Original scientific papers UDK 661.12:66.012
doi:10.5767/anurs.cmat.110201.en.027M

SHELL-NANOSTRUCTURED MATERIALS FOR BIOPHARMACY AND BIOMEDICINE

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Abstract: Based on our research in ultrathin crystal structures performed so far, superlattices, Q-wires and Q-dots, we will consider the materials that can act as carriers for medicines and tagged substances. For this purpose we established a shell-model of ultrathin molecular crystals and investigated their dielectric, particularly optic characteristics. We conducted this research with the help of two-time dependent Green's function method, adjusted to ultrathin crystalline structure analysis. It is shown that specific resonant absorption lines appear in these structures, the number of which depends on crystal layers position and on values of parameters on shell-structure boundary surfaces. The absorption of electromagnetic radiation declines in infrared part and its detection is a relatively easy process.

In this paper we will analyze application of nanomaterials in biomedicine, that is to say we will present the recent accomplishments in basic and clinical nanomedicine. Achieving full potential of nanomedicine may be years of even decades away, however, potential advances in drug delivery, diagnosis, and development of nanotechnology-related drugs start to change the landscape of medicine. Site-specific targeted drug delivery (made possible by the availability of unique delivery platforms, such as dendrimers, nanoparticles and nanoliposomes) and personalized medicine (result of the advance in pharmacogenetics) are just a few concepts on the horizon of research. In this paper, especially, we have analyzed the changes in basic physical properties of spherical-shaped nanoparticles that can be made in several (nano)layers and have, at the same time, multiple applications in medicine.

Keywords: shell model, nanomaterials, biopharmacy, nanomedicine.

1. INTRODUCTION

Science is nowadays very interested in low-dimensional systems, the dimensions of order of even few nanometers, which, in practical application, demonstrate exceptional characteristics in various fields. The need to minimize dimensions was imposed by a number of inter-related and mutually dependent requests of modern civilization, probably key to its further survival and sustainable development, which can generally be categorized as belonging to the fields of energy, health and ecology. In that sense, the subject of the research in this paper will include nanomaterials in the field of biopharmaceutical technology for biomedical application [1]. This includes the very precise encapsulated drug delivery, on exactly defined place in the human tissue or organ and disintegration of capsule – drug carrier, so that the medicament can start producing its effect.

The goal of multidisciplinary researches with biocompatible molecular nanomaterials is to find the parameters and the possibilities to construct border surfaces that will, in interaction with biological environment, create such properties of nanolayers that are convenient for use for layers of drug carrier capsules, biochips and biomarkers. These layers should demonstrate controlled disintegration of structure, better differencing of dielectric properties, discrete selective luminescence and appropriate bioporosity as all these are the requirements of contemporary nanomedicine [2]. The ultimate goal of the proposed research is to gather, test and verify, in experimental manner, the results of theoretical research aimed at improvement of the proposed models for creating the structures of biocompatible nano-layers for na-

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nomedicine, by using contemporary methods and latest devices based on electronic microscopy (AFM, MFM and OMF).

In this paper we will analyze application of nanomaterials in biomedicine, that is to say we will present recent accomplishments in basic and clinical nanomedicine. Numerous novel nanomedicine-related applications are under development or are in a research phase, and the process of converting basic research in nanomedicine into commercially viable products will be long and difficult. Achieving full potential of nanomedicine may be years of even decades away, however, potential advances in drug delivery, diagnosis, and development of nanotechnology-related drugs start to change the landscape of medicine. Site-specific targeted drug delivery (made possible by the availability of unique delivery platforms, such as dendrimers, nanoparticles and nanoliposomes) and personalized medicine (result of the advance in pharmacogenetics) are just a few concepts on the horizon of research.

2. NANOTECHNOLOGY, NANOPHARMACY AND NANOMEDICINE

One of the problems facing nanotechnology is in the confusion and disagreement among experts about its definition. Nanotechnology is an umbrella term used to define the products, processes, and properties at the nano/micro scale that have resulted from the convergence of physical, chemical, and life sciences.

To add to this confusion, experts point out that nanotechnology is not new a technology. For example, nanoscale carbon particles (‘‘high-tech soot nanoparticles’’) have been used as a reinforcing additive in tires for more than a century. Similarly, protein vaccines fall within the NNI definition of nanotechnology. In fact, the scale of many biologic structures is similar to components involved with nanotechnology. For example, peptides are similar in size to Q-dots (~10 nm), and some viruses are the same size as drug-delivery nanoparticles (~100 nm). Hence, most of molecular medicine and biotechnology may be considered nanotechnology.

A more appropriate and practical definition of nanotechnology, unconstrained by size, was proposed in [3,4]: “The design, characterization, production, and application of structures, devices, and systems by controlled manipulation of size and shape at the nanometer scale (atomic, molecular, and macromolecular scale) that produces structures, devices, and systems with at least one novel/superior characteristic or property.”’ Although the definition is arbitrary, industry and governments are clearly beginning to envision nanotechnology’s enormous potential. The process of converting basic research in nanotechnology and nanomedicine into commercially viable products may be long and difficult, but governments across the globe are impressed by its potential and are staking their claims by doling out billions of dollars, euros, and yen for research. International rivalries are growing [5–7].

Nanomedicine has been defined as ‘‘the monitoring, repair, construction, and control of human biological systems at the molecular level, using engineered nanodevices and nanostructures’’ [3–5]. Therefore, nanomedicine adopts the concepts of nanoscale manipulation and assembly in applications at the clinical level of medical sciences. In a broad sense, nanomedicine is the application of nanoscale technologies to the practice of medicine. It is used for the diagnosis, prevention, and treatment of disease and to gain an increased understanding of complex underlying disease mechanisms. Although nanotechnology is an established discipline, commercial nanomedicine (with its broad range of ideas, hypotheses, concepts, and undeveloped clinical devices) is still at a nascent stage of development.

For example, there are many nanodevices (eg, Q-dots – Fig. 1, and dendrimers – Fig. 2, from [8]) that are widespread and broadly marketed, but have yet to find their way into a wide range of clinical devices. This is a consequence of the extremely complex and demanding requirements of clinical trials by the FDA, which can take years before a product makes the long trek from a concept in the laboratory to a commercially viable medical product for the consumer.

Currently, nanomedicine involves detection of particles; drug delivery systems, emulsions, and carriers for delivering vaccines; and nanofabricated biomaterials with unusual properties of strength, hardness, reduced friction, and improved biocompatibility. More exotic concepts (eg, nanomachines that could move through the body, troubleshooting and repairing tiny brain or cardiovascular lesions) lie in the future.

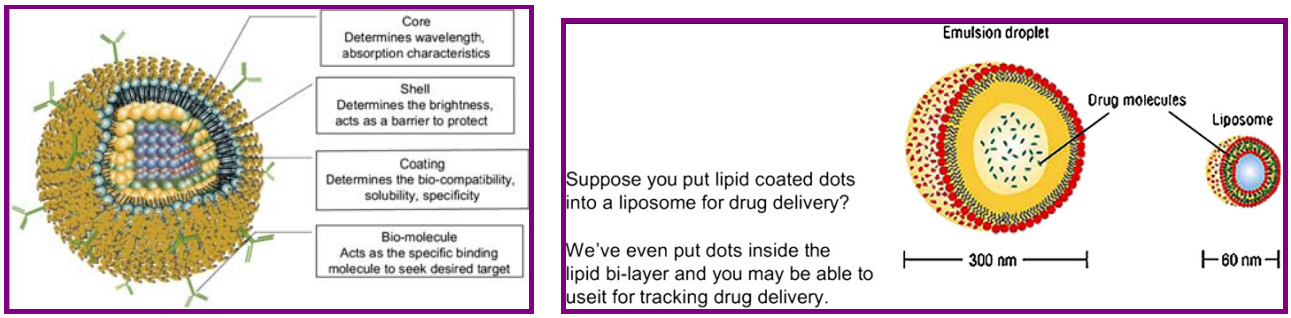

Figure 1. Structure and applications of Q-dots for drug delivery

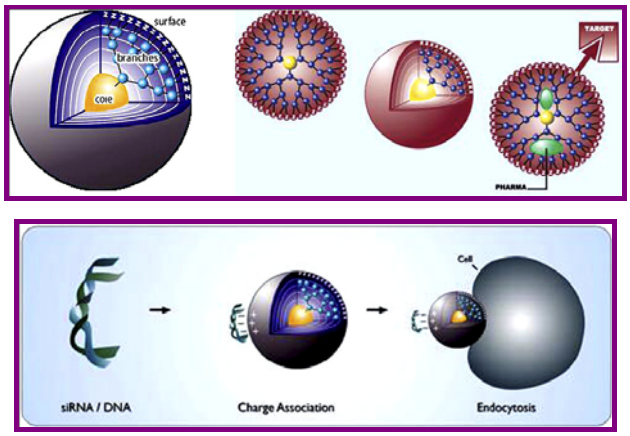

Figure 2. Structure of dendritic NanoTechnologies' vehicle for drug delivery/gene silencing[1]

2.1. Real benefits of nanomedicine and areas of potential development

As envisioned earlier, applications of nanotechnology to medical sciences hold a wealth of promises. But "nano" has been promoted so enthusiastically that the hype may exceed reality, especially given the immense lag time between discovery and actual products in biomedical sciences. Nanomedicine is even more problematic because its wide scope is full of potential, yet it is still beset by many fundamental questions. Given these caveats, the recognizable benefits of nanomedicine are in the area of materials that can act as carriers for medicines and tagged compounds for visualizing cancers and other lesions.

As reported in [3], there are expectations that in the coming years significant research will be undertaken in the following areas of nanomedicine:

− Synthesis and use of novel nanomaterials and nanostructures (eg, less antigenic);

− Biomimetic nanostructures (synthetic products developed from an understanding of biologic systems);

− Analytic methods and instruments for studying single biomolecules;

− Devices and nanosensors for early point-of-care detection of diseases and pathogens (eg, polymerase chain reaction-coupled micro/nano-fluidic devices);

− Identification of novel biologic targets/receptors/ligands for imaging, diagnosis, and therapy (eg, for cancers and for neurodegenerative and cardiovascular diseases);

− Construction of multifunctional biologic nanostructures, devices, and systems for diagnosis and combined drug delivery (theranostics);

− Nanotechnology for tissue engineering (nanostructured scaffolds) and regenerative medicine;

− Fabrication of noninvasive in vivo analytic nanotools with improved sensitivity and resolution for molecular imaging and for studying pathologic processes in vivo;

− Stimuli-sensitive nanodevices and physically targeted treatments.

Specifically, in the drug-delivery arena, nanotechnology is poised to deliver to the market evolutionary and revolutionary products [5]. Some products could be available immediately, whereas others will appear in the distant future and include:

− Miniaturized nanofluidic devices and systems that transport fluids more efficiently to the site of delivery, preventing turbulence and mixing (because fluids move with laminar flow through micro/nanochannels);

− More efficient site-specific or precision targeting by way of nanodrugs, resulting in with reduced systemic side effects and better patient compliance;

− Close-looped drug delivery nanodevices and implants containing sensors (to monitor biomolecules) and drug reservoirs (for precise delivery) on the same chip;

− Microsurgical devices, molecular motors, or nanobots that are capable of navigating througho-

[1] Promising nanoparticles: researchers are working to convert dendrimers like these into useful drug-delivery tools. Dendrimers are already used widely in the laboratory. Qiagen's Superfect DNA transfection reagent is a dendrimer whose positively charged surface binds the nucleic acid's negatively charged phosphate backbone. siRNA, silencing RNA.

ut the body to repair damaged sites, destroy tumors or viruses, and even perform gene therapy.

Nanomedicine also aims to learn from nature to understand the structure and function of biologic devices and to use nature's solutions to advance science and engineering. This approach is referred to as "biomimicry". Evolution has produced an overwhelming number and variety of biologic devices, compounds, and processes that function at the nanometer or molecular level and that provide performance that is unsurpassed by synthetic technologies. When nanotechnology is combined with molecular biology, the possible applications at this frontier are widespread, sounding like the stuff of science fiction. Nanomedicine can be characterized as a primitive technology that takes advantage of the properties of highly evolved natural products, such as nucleic acids and proteins, by attempting to harness them to achieve new and useful functions at the nanoscale. The construction principles used in this field often originate in biology, and the goals often are biomimetic or aimed at the solution of long-standing research problems. The concept of self-assembly is at the heart of the approaches in this field. Self-assembly of ordered elements is a defining property of life.

In the nanodiagnostics area, much of the research has been focused on biochips, devices containing numerous biologic sensors. Nanotechnology has been proposed to increase the density of such sensors on the biochips and to provide alternative detection mechanisms.

Nanoparticulate drug delivery vehicles [9] would allow faster drug absorption, controlled dosage releases, and shielding from the body's immune system-enhancing the effectiveness of existing drugs. Researchers are also investigating novel treatments using nanoparticles, such as dendrimers, as delivery devices to insert genes into cells.

Nanotechnology is being applied to the drug discovery and development process as well. The drug discovery process is time consuming and expensive (8-14 years at a cost of ~$1 billion dollars). Nanotechnology will result in a reduction of the cost of drug discovery, design, and development. In addition, nanotechnology will enhance the drug discovery process itself through miniaturization, automation, speed, and reliability of assays. This will result in the faster introduction of new, cost-effective products to the market. For example, nanotechnology can be applied to current microarray technologies, exponentially increasing the hit rate for promising compounds being screened as candidates for the pipeline of drug development. Inexpensive and higher throughput DNA sequencers based on nanotechnology can reduce the time for drug discovery and diagnosis.

2.2. Quantum particles for nanomedicine applications

Nanomedicine attempts to exploit the self-assembly and ordered proximity of nanoscale structures found in biology. The specific model of crystal structures that involve a series of ultrathin films "glued together" is called superlattice [10], whereas the models that are limited/restricted along two spatial dimensions and of small size along these directions are known as quantum wires or nanorods [11]. The model of crystal structures which are small-sized and limited along all three dimensions are known as quantum dots (Q-dots) [12]; they may be of different shapes, however, the shapes most commonly found in researches are those rectangular (nanoparallelepipeds) and disc-shaped (hollow and solid discs).

Q-dots figure prominently in the investigation of dynamic processes in living systems. Their properties have been reviewed extensively [13]. These colloidal semiconductors are single crystals whose size and shape can be controlled precisely, which determines their absorption and emission properties. Thus, the investigator can precisely design fluorophores whose emission is related directly to their size (so called ''quantum confinement''), such that the Q-dot will emit photons in a tightly defined color range. Even single molecules can be tracked. The specificity of Q-dots may be realized, for example, by coating them with streptavidin and then conjugating them to a biotinylated antibody. In this state, the Q-dot can bind to a specific cellular receptor or other cellular target. In addition to a recognition moiety, different functionalities can be added to individual Q-dots, resulting in multipotent probes. By coating Q-dots with natural peptides, it is possible to produce particles with excellent biocompatibility, colloidal properties, and photophysics. Q-dots possess the striking property of resistance to photobleaching over long periods of time, making them useful for long-term, three-dimensional studies. Moreover, they are extremely bright, displaying 10 to 20 times the emission level of organic fluors [14].

Dendrimers are a major architectural class of nanoscale chemical polymers [15]. The term describes a large, synthetically produced precisely defined polymer in which the atoms are arranged in many branches and subbranches radiating out from a central core [16]. Dendrimers are built from a starting atom, such as nitrogen, to which carbon and other elements are added by a repeating series of chemical

reactions that produce a spherical branching structure. As the process repeats, successive layers are added, and the sphere can be expanded to the size required by the investigator. The result is a spherical macromolecular structure whose size is similar to albumin and hemoglobin, but smaller than such multimers as the gigantic IgM antibody complex. By manipulating the chemistry of dendrimers, the geometry and properties of their structure can be altered to perform a vast array of functions, including acting as MRI contrast agents. By altering the size of the dendrimers, their properties of elimination through excretion can be changed profoundly, with the consequence that a range of patterns of localization in kidneys, lymphatics, liver, and blood pool can be specified. This new class of contrast agents has the potential for extensive applications in MRI. By the same rationale, dendrimers can be engineered for nano-based drug delivery.

Dendrimers can be designed to the appropriate size to encapsulate a drug, allowing for optimum delivery. The degree of encapsulation can dictate the rate of release in a controlled manner. The nanodimensions of the dendrimers can be specified so as to fit a specific receptor, thereby targeting delivery of the drug. Although traditional drug delivery is monovalent, dendrimers can be engineered to carry a large number of drug molecules on their spherical exteriors in such a fashion that interaction with the receptor-studded cellular membrane mimics the natural binding of a large viral entity to the target cell.

Diagnosing, treating, and following the progress of therapy for individual malignancies are the principal goals of oncologists for which nanotechnology offers solutions. The ability to shape molecules with great precision is opening the door to a new generation of drugs, imaging agents, and diagnostics. Because nanotechnology offers more than just a tool, but rather a pervasive concept, it promises to dominate the entire enterprise of cancer diagnostics and therapeutics. Already, a half-dozen nanoparticles-based imaging and therapeutic agents are in various stages of development. Nanotechnology provides tools for developing personalized medical treatments by tracking and identifying receptors and other cell surface proteins specific to individual tumor cells. For example, iron oxide nanoparticles coupled to the therapeutic antibody trastuzumab have been targeted and bound to the HER-2/neu cell membrane receptor, eliciting detectable changes in ultrasound responses from human breast cancer cells [17]. These findings serve as proof-of-concept data for the development of a diagnostic test for trastuzumab response in patients who have breast cancer.

2.3. Nanoparticulate drug delivery system

Several terminologies have been used to describe nanoparticulate drug delivery systems (NDDS). In most cases, either polymers or lipids are used as carriers for the drug, and the delivery systems have particle size distribution from few nanometers to few hundred nanometers (Table 1).

Protein-based nanoparticulate drug delivery systems are defined as proteins being biodegradable, biocompatible, very versatile molecules, and can be used as drug carriers [19]. A protein-based nanoparticulate drug delivery system is already in the market but protein macromolecules offer many advantages over their synthetic counterparts (synthetic polymers that are commonly used as drug carriers). Owing to the presence of several synthetic functional groups in protein molecules, these molecules are more versatile and can offer covalent or noncovalent modifications of the molecules when used as drug carriers. Owing to this property, these can be used for delivering different drug molecules. As these protein molecules are biocompatible and biodegradable, this is a distinct advantage over their synthetic counterparts. More detailed description of these protein carriers is described elsewhere. Some of the natural organic and protein molecules are also described as carriers for drug. These are fabricated as nanoparticles or nanofibers for delivering the drugs [20].

Since the first nanoparticulate drug delivery systems as Liposome proposed in 1974 [21] lead to several breakthrough discoveries by using nanoparticles as drug carriers resulting from cutting-edge researches based on multidisciplinary approaches, many more applications have developed. Several research reports have been published on the applications of nanoparticulate drug delivery systems using various drug entities and polymers and different forms of drug delivery systems. Table 2 provides details of several of these research reports [18].

As reported in [18,22] NDDS applications are in connection with the following areas of nanomedicine:

- Blood–brain barrier cancer treatment;
- Antibody targeting;
- Vaccine delivery;
- Nanostructured lipid carriers;
- Mucoadhesive and improving the gastrointestinal tract absorption;
- Hydrogel nanoparticles;
- Nanoparticles in diagnostic medicine;
- Nanovehicular intracellular deliverer.

Table 1. Types of terminologies used for NDDS

S. No.	Terminologies used	Particle size distribution (nm)
Polymeric systems		
1	Dendrimers	1-10
2	Polymer micelles	10-100
3	Niosomes	10-150
4	Nanoparticles	50-500
5	Nanocapsules	100-300
6	Nanogels	200-800
7	Polymer–drug nanoconjugates	1-15
8	Chitosan polymers	100-800
9	Methacrylate polymers	100-800
Lipid systems		
1	Solid lipid nanoparticles	50-400
2	Lipid nanostructured systems	200-800
3	Cubosomes	50-700
4	Liposomes	10-1000
5	Polymerosomes	100-300
6	Immunoliposomes	100-150
Protein/peptide nanotubes		
1	Peptide nanotubes	1-100
2	Fusion proteins and immunotoxins	3-15
Metal nanostructures		
1	Metal colloids	1-50
2	Carbon nanotubes	1–10 (diameter) and 1–1000 (length)
3	Fullerene	1-10
4	Gold nanoparticles	100-200
5	Gold nanoshells	10-130
6	Silicone nanoparticles	–
7	Magnetic colloids	100-600

The industrial scene of nanotechnology developments is very promising. The application of nanotechnology to drug delivery is widely expected to create novel therapeutics, capable of changing the landscape of pharmaceutical and biotechnology industries. Various nanotechnology platforms are being investigated, either in development or in clinical stages, and many areas of interest where there will be effective and safer targeted therapeutics for a myriad of clinical applications. It will be evolving out very soon for the benefit of humanity at large.

3. NANOSPHERES AND NANOCAPSULES

Nanocapsule, made in Würzburg [23]: Thousands of similar molecules are packed together to create a capsule that is filled with molecules of a different kind (Fig. 3). The diameter of one capsule is a mere 20 to 50 nanometers, which is one ten-thousandth of a pinhead.

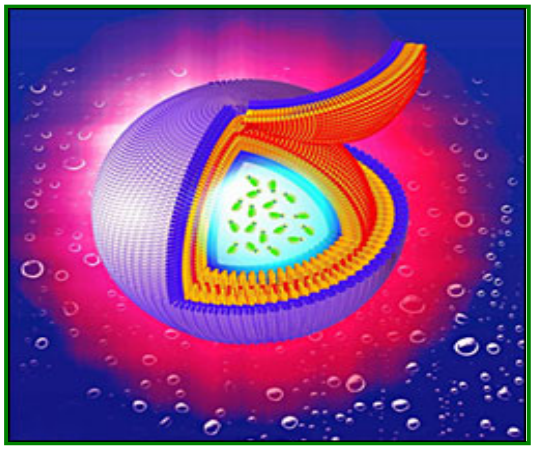

Figure 3. Spherical (nano)capsule

Table 2. Some recent research reports covering various applications of NDDS

Drug used	Polymer used	Form of the drug delivery systems suggested	Therapeutic indication
Oridonin	Poly(D,L-lactic acid)	Nanocapsules	Multiple myeloma
Cisplatin	Phosphatidylethanolamine	Liposomes	Melanomas
Aclarubicin	Albumin-conjugated PEGylated drug	Nanoparticles	Glioma
Amphotericin B	Lipoproteins	Nanodisks	Antibiotic
Docetaxel	PEG derivatives	Nanosized PEG drug assembly	Cancer
Ceramide and paclitaxel	Lipid carriers	Nanoemulsions	Cancer
Cisplatin	Hyaluronic acid-drug conjugate	Nanoparticles	Cancer
Fludarabine and mitoxantrone	Lipid carriers	Liposomes	Lymphoproliferative disorder
Estradiol	PLGA	Nanoparticles	Hormone
Cyclosporine	Polymeric micelles delivery	Colloidal	Antibiotics
Flurbiprofen	PLGA	Nanospheres	Ocular delivery
Insulin	Sodium alginate and chitosan	Nanospheres	Diabetes mellitus
Thymopentin	Poly(butyl cyanoacrylate) polymer	Nanoparticles	Protein peptide drug for cancer treatment
Indinavir	Lipids	Lipid-drug conjugates	AIDS treatment
Cyclosporin	Poly sorbate 80	Nanodispersion	Pulmonary infections
Ketoprofen and diflunlsal	Polyamidoamine dendrimers	Drug-polymer complex suspension	Anti-inflammatory
Halofantrine and procubol	Cremaphore RH 40	Self-emulsifying nanoemulsion system	Lipophilic drug models
Etoposide	Poly(D,L-lactide) block copolymers	Nanoparticles	Cancer

Abbreviations: PEG, poly(ethylene glycol); PEO, poly(ethylene oxide); PLGA, poly(lactic-glycolic acid); PPO, poly(phenylene oxide).

Nanocapsules possess a property that is important in photosynthesis in plants: the molecules inside the capsule absorb light energy and emit some of this again in the form of fluorescent light. The rest of it, however, is transmitted by energy transfer to the capsule molecules, which then also cast fluorescent light. As far as photosynthesis is concerned nothing different happens, to put it simply: molecules harness energy from sunlight and transmit it to other molecules in a complex process, at the end of which the energy is bound chemically.

These nanocapsules are comprised of a unique material [24]: on the basis of so-called amphiphilic perylene bisimides. If the base material, which can be isolated as a powder, is placed in water, its molecules automatically form so-called vesicles, though these are not stable at that point. It is only through photopolymerization with light that they become robust nanocapsules that are stable in an aqueous solution – regardless of its pH value. The researchers have access to an extremely sensitive nanoprobe: the pH value of an aqueous solution can be determined with nanoscale spatial resolution over the wavelength of the fluorescent light emitted by the nanocapsules. This means that nanocapsules are not just an option for artificial photosynthesis, they can also be used for diagnostic applications. For example, they could be equipped with special surface structures that purposefully dock to tumor cells and then make these visible by means of fluorescence.

Gold has received much interest in the field of biomedical engineering. With the advent of numerous tools, techniques, and concepts related to nanotechnology, in combination with the inherent property of gold to form functionalized bioconjugates via simple chemistry, gold has found importance in various biodiagnostic and therapeutic applications [25]. Herein, we detail the progress made in the functionalization of gold surfaces, both planar and particulates, at the nanoscale for diagnostic and therapeutic

applications. The unique chemical and physical properties of gold render it as effective sensing and delivery systems for pharmaceutical applications. The various properties of gold nanoparticles (GNPs) are mostly size dependent and surface characterized; therefore, the controlled synthesis of GNPs is important for bio-nanotechnological applications. Gold is mostly considered inert and nontoxic. Although gold can be directly used for biomedical applications, unique applications of this inert metal require functionalization with other biomolecules or biocompatible polymeric systems.

Surface modification of gold particles with stabilizing agents can be achieved by many methods. The thiol gold chemistry is used as the key mechanism for grafting small biomolecules and short-chain, end-functionalized polymeric stabilizers to gold. These monolayer-protected clusters of 1,5 to 6 nm are prepared by the reduction of $HAuCl_4$ by sodium borohydride ($NaBH_4$) in the presence of alkanethiol-capping agents. Table 3 provides a list of "grafting to" surface-modified particles, as synthesized by various researchers for biorelated diagnostic and therapeutic applications.

Table 3. Postsynthetic functionalization methods used for the preparation of modified biodiagnostic and therapeutic GNPs

Type of gold nanoparticles	Functional group attached
Biomolecule protected	Peptide Phospholipids Synthetic lipids Microorganism Viruses
"Green" chemistry	Ionic liquids Polysaccharides: chitosan Polysaccharides: sucrose
Dendrimer protected	Poly(amidoamine) based Other dendrimers
Polymer protected	Linear polymer Hyperbranched polymer Amphiphilic polymer Environmentally PEG functionalized Bioconjugated PEG

Over the past decade, nanotechnology for biomolecular detection has made enormous advancements. Nanoparticles, in particular, have been developed for accurate, sensitive, and selective biosensing devices due to their unique size-related, ease-of-functionalization, and unique physical properties (electrical, optical, electrochemical, and magnetic). GNPs are mostly used in biomedical field as labels for biomolecular detection in the place of conventional molecular fluorophores, where their unique size-tuned optical properties are exploited.

The inert and nontoxic property of gold along with the ready addition of biological molecules and antibodies capitalizing on the thiol–gold chemistry has rendered gold applicable in a variety of therapeutic systems, ranging from drug and biomolecular delivery to hyperthermia to active and passive targeting. GNPs have recently emerged as an attractive platform for the delivery of small drug molecules and large biomolecules to specific targets. The release of these therapeutic agents can be triggered by cellular chemical – e.g., glutathione (GSH), pH, or external – e.g., light stimuli.

One of the main advantages of using gold particles at the nanoscale is its surface-to-volume ratio. GNPs can be loaded on their surface to form drug delivery systems. These systems can be used for chemotherapeutic delivery to tumor cells. The enhanced permeation and retention effect as provided by passive targeting has been used for treating carcinogenic tumors. The surface-to-volume ratio was utilized to prepare passive targeting GNPs conjugated with chemotherapeutic paclitaxel and diatomic cytotoxic singlet oxygen ($^1O_2$), as well as nitric oxide (NO) GNP reservoirs. Nitric oxide was released from water-soluble nanocontainers when a pH stimulus (pH = 3) was given to these drug delivery systems. Since tumor tissues have mild acidic environment, NO-carrying GNPs can potentially be used effectively to treat cancer.

By attaching a short peptide to hollow gold nanospheres, researchers have developed a way for the particles to seek out and "cook" cancer cells, according to the American Chemical Society. The cancer-destroying nanospheres show particular promise as a minimally invasive future treatment for malignant melanoma, the most serious form of skin cancer, the researchers say. Researchers say that, by attaching a protein fragment, the nanospheres are drawn directly to melanoma cells, while avoiding healthy skin cells. After collecting inside the cancer, the nanospheres heat up when exposed to near-infrared light, which penetrates deeply through the surface of the skin. In recent studies in mice, the hollow gold nanospheres did eight times more damage to skin tumors than the same nanospheres without the targeting peptides, the researchers say.

"This technique is very promising and exciting, it's basically like putting a cancer cell in hot water and boiling it to death, the more heat the metal nanospheres generate, the better." explained study co-author Jin Zhang [26]. This form of cancer the-

rapy is actually a variation of photothermal ablation, also known as photoablation therapy (PAT), a technique in which doctors use light to burn tumors. Because the technique can destroy healthy skin cells, doctors must carefully control the duration and intensity of treatment. Researchers now know that PAT can be greatly enhanced by applying a light absorbing material, such as metal nanoparticles, to the tumor. Although researchers have developed various types of metal nanoparticles to help improve this technique, many materials show poor penetration into cancer cells and limited heat-carrying capacities. These particles include solid gold nanoparticles and nanorods that lack the desired combination of spherical shape and strong near-infrared light absorption for effective PAT, scientists say.

The gold nanoshells, which are nearly perfect spheres, range from 30 to 50 nm – thousands of times smaller than the width of a human hair. The shells also are much smaller than other nanoparticles previously designed for photoablation therapy, he said. Another advantage is that gold is safer and has fewer side effects in the body than other metal nanoparticles. In collaboration with Chun Li, equipped the nanospheres with a peptide to a protein receptor that is abundant in melanoma cells, giving the nanospheres the ability to target and destroy skin cancer. In tests using mice, the resulting nanospheres were found to be significantly more effective than solid gold nanoparticles because of much stronger near-IR light absorption of the hollow nanospheres, the researchers say.

Mirkin and colleagues [27] have published extensively on the use of gold nanoparticles to measure the presence of cancer-associated DNA and protein signatures. The gold nanoparticles are coupled to DNA detectors or antibodies and printed as conductivity bridges. When the antigen or signature DNA for a cancer-related marker is present in a sample, it will bind to the bridge. These molecules can be collected by detector DNAs or antibodies labeled with metal nanoparticles, completing an electrical circuit, thereby producing an extremely sensitive response that is up to a million times more sensitive than ELISAs.

Early cancer detection using Q-dots has been the subject of extensive studies. Kim and colleagues [28] described the use of Q-dots composed of an inner cadmium tellurium core surrounded by a cadmium selenium layer and capped with an organic compound to make the particles water soluble. When injected into pigs, lymphatic cells cleared the Q-dots and routed them to the lymph nodes. By shining infrared lamps on the skin of the subject animals, the lymph nodes could be identified and localized easily because of their emission of wavelengths in the infrared range. This technology should prove useful for localizing tumors near the skin. An analogous approach is being considered for localizing deep tumors, far from the surface, using magnetic nanoparticles. Nanoparticles also have been used as luminescent probes for optical imaging [29] and as magnetic probes for nuclear MRI. The use of near-infrared luminescent nanoparticles for deep tissue optical imaging was described by Morgan and colleagues [30], who demonstrated the use of nanocrystals (a term synonymous with Q-dots) as an angiographic contrast agent for vessels supplying a murine squamous cell carcinoma.

4. ULTRATHIN SHELL-MODEL OF MOLECULAR CRYSTALS

Based on our research in ultrathin crystal structures performed so far, films, superlattices, Q-wires and Q-dots [31−33], we will consider the materials that can act as carriers for medicines and tagged substances. For this purpose we have established a spherical shell-model of ultrathin molecular crystals and investigated their mechanic – especially elastic and thermodynamic properties, then their conductive and, in addition – their dielectric, particularly optic-absorption characteristics.

As in our previous researches into the properties of the structures that are extremely limited in space (however linearly), here we will also use the previous experience in methodology and goals of researches, as well as in expected results. Our future researches can be classified into the following phenomena and areas:

− When studying and analyzing the mechanical and elastic properties of core-shell crystalline nanomodels because we are interested in, say, heat capacity or the influence of externally stimulated electromagnetic radiation on the (in)stability of this crystalline nanostructure, we will take into consideration all the methods applied and the results obtained from our long-term work on modeling and investigation of the properties of phonon ultrathin films, Fig. 4);

− When we deal with transport characteristics of core-shell crystalline nanomodels because we are interested in, e.g. heat capacity or the influence of the presence of rapidly changing external electromagnetic radiation on the electromagnetic conductivity of this crystalline nanostructure, we will take into consideration all the methods applied and the results obtained from our long work on modeling and investigations of electron ultrathin films (Fig 5);

− During researches into optical properties of core-shell crystalline nanomodel because we are interested in, e.g. selective absorption or reversible (fluo-luminescent) influence of externally stimulated electromagnetic radiation on the (in)stability of this nanostructure, we will take into consideration all the methods applied and the results obtained from our long work on modeling and investigations of exciton ultrathin films (Fig. 6).

− For the time being, we are not going to deal with magnetic characteristics of core-shell crystalline nanomodels, since that is not currently the object of our interest, although there is a direct nano-connection through the hemoglobin blood composition.

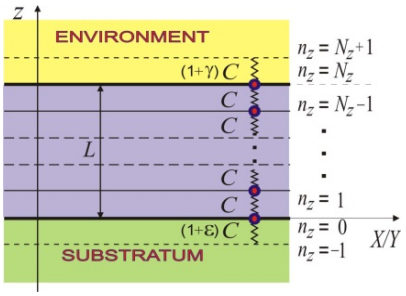

Figure 4. Phonon ultrathin-film crystalline model

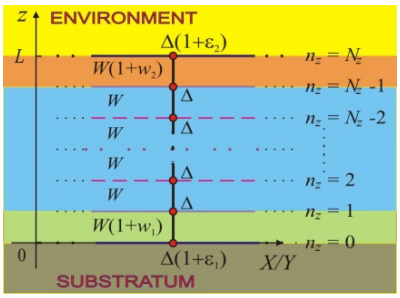

Figure 5. Electron ultrathin-film crystalline model

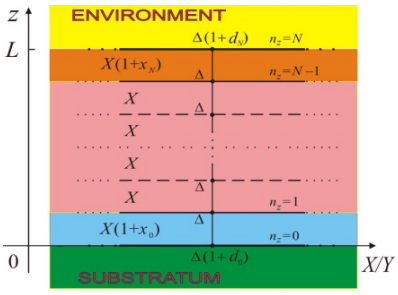

Figure 6. Exciton ultrathin-film crystalline model

The most significant results that we have achieved in our previous researches [32-35], concerning the formation and the analysis of the core-shell crystalline nanomodel and its potential application in nanomedicine, can be briefly defined in the following way: on bordering surfaces of the nanofilm (here it is a nanoshell), due to extreme localization of elementary excitations, all the physical properties of the material change, therefore:

− Small, thermally or mechanically stimulated disturbances can become surface waves of great amplitude, i.e. energies that can imply the braking up of crystallographic connections between the atoms of bordering planes and the decomposition of the bordering layer, and then of all the other atoms;

− Heat can be more easily absorbed and surface conducted, which allows the nanolayer to be supplied with additional energy which is necessary to melt the material on bordering layers first, and the other layers afterwards;

− External electromagnetic radiation can be selected by frequencies and partially absorbed, whereas an intense luminescence is also to be expected to occur.

Where do we get the connection between core-shell models with these film models from? All nano or ultrathin films are structures that are extremely limited along one dimension, usually chosen as z-direction, so that the thickness of the film was: $L = N{\cdot}a$, where N (< 10) represents the number of film layers, whereas a is the thickness of crystallographic layer (the distance between the two bordering crystallographic planes). Core-shell model (Fig. 7) has an ultrathin crystalline layer around the core (which is the carrier of medicines, probes,…), and this nanolayer is limited along one dimension, or, in other words, along one coordinate. We have here a radial limitation/restriction:

$$r \in [R, R+L]; \quad L = N \cdot a; \quad N \le 10,$$

with several crystallographic layers.

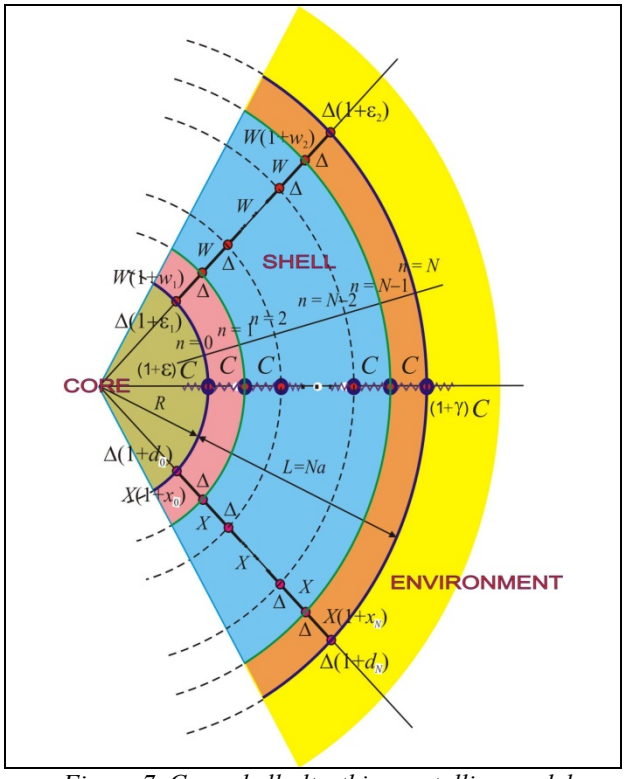

Figure 7. Core-shell ultrathin crystalline model

Seemingly, no big difficulties during the application of already known method of theoretical research are expected. We conducted this research with the help of two-time dependent Green's function method, adjusted to ultrathin crystalline structure analysis. However, we will have to bear in mind that basic crystallographic data for the planes positioned to the centre of the core – differ: for example, distances between the atoms in crystal grids increase as we move further from the centre of the core. This results in the changes of elementary interactions. This is what we will certainly bear in mind; moreover, that can have positive effects on the description of quantum effects, and perhaps, some new ones may appear.

5. CONCLUSION

Nanomedicine is a global business enterprise impacting universities, startups, and boardrooms of multinational corporations alike. Industry and governments clearly are beginning to envision nanomedicine's enormous potential. As long as government expenditure encourages facile technology transfer to the private sector, nanotechnology eventually will blossom as a source for corporate investment and revenue. However, for nanomedicine (and nanotechnology) to truly become a global mega trend, the hype must be separated from reality. In addition, societal, environmental, and ethical concerns will need to be addressed as scientific advances occur.

New – nanotechnologies may offer the only hope for systematic, affordable, and long-term improvements to the health status of our population. This is because nanotherapies (combined with related advances in surgery, therapeutics, diagnostics, and computerization) could din the long rundle much more economical, effective, and safe and could greatly reduce the cost of or substantially eliminate current medical procedures. Clearly, nanomedicine holds great promise at this incremental level, given the many applications in drug delivery, diagnostics, detection, discovery, sensing, and imaging. Life science operations will continue to benefit from the ongoing research in nanopharmaceuticals because they have the ability to enhance the delivery and effectiveness of traditional drugs while revolutionizing and accelerating future drug discovery and development improving productivity and providing new drug delivery techniques.

Recent advances in creating nanomaterials have created new opportunities in biomedical research and clinical applications. High-quality nanomaterials, of well-controlled size and shape, are a new class of building blocks to enable the establishment of assays for monitoring molecular signals in biological systems and living organisms. Many of these new nanoassays have higher sensitivity, selectivity and throughput than conventional bioanalytical methods. On the one hand, these nanoassays will be capable of detecting biochemical changes at the single-molecule level in living cells. Conversely, these assays will lead to low-cost, point-of-care devices for rapid diagnosis of pathogenic and genetic diseases (e.g., HIV and cancer). In addition, nanomaterials have been used as advanced contrast agents for clinical imaging technologies, such as MRI, computer tomography and ultrasound. Moreover, the use of nanomaterials will lead to the invention of 'smart' drug-delivery vehicles, new therapies and even new scalpel-free surgery methods.

These new opportunities stem primarily from the novel nature of nanomaterials. Owing to their size-dependent effects, nanomaterials exhibit new physical and chemical properties compared with conventional bulk and molecular materials. In general, nanomaterials include inorganic, organic and inorganic/organic composite nanostructures, such as nanoparticles, nanowires and nanopatterns.

The application of nanotechnology to drug delivery is widely expected to change the landscape of pharmaceutical and biotechnology industries for the foreseeable future. The pipelines of pharmaceutical companies are believed to be drying up in many cases, and a number of blockbuster drugs will come off patent in the near-term. The development of nanotechnology products may play an important role in adding a new armamentarium of therapeutics to the pipelines of pharmaceutical companies.

Using nanotechnology, it may be possible to achieve: improved delivery of poorly water-soluble drugs, targeted delivery of drugs in a cell- or tissue-specific manner, transcytosis of drugs across tight epithelial and endothelial barriers, delivery of large macromolecule drugs to intracellular sites of action, co-delivery of two or more drugs or therapeutic modality for combination therapy, visualization of sites of drug delivery by combining therapeutic agents with imaging modalities and real-time read on the *in vivo* efficacy of a therapeutic agent. Additionally, the manufacturing complexity of nanotechnology therapeutics may also create a significant hurdle for generic drug companies to develop equivalent therapeutics readily. These are just a few of the many compelling reasons that nanotechnology holds enormous promise for drug delivery.

This paper presents readers with current exciting developments in the use of nanoparticles and

nanopatterns for biomedical diagnosis and drug delivery, as well as our thoughts on theoretical postulates of the researches of properties of nanocore-shell models.

ACKNOWLEDGEMENTS

This work was partially supported by the Ministry of Science and Technological Development of the Republic Serbia and by the Ministry of Science and Technology of the Republic Srpska.

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SHELL НАНОСТРУКТУРИРАНИ МАТЕРИЈАЛИ
ЗА БИОФАРМАЦИЈУ И БИОМЕДИЦИНУ

Сажетак: На основу наших досадашњих истраживања ултратанких структура, суперрешетки, квантних жица и квантних тачака, размотрићемо материјале који могу послужити као носачи лијекова и означених супстанци. У ову сврху формирали смо 'shell' модел ултратанких молекуларних кристала и истраживали њихове диелектричке, те нарочите оптичке карактеристике. Ово истраживање смо спровели уз помоћ метода двовременске функције Грина, прилагођеног анализи ултратанких кристалних структура. Показано је да се у овим структурама јављају специфичне резонантне апсорпционе линије, чији број зависи од положаја кристалних слојева и од вриједности параматера на површинама границе shell структура. Апсорпција електромагнетног зрачења опада у инфрацрвеном дијелу те је његово откривање релативно једноставан процес.

У овом раду анализира се примјена наноматеријала у биомедицини, односно представљају најновија достигнућа у основној и клиничкој наномедицини. Могуће је да ће протећи још доста година или чак и деценија док се не постигне пуни потенцијал наномедицине. Међутим, потенцијални помаци у испоруци лијекова, дијагностиковању и развоју лијекова везаних за нанотехнологију већ мијењају изглед медицине. Циљана испорука лијекова у обољела мјеста (омогућена постојањем јединствених платформи за испоруку, као што су дендримери, наночестице и нанолипосоми) и персонализована медицина (резултат напретка у фармакогенетици), само су неки концепти на хоризонту истраживања. У овом раду посебно смо анализирали промјене основних физичких својстава наночестица сферног облика које могу бити израђене у више (нано)слојева и који истовремено имају вишеструку примјену у медицини.

Кључне ријечи: shell модел, наноматеријали, биофармација, наномедицина.