

**NANOMATERIALS IN BIOMEDICINE
– PHARMACOLOGY AND STOMATOLOGY APPLICATIONS –****Dragoljub Lj. Mirjanić***Academy of Sciences and Arts of the Republic of Srpska – B&H, mirjanicd@gmail.com,***Ana J. Šetrajčić-Tomić***Medical Faculty, Department of Pharmacy,
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Department of Stomatology, Republic of Srpska, B&H***Jovan P. Šetrajčić^{1†}**¹*University of Novi Sad, Faculty of Sciences, Department of Physics, Vojvodina – Serbia, bora@df.uns.ac.rs*[†]*Academy of Sciences and Arts of the Republic of Srpska – B&H***Abstract**

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. Numerous novel nanomedicine-related applications are under development or are in the 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) is just a few concepts on the horizon of research. Based on our research in ultrathin crystal structures performed so far, superlattices, quantum wires and Q-dots, we will consider the materials that can act as carriers for medicines and tagged substances.

Keywords: nanomaterials, biomedicine, nanomedicine, ultrathin structures.**INTRODUCTION**

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. It is true that the process of converting basic research in nanotechnology and nanomedicine into commercially viable products is long and hard, but governments worldwide are impressed with its potential and express their demands to extract billions of dollars, euros and yen for research [1–6].

More broadly, nanomedicine is the application of technology at the nano-scale in medical practice. It is used for diagnosis, prevention and treatment of disease and to gain know-

ledge of complex mechanisms underlying the disease. Although the established disciplines of nanotechnology, nanomedicine commercial (with its wide range of ideas, hypotheses, concepts and lack of clinical devices) is still in early stages of development. For example, there are many nanodevices (eg, Q-dots and dendrimers – Fig. 1, from [1–3]) that are widely distributed and represented in the sale, but has yet to find its place in a wide variety of clinical devices. Currently nanomedicine involves detection of particles, drug delivery systems, emulsions and carriers for delivery of vaccines, and nano-biomaterials produced from the unusual properties of strength, hardness, reduced friction and increased biocompatibility. Exotic concepts (such as nano-machines that could move through the body, troubleshooting and repair of micro-and cardiovascular lesions in the brain) are a thing of the future.

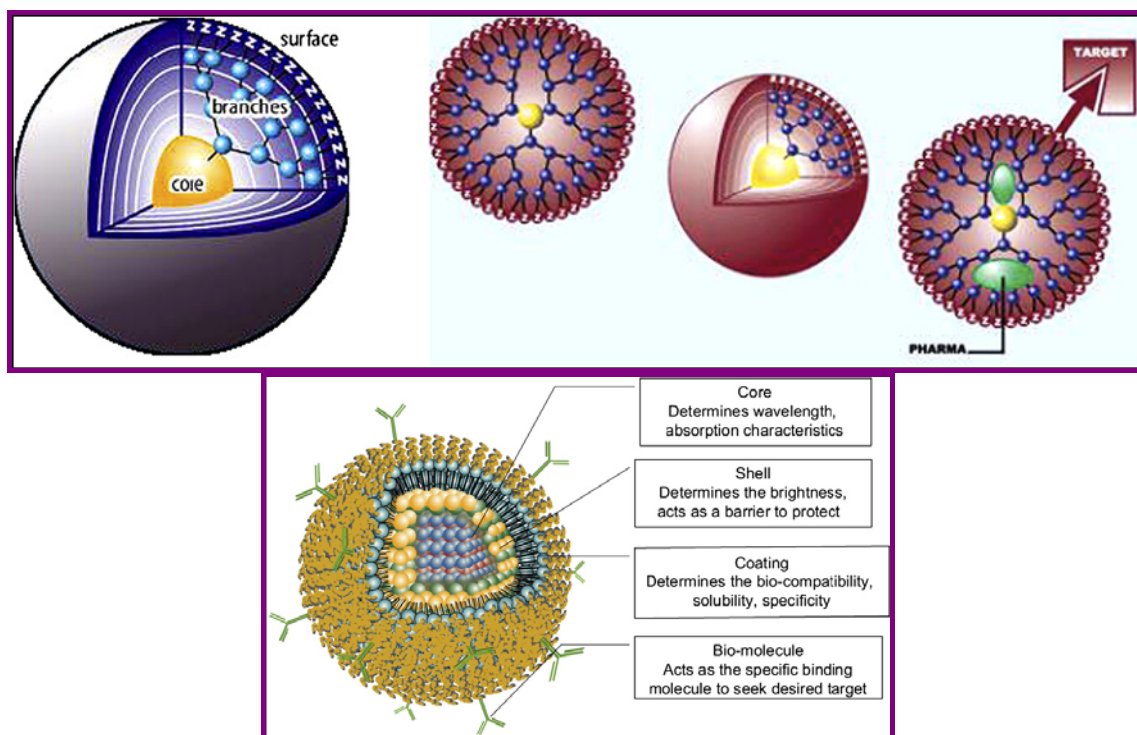


Figure 1: Structure and applications of dendrimers and Q-dots for drug delivery

We present the technology and techniques in nanomedicine that can be expected in the near future:

- Biopharmaceutic: drug delivery (delivery of medication), medication incapsulation functional carriers of drugs, drug discovery;
- Materials that can be implanted: repair and replacement of tissue covering the implant, scaffold for tissue regeneration, structural materials for implants, bone repair, bioresorbable materials, smart materials;
- Devices that can be implanted: devices for assessment and treatment, sensors that can be implanted, medical devices that can be implanted, sensory aids, implants corneas, cochlear implants;
- Surgical tools: tools for the operation, intelligent instruments, surgical robots, diagnostic tools, genetic testing, technologies ultra-sensitive labeling and detection, distributed hundreds of compounds and multiple analysis, imaging (recording), labels, nanoparticles, recording devices, understanding of basic life processes.

It is expected that in the years to be undertaken significant research, specifically in the field of drug delivery, nanotechnology is poised to deliver market evolutionary and revolutionary products. Some products may be available

soon, while others occur in the distant future and will include:

- Miniature nano-fluid devices and systems that efficiently transport fluids to the place of delivery, preventing turbulence and mixing (because fluids move laminar flow through micro/nano-cannels);
- More efficient routing to a specific location or precise alignment to support nano-medicines, resulting in reduced systemic contraindications and better collaboration of the patient;
- Nanodevices for drug delivery and implants containing sensors (to monitor biomolecules) and drug reservoirs (for precise delivery) on the same chip.

Arrangements for delivery of drugs based on nanoparticles [7–9] would allow for faster absorption of drugs, controlled release dose, and protection from the immune system – thus increasing the effectiveness of existing drugs. The researchers also tested a new treatment using nanoparticles such as dendrimers, as a means of delivery devices to insert genes into cells.

2. The application of nanotechnology in drug delivery

Very slow progress in the treatment of serious illness led to the adoption of a multidisciplinary approach to targeted drug

delivery and release, supported by the nano-science and nanotechnology. New drug delivery systems combine the science of polymers, pharmaceuticals, biocoupling chemistry and molecular biology. The goal is better control of pharmacokinetic, pharmacodynamics, non-specific toxicity, immunogenicity and biorecognition system in pursuit of improved efficiency.

Delivery systems and targeting of drugs in development aim to reduce drug degradation and loss, prevent harmful side effects and increase the availability of drugs at the site of disease. Drug carriers include micro and nanoparticles, micro and nanocapsules, lipoproteins, liposomes, and micelles, which can be so easily made to fall apart, responding to a stimulus, and be specific in their place [10–14]. Targeting mechanisms can be either passive or active. An example of passive targeting is preferred accumulation chemotherapeutic agents in solid tumors as a result of differences in vascularization cancer tissue compared to healthy tissue. Active targeting involves the chemical “decorate” the surface of the transferor which allows drug molecules to be selectively attached to diseased cells.

Controlled release of drugs is also important for the success of therapy. Controlled release can be sustained or pulsate. Sustainable (or continuous) release drug involves polymers or other (new) suitable materials that release drug at a controlled rate, diffusion or degradation of the material flow over time. Pulsatile release is often preferable, because what good mimics the way the body naturally produces hormones such as insulin. Achieved by using capsules – transferor drug, which react to certain stimuli (eg exposure to laser light, microwaves or ultrasound, a change in pH or temperature treatment).

Other nano-drug delivery approaches are focused on crossing certain physical barriers, such as the blood-brain barrier, or on finding alternative and acceptable routes for the delivery of a new generation of drugs based on proteins, which will be used through the gastrointestinal tract which can cause degradation. Nanoscience and nanotechnology are thus the basis of innovative techniques and drug delivery offers great potential for the benefit of patients and new markets, companies that manufacture pharmaceuticals and drug delivery systems.

2.1. Drug delivery systems

Drug carriers

Successful system for the transfer of drugs needs to demonstrate optimal drug loading and good qualities of his release, a long duration in storage, and low toxicity. Colloidal systems, such as micellar solutions, dispersions with bladder and liquid crystal displays, as well as nanoparticle dispersions consisting of small particles with diameter of 10 – 400 nm, show great potential as carriers in drug delivery systems [12].

Micelles – is an aggregate of surfactant molecules dispersed in a liquid colloid (Fig. 2). Drugs can be trapped in the core of micelles and transported at concentrations even higher than the actual solubility in water. The feature that makes the micelles attractive is that their size and shape are subject to change. Can form and extra thin shell around the micelles and to effectively protect content and prevent recognition by retikuloendotelial system, including the premature removal from the blood system. Micelles can be chemically modified to selectively target a wide range of sites of disease.

Liposomes – were bubbles that consist of one or more chemically active fatty bilayer (Fig. 2). Drug molecules can be encapsulated and dissolved within the bilayer. Some (channel) proteins can be incorporated into the liposome membrane and act as a selective filter allowing only diffusion of small soluble particles such as ions, nutrients and antibiotics. Thus, the drugs, encapsulated in this liposomic “nano-cage, effectively protected from premature degradation, but the drug molecule can move through the channel protein when it launched an external stimulation.

Dendrimers – polymer macromolecules are nanometer-sized (Fig. 1). Composed of a central core unit of branches and terminal functional groups. Core chemistry determines the properties of soluble cavity within the core and external chemical groups determine the solubility and chemical behavior of the dendrimers. Targeting is achieved hanging specific conjunctions of the outer surface dendrimers allowing it to bond to the place of disease, while its stability and protection from phagocytes achieved “decoration” dendrimers chains of polyethylene glycol.

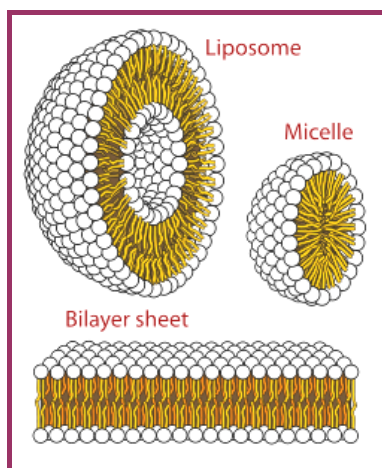


Figure 2: Cross section view of the structures that can be formed by phospholipids in aqueous solutions

Liquid crystals – combine the properties of the liquid and solid state. Liquid crystals can be designed to form different geometries, with alternate polar and non-polar layers (ie, lamellar phases), in which the aqueous solution of drug may be more integrated.

Nanoparticles – including nano-spheres and nanocapsules, or Q-point (Fig. 1) can be amorphous or crystalline. Are able to absorb and/or encapsulate a drug, and thus protect them from chemical or enzymatic degradation. In nanocapsules, the drug is limited to a cavity surrounded by a polymer membrane or polycrystalline, while nanospheres matrix systems in which the drug physically and uniformly dispersed. In previous years, only the biodegradable polymer nanoparticles attracted considerable attention in the drug release by targeting a specific organ / tissue, as carriers of DNA in gene therapy and because of their ability to deliver proteins, peptides and genes by mouth, is now being used by various stimuli that initiate dispersion of nanocapsules in a given time and in a defined area (Fig. 3).

Hydrogels – are three-dimensional polymer networks that swell but not dissolve in water environment. They are used to regulate drug release in reservoir systems or as carriers in devices for the controlled release of drugs swelling. In the foreground of controlled drug delivery, hydrogels as intelligent gel systems on the environment and sensitive to stimuli, can modulate drug release in response to pH, temperature, ionic strength, electric and / or magnetic fields, ultrasound, or the difference between the specific concentration of analyte.

The release can be designed to occur in specific parts of the body. Hydrogels as drug delivery systems are very promising when combined with the technique of molecular fingerprint.



Figure 3: Gene Delivery Using Ultrasound – The presence of gas in the bubble filled with a scattering of genes allows them

Molecularly imprinted polymers – have enormous potential for drug delivery systems. Examples include: frequency of scheduled delivery of drugs, where drug diffusion from the system must follow a certain profile frequency; activation modulated delivery of drugs, where drug release is activated by some physical, chemical or biochemical processes, and retroactive rule-based delivery service, where the rate of drug release is regulated concentration of the moving agents, which are activated by concentrations of drug in the body.

Coupling of biological molecules (peptides) and synthetic polymers – is an effective way to improve control over the formation of nanostructures synthetic polymers or ultra-thin polycrystalline layers, which can be used as a delivery system of drugs. Coupling suitable synthetic polymers and peptides or proteins can reduce toxicity, preventive effect on autoimmune antigens and side effects improve blood circulation time and enhance the solubility of the drug. Modification of synthetic polymers peptide sequences that can act as antibodies to specific epitopes, may also prevent active targeting random distribution of the drug for a patient's entire body. Functionalization of synthetic polymers made from the peptide sequences extracellular matrix proteins, for example, effectively mediating cell adhesion. In addition, the ability of cationic peptide sequences to complex DNA and oligonucleotides offers prospects for developing non-viral vectors for gene delivery based on synthetic polymer hybrid materials.

In-situ forming implants – are generating liquid formation (semi-) solid depot after sub-

cutaneous injection is an attractive delivery system for parenteral (non-oral) application because they are less invasive and painful compared to implants. They allow the drug to be delivered locally or systematically over extended periods of time, typically up to several months. These systems can reduce the depot side effects by achieving constant, "such as infusion" profile of drugs, which is especially important for delivery of proteins with narrow therapeutic indices. Also provide the advantage of being relatively simple and that their production is cheap.

Ways of introducing drugs suppliers

Choice of drug is often influenced by the manner in which they entered, because it can make the difference between success and failure of the drug [12]. The choice of delivery times depend on patient acceptance, which are important drug properties (eg solubility), the ability to target spot disease, or effectiveness in working with a particular disease.

Peroral is the most important or most common drug delivery route, as it offers the advantages of convenience, ease in handling and savings in cost of production. Drugs based on proteins and peptides offer the greatest potential for more effective therapeutics, but not easily pass through the mucus surfaces and biological membranes, are prone to rapid clearance in the liver and other tissues of the body (such as hydrolysis caused by acid in the stomach, enzymatic degradation throughout the gastrointestinal tract, bacterial fermentation in the colon and the like.), and require precise dosing.

Parenteral routes entries are done intravenously, intramuscularly or subcutaneously. Eg. liposomes are introduced intravenously, a nanoparticle drug carriers have great potential for nasal delivery and under-linguistic means, but for hard-to-eye, brain and inter-articular cavity. In addition, there is the possibility of improving ocular bioavailability of drugs if it is given by colloidal carriers of drugs.

Pulmonary drug delivery is achieved in various ways: via aerosols, by inhalator systems measured doses, powder (dry powder inhalers) and solutions (obscures), which may contain nanostructures such as liposomes, micelles, nanoparticles and dendrimers. Such drug delivery offers local targeting for the treatment of respi-

ratory diseases and is capable of systemic use. However, success in treatment was decreased (in) accessible to proteases in the lungs and the barrier between capillary blood and alveolar air.

Transdermal drug delivery is a noninvasive technique, well accepted by patients, and can be used for providing local delivery in the period over several days, and is suitable for patients in an unconscious state. Limitations include the slow rate of penetration, lack of flexibility in dosage and / or precision, and restriction to relatively low doses of the drug.

Trans-tissue and *local* delivery systems of medicines are systems that need to be firmly connected to the cut tissue during surgery. The aim is to produce enhanced pharmacological effect, while reducing systemic toxicity related to the input. Trans-tissue systems include: gelatin gels filled with the drug, which was formed in-situ and adhere to the cut tissue, releasing drugs, proteins or gene-encoded adenoviruses; gels fixed antibodies (citokininska barrier) that form a barrier on the target tissue can prevent the penetration cytokinins in the tissue, cell delivery, including oral mucosal gene transduced epithelial cellular implanted list; controlled delivery device – rechargeable drug infusion device that can be attached to the cut position.

Gene delivery is a challenging task in the treatment of genetic diseases. Plasmid DNA must be inserted in the target cell. It must then be transcribed, and the genetic information ultimately translated into the corresponding protein. To achieve this a number of obstacles must be overcome. Gene delivery system must be sighted on the target cell, transported through the cell membrane, was taken and broken down to endolizoms, and plasmid DNA was transferred within the cell to the nucleus.

2.2. Nano-encapsulated model

Nanomedicine is trying to exploit the self-merging and ordered structures at nanoscale proximity of which are in biology [10–14]. Specific model of crystal structures that represent a series of "glued" ultra-thin films is called superlattices [15], and models that are limited along two spatial directions and small in size along the two directions in the literature are called quantum wires or nanorods [16]. Model of crystal structure – tours, which are

limited along all three spatial directions and they are very small, in the literature are known as quantum dots (Q-dots) [17], may be of different shapes, but the research is appearing rectangular (nanocuboids) and discoid (hollow or filled discs) or spherical forms, such as Fig. 4.

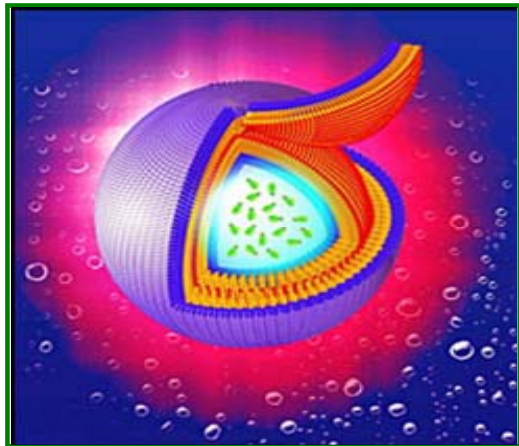


Figure 4: Spherical (nano)capsule – Thousands of similar molecules are packed together to create a capsule that is filled with molecules of a different kind; the diameter of one capsule is a mere 20 to 50 nanometers, which is one ten-thousandth of a pinhead.

Based on our research in ultrathin crystal structures performed so far, films, superlattices, Q-wires and Q-dots [18–20], 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 earlier works to study the spatial properties of highly (but – linear) limited structures, and here we use the former gained rich experience in research methodology and objectives, of course, as well as expected results. Our future research can be classified into the following phenomena and areas:

- When we studied and analyzed the mechanical and elastic properties of core-shell crystalline nanomodel because we will be interested for example. thermal capacitance and the impact of increased external electromagnetic radiation on the (in)stability of the crystalline nanostructures, we will have in mind all the applied methods and the results of our ex-

tensive work on modeling and testing of the phonon properties of ultra-thin films (Fig. 5.1);

- When we are interested in transport specific core-shell crystalline nanomodel because we will be interested for example. thermal capacitance or effect of the fast-changing external electromagnetic radiation to electromagnetic conductivity of crystalline nanostructures, we will have in mind all the applied methods and the results of our extensive work on modeling and testing of electronic properties of ultrathin films (Fig. 5.2);
- Investigations of optical properties of core-shell crystalline nanomodel because we will be interested for example. selective absorption or return (fluoro-luminescent) stimulatory effect of external electromagnetic radiation on the (in)stability of the crystalline nanostructures, we will have in mind all the applied methods and the results of our extensive work on the modeling and study the characteristics of excitation ultrathin films (Fig. 5.3).

The most important results that we obtained in previous studies [18–20], in connection with the formation and analysis of core-shell crystal model and its possible application in nanomedicine, in short can be formulated as follows. At the border surfaces of nanofilm (here it will be nanoshell), because of the localization of elementary excitations, change all the physical properties of materials, and:

- small thermally or mechanically stimulated conditions may develop into large amplitude surface waves, ie. energy, which may imply breaking of ties between the crystallographic boundary planes of atoms and the dissolution of the boundary layer, and then all the others;
- easier to absorb heat and can better carry out surface and thus the nanolayer can provide extra energy necessary for melting materials at the border first and then the other (inner) layers;
- External electromagnetic radiation can be selected according to their frequencies and partially absorbed, and to expect the emergence of very intense luminescence.
- Where we link core-shell model with these models films?
- All nano- or ultra-thin films have structures that are very spatially restricted along one direction, usually we have chosen the z-di-

rection, so that the film thickness was: $L = N \cdot a$, where $N (< 10)$ represents the number of films, and a the thickness of crystallographic layer (the distance between two adjacent crystallographic planes). Core-shell model (Fig. 5) has ultrathin crystalline layer around the core (which is carrier of drugs, probes, ...) and the nanolayer is restricted along one direction, or rather – along one coordinate. Here it comes radial limit:

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

- with several crystallographic layers.

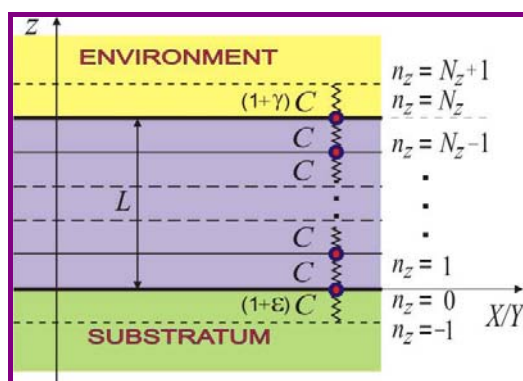


Figure 5.1: Phonon ultrathin-film crystalline model

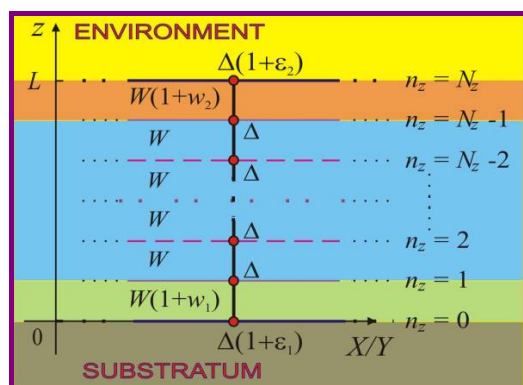


Figure 5.2: Electron ultrathin-film crystalline model

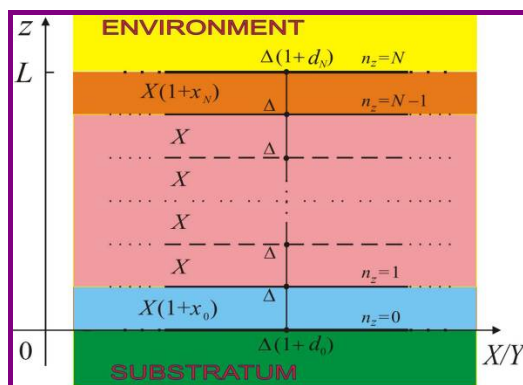


Figure 5.3: Exciton ultrathin-film crystalline model

On-the look, do not expect great difficulty in applying the already known methods of theoretical research: we conducted this research with the help of two-time dependent Green's function method, adjusted to ultrathin crystalline structure analysis. However we have to keep in mind that the basic crystallographic data are different in the planes whose position relative to the center core – different: eg. the distance between atoms in the crystal lattice increases as they move away from the center of the nucleus. As a consequence, to change the elementary interaction ... We will certainly take into account, what is more – it can have a positive impact on the occurrence of quantum size effects, and it is possible to show up and completely new effects.

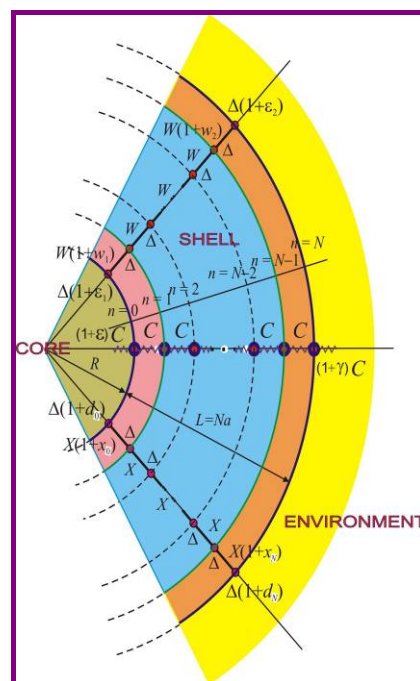


Figure 6: Core-shell ultrathin crystalline model

3. CONCLUSION REMARKS

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 for biomedical and nanopatterns diagnosis and drug delivery, as well as our thinking about the theoretic studies of the properties of nano-core-shell model.

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