lymph nodes.

7. Specific materials

7.1 Polymers

Despite the classical clinical biomaterials/implants such as pacemaker, catheter, modern implants and prostheses consist of several materials therefore the biocompatibility means multicomponent guest materials in host (tissue) environment. The plastic materials—nowadays—are undergoing rapid development. Especially due to the high compact of plastic industry, the materials are more aesthetic, safe and of better quality.

Among plastics, the most commonly used biocompatible materials are:

- Polyvinyl chloride (PVC)
- Polytetrafluoroethylene (PTFE, Teflon)
- Polypropylene (PP)
- Polyurethane (PU)
- Polymethyl metacrylate (PMAA)

- Polycarbonate (PC)
- Polyether ether ketone (PEEK)
- Ultrahigh molecular weight polyethylene (UHMWPE)
- Polydimethyl-siloxane (PDMS)

7.2 Diamond

One such substrate material that has recently been gaining in popularity is thin-film diamond. In early reports, very low toxicity was observed when diamond particles were injected as a suspension into live animals. Subsequently, it was established that diamond films as a cell culture substrate can successfully support a wide range of adherent cells. One of the most important properties of the diamond film is that it is bioinert, no coagulation and no inflammatory reactions [11]. One of its further advantages is the controllable electrical conductivity and the possibility of surface patterning.

7.3 Graphene oxide (GO)

Graphene oxide (GO) is a unique material that can be viewed as a single monomolecular layer of graphite with various oxygen containing functionalities such as epoxide, carbonyl, carboxyl and hydroxyl groups. The reduced GO forms (rGO) which contains residual oxygens, some structural defects and other heteroatoms make it more functionally. Nevertheless, since rGO can be made as a thin film from an aqueous dispersion of GO in water and has moderate conductivity, it is attractive for use in electronic devices. In addition to being components in electronic devices, GO and rGO have been used in nanocomposite materials, polymer composite materials, energy storage devices, biomedical applications and catalysis and as a surfactant [12].

One use of GO in the biomedical field is as a component in drug delivery. Functionalized nanographene oxide (nGO) has been used in several studies on targeted delivery of anticancer drugs. Polyethylene glycol (PEG)-functionalized nGO with a camptothecin derivative (nGO-PEG-SN38), adsorbed onto the surface, was used as a water- and serum-soluble source of the drug. nGO-PEG-SN38 was shown to be three orders of magnitude more effective than irinotecan (CPT-11), an FDA-approved SN38 prodrug, at reducing the cell viability of human colon cancer cell lines HTC-116 [13]. GO has also been used as a fluorescence quenching material in biosensors which utilise the fluorescence resonance energy transfer (FRET) effect.

8. Conclusions

Nanostructures in their different forms, thin films, matrices, etc., have a wide range of possible utilizations due to their small—comparable to molecules—sizes, their physicochemical activity, etc. Applications/manufacturing methods are presented in this chapter focusing on making interest in life and medical sciences.

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