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REVIEW PAPER

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Nanomedicine – a review

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ABSTRACT

Introduction and aim. Nanomedicine is a discipline of technology and science, the potential of which has recently fascinated scientists in the fields of physics, biotechnology, chemistry and medicine. This department deals with everything on the nano scale, i.e. on the level of individual atoms and molecules.

This work presents the nano scale, i.e. on the level of individual atoms and molecules. Nanotechnology is currently one of the most popular and dynamically developing fields, not only in electronics, but above all in pharmacy and medicine.

Material and methods. In this article a narrative review regarding nanomedicine.

Analysis of the literature. The desire to summarize information about nanomedicine application of singlet oxygen is presented. Nanotechnology is a discipline of technology and science, the potential of which has recently fascinated scientists in the fields of physics, biotechnology, chemistry and medicine.

Conclusion. The use of nanostructures is currently very efficient. The areas in which the potential of nanoparticles is constantly researched and confirmed by numerous articles are: radio- and chemotherapy, cancer diagnostics and imaging medicine (MRI and fluorescence imaging).

Keywords. nanomedicine, nanoscale, nanostructure

Introduction

In order to be able to explain the concept of nanostructures and to present the application of nanotechnology in various fields of science, the prefix nano should be specified and explained. Nano is a unit of measure prefix with the symbol n, which stands for a multiplier of 10^{-9} (one billionth of a part).[1] The name of the nano prefix comes from the Greek language (Greek: nanos, meaning dwarf). It is therefore a very small size that cannot be observed with the human eye.[2]

Nanotechnology is a relatively young technique, the origins of which date back to 1959, when Richard Feynman, an American physicist and Nobel Prize winner in physics, gave a lecture at the American Physical Society congress, entitled There's Plenty of Room at the Bottom.[2] Feynman presented the concept of miniaturization and the possibilities of using technology in the nanometer range. In the following years, numerous studies in the field of semiconductor and lithographic techniques made it possible to distinguish another physical field under the name of nanotechnology. The term was first used by a scientist, Professor Norio Taniguchi from the University of Tokyo during a scientific conference.[3] Since then, this field has been constantly evolving, and the application of nanostructures in electronics, physics and biology, chemistry and medicine is constantly being researched and multiplied.

Aim

The aim of this work is to present the review of nanomedicine.

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Material and methods

This article is a review done in regards to discuss the role of nanomedicine in current treatment and diagnostics.

Analysis of literature

Currently, there is a division of nanostructures into naturally occurring in nature and made by human. Natural nanoparticles result from the decomposition of plant or animal remains, as a result of the erosion of geological materials, volcanic fumes or as a result of the combustion of mineral fuels.[4] Another type of classification of nanostructures is their chemical composition. This division distinguishes between organic and inorganic nanoparticles. The last classification criterion is division due to the mutual relation of dimensions and their number. According to this criterion, the following structures can be distinguished: three-dimensional, two-dimensional, one-dimensional and zero-dimensional.[5] Table 1 shows the classification of nanostructures.

Table 1. The classification of nanostructures based on three criteria

Due to the way it is received	Due to the chemical composition	Due to the size
Natural	Organic	Three-dimensional (3D)
Human-mad	Inorganic	Two-dimensional (2D)
		One-dimensional (1D)
		Zero-dimensional (0D)

Organic nanostructures include: fullerenes, viruses, dendrimers and carbon nanotubes. On the other hand, inorganic nanostructures are compounds such as: zirconium oxide (ZrO_2), calcium, silver, gold or platinum.[6] Due to the last point of the criterion, the following structures can be distinguished:

- 3D (these are materials made of nanometer-sized monoblocks), fullerenes, colloidal particles, quasi-crystals, nanoporous silicon or semiconductor quantum dots;
- 2D: nanofibers, carbon nanotubes, magnetic and metallic nanowires;
- 1D: nano-layer materials, aluminum nano-dust, nano-grained surface layers or semiconductor quantum studs;
- 0D (these are structures having nanometer dimensions in three directions), an example of which is a quantum dot.

Methods of obtaining nanostructures

Thanks to the research carried out in the field of solid state physics, it is possible to obtain nanostructures by various methods, adapting a given technique to the scope and method of intended use of the compounds produced. The most popular techniques are the "top down" and "bottom up" methods.[7] The first of the top-down methods means obtaining structures by grinding, dividing or disintegrating macroscopic materials. This technique includes: high-energy grinding, lithographic process and standard material processing. High-Energy Ball-Milling HEBM is a common method of obtaining nanomaterials. The starting material is a pre-powdered alloy (<100μm) with a specific chemical composition and a specific crystallographic structure, in contrast to the mechanical synthesis process where high purity metal powders are used. During the process, stresses are induced in the material. After several dozen hours, amorphous material is obtained. The applied heat treatment (crystallization) causes the return to the crystal structure, the so-called output. In turn, the lithographic process is quite commonly used in the electronics industry. It is used mainly for the production of integrated circuits and transistors with a silicon substrate.[8] This technique consists of several steps. The first is to apply a protective and photosensitive layer to the surface of the substrate. In the second step, a pattern in the shape of a negative or a positive of the structure to be created is applied to the protective layer. Then the whole is irradiated and etched. The etching agent acts on places not covered with a protective layer. In this way, the desired layer structure is obtained. In turn, the "bottom up" method is characterized by the formation of nanoparticles from individual atoms, i.e. the creation of structures from scratch. This technique includes methods such as vapor deposition, plasma assisted deposition, and molecular beam epitaxy. Physical vapor deposition (PVD) uses the spraying of solid materials (the so-called target), from which the layer is to be made, eg by means of an electron beam. A properly prepared substrate (the so-called substrate) with a strictly controlled temperature is placed near the sprayed material. The sprayed material settles slowly on the substrate. The thickness of the obtained layer and its structure depend on the deposition time, spray rate and the temperature of the substrate, as well as on the composition of the diluted gas atmosphere. On the other hand, the method of applying thin layers with the use of plasma (Plasma Assisted Chemical Vapor Deposition) enables the deposition of thin layers on electrically conductive and non-conductive materials, using radio frequency and low frequency current discharges. It aims to create hard surface layers and layers with special surface and volume properties. Generally, in this process, chemical reactions take place under the conditions of electrical activation of the gaseous environment. The last example is the Molecular Beam Epitaxy (MBE), which consists in depositing thin semiconductor layers from molecular (atomic) beams in high vacuum (<10-7 Pa). Thanks to the use of various types of techniques, it is possible to obtain the desired nanostructures depending on the destination and application direction.

Biological and medical use of nanostructures

As already mentioned, the potential of nanostructures is enormous. More and more research is being created, and thus scientific publications about the potential and explored possibilities of nanoparticles not only in industry, electronics and physics, but also in the field of chemistry and biology.[9] The term nanomedicine characterizes all branches of medicine in which research and diagnostic activities with a nanometer range are used. It covers such areas as: pharmacy, surgery, diagnostics, oncology and many others.

Nanopharmacology

The main goals of nanopharmacology are target therapy (TT) and the controlled drug delivery system (DDS). The use of nanoparticles in pharmacology enables precise transport of the drug in the appropriate concentration to the neoplastic site, without disturbing the structure of normal (healthy) cells.[10] Currently, there are several types of nanoparticles that enable the transport of various types of drugs. These include: polymer and magnetic nanoparticles, liposomes, polymeric micelles, dendrimers and nanotubes.

Polymer nanoparticles are stable, colloidal structures in the form of nanospheres and nanocapsules. They can come from synthetic and natural polymers. Polymers (from the Greek polymeres - multi-part, made of many parts) are chemical compounds containing a large number of repeating structural elements, called mers. Synthetic polymers include: polycaprolactone, polyacrylamide and poly (methyl methacrylate).[11] On the other hand, natural polymers are mainly gelatin, heparin, chitosan and albumin. Nanoparticles made of polymers improve the efficiency of transporting currently administered drugs or proteins to specific cells, which means that the compounds are no longer so toxic and harmful to healthy, i.e. uninfected cells. The size of the nanostructures allows for increased drug penetration through cell membranes and thus increased stability, which means that the administered drug remains much longer in the patient's circulatory system. The most popular materials in nanopharmacology are biodegradable polymers (CS, PLA, gelatin, HMPA (N- (2-hydroxypropyl) methacrylamide). Table 2 presents a list of selected biodegradable polymers along with the labeling of the product that is formed as a result of the decomposition of a given polymer. due to the fact that these polymers are completely degraded in the human body, and thus can be easily excreted, and they do not stimulate the immune system.

According to numerous articles, the drug, created by combining albumin with paclitaxel (albumin-bound paclitaxel) – in 2005, abraxane was approved for the treatment of breast cancer in the United States. The paclitaxel capsule in albumin molecules makes it unnecessary to administer toxic solvents of this type of drug.[12] Moreover, albumin facilitates the penetration of substances through endothelial cells by means of the albumin gp-60 receptor. There is ongoing research into the use of abraxane to treat other types of cancer. An example would be non-small cell lung cancer.

Table 2. Examples of biodegradable polymers.

Polymer	Product resulting from degradation
Polylactide (PLA)	Lactic acid
Polyglycolide (PGA)	Glycolic acid
Poly (ε-caprolactone) (PCL)	Caproic acid
Polyidioxanone (PDS)	Glyoxylic acid
Poly (β-hydroxybutyrate) (PHB)	Hydroxybutyric acid

In turn, magnetic nanoparticles are compounds that exhibit magnetic properties. In medicine, there are examples of iron-based nanostructures. Iron is the basic building factor of many body structures, including liver, spleen or heart. Additionally, it forms the basis of important biological compounds such as hemoglobin, myoglobin and ferritin. Due to their magnetic properties, iron nanoparticles are used in various fields of medicine. These structures are used at the diagnostic and therapeutic level. They can be used for: cell analysis, biological material purification, and, above all, as MRI (Magnetic Resonance Imaging) imaging agents.[13] However, at the therapeutic level, they can be used as drug carriers and in radiotherapy combined with MRI. In addition, at the level of experimental and experimental research there are also research projects on iron nanostructures based on the core-shell structure. Core-shell nanoparticles are made of a silicon core covered with a thin layer of gold, to which biological ligands can be additionally attached. Due to the high absorption capacity and the possibility of dispersing electromagnetic radiation in the range from visible radiation to near infrared radiation (0.38 μm-5 μm), it is possible to use them in optics and in medical imaging. They are mainly used in targeted therapy in the photodynamic method.[14] Thanks to numerous scientific studies, it has been confirmed that nanomaterials in combination with photosensitizers can increase the efficiency of photodynamic therapy and eliminate its side effects. Photodynamic therapy is a multi-step treatment procedure that uses photosensitive substances that respond to a specific type of light. When exposed, these substances become toxic to cancer cells and other diseased cells. In order to be able to carry out a photodynamic reaction, it is necessary to use three basic components such as: a photosensitizer, which locates in the treated tissue and sensitizes it to light, and a light source of an appropriate wavelength, which is excited by the photosensitizer accumulated in the tumor tissue. Dissolved oxygen in the tissue is also necessary. The condition for initiating the photochem-

ical reaction is the correlation of the emission band of the light source with the dye absorption band. Thanks to the use of nanomaterials, it is also possible to reduce the toxic photosensitizer that can enter healthy tissues. Core-shell nanoparticles were used by the Hirsch team to treat mouse tumors in vivo and in vitro on the SKBR3 cell line. These nanoparticles were injected interstitial into the neoplastic lesion and in the next stage were irradiated with low doses of near-infrared radiation (0.82 μm).[15] After the experiment, strong heating of the inside of cancer cells was noticed, causing their destruction, while maintaining the metabolic balance of healthy cells surrounding the pathological area.

Liposomes (called liposomes) are another group of nanoparticles that improve the transport of drugs to various places in the living organism. They are colloidal structures having a spherical shape. Constructed of a lipid bilayer, they surround the water zone in which the drug is placed.[16] Liposomes are made of synthetic or natural phospholipids with a diameter of approx. 100 nm. Their membrane (sheath) is built in the same way as the cell membranes surrounding cell organelles.

Liposomes occur naturally in living organisms (e.g. as blood lipoproteins) and are produced on a laboratory and industrial scale (e.g. used in the production of drugs). For this reason, there is now a division into artificial and natural liposomes.[17] Artificial liposomes can be divided in terms of size, number of envelope layers and the way they are made. Table 3 shows the generally accepted division of artificial liposomes.

Table 3. Division of artificial liposomes

Liposomes with more than one lipid layer	Single-layer liposomes	Liposomes with lots of vesicles
Multilayer liposomes (MLV) 0.4-10 μm in size	Small unilamellar liposomes (SUV) with a size of 0.02-0.03 μm	Multiple vesicle liposomes (MVV)>1 μm in size
Oligolamellar vesicles (OLV)	Large unilamellar liposomes (LUV) with a size of 0.05-1 μm	
	Giant unilayer liposomes (GUV)	

In turn, the group of natural liposomes includes: lipids (e.g. cholesterol, triglycerides), which are transported in the body's water environment with blood and tissue fluid in the form of lipoprotein particles. They take the form of vesicles or disks surrounded by a double or single lipid layer of the membrane, made of phospholipids (which consist of a hydrophilic "head" and a hydrophobic "tail") and a surrounding chain (apolipoprotein protein).[18] Due to this structure, hydrophilic and hydrophobic substances can be stored in the liposome in various ways. Additionally, there are a number of other advantages of using liposomes as nanocarriers. These benefits include: improved bioavailability of drugs placed inside, a significant reduction in the toxicity of the released substances, controlled release of various types of substances as a result of internal or external factors, and (one of the most important) the possibility of gradual release of substances by liposomes in neoplastic tissues. One of the antibiotics that is transported through the liposomes is the anthracycline antibiotics (daunorubicin and doxorubicin). They are readily available. Daunorubicin (Doxorubicin-Ebewe) is an anti-cancer antibiotic used in cancer chemotherapy. This preparation is mainly used in the treatment of soft tissue sarcomas and sarcomas derived from bone tissues. However, the use of doxorubicin is very limited due to its high cytotoxicity.[19-21]

In turn, polymeric micelles are amphiphilic spherical structures, built of a hydrophobic core and a hydrophilic shell. The core acts as a drug depot, the hydrophilic shell of which stabilizes. Moreover, thanks to its properties, these polymers are water-soluble. The substances can be placed inside the micelles in various ways, which enables the drug to act more effectively. Polymer micelles are used in the treatment of lung, breast, ovary and colon cancer.

Dendrimers and carbon nanotubes

Dendrimers (Greek: dendros, tree) are polymers with a size of approx. 20 nm. They are characterized by a branched, three-dimensional structure. Their shape resembles a sphere. In the structural structure, a multifunctional core is distinguished from which the dendrimer branches depart.[22] These branches are called dendrons, with free functional groups at their end. These groups can be changed by various kinds of substituents while changing the properties of the dendrimers. In general, there are two generations of dendrimers, half and complete. Half dendrimers are terminated with a carboxyl group (-COOH), while complete dendrimers have, among others, amino ($-NH_2$) and hydroxyl (-OH) groups. Due to the chemical structure of the dendrimer, its shape and thus the level of activity are determined. Thanks to the vacancies in the construction site, the so-called cavities, dendrimers are a kind of reservoir of various molecules, which enables the delivery of drugs directly to the affected areas. On the basis of numerous studies and publications, dendrimers are used primarily as a transport of drugs such as cisplatin and doxorubicin.

Carbon nanotubes (carbon nanotubes) are graphene planes rolled into thin tubes with a diameter of approx. 1 nm and a length ranging from a few nanometers to several millimeters. Due to the number of layers, nanotubes are divided into mono- and polyhedral. They are formed in the process of slow condensation of hot vapors of carbon atoms.[23] They are characterized by high mechanical strength and high thermal conductivity. Due to

their structure, nanotubes are very difficult to dissolve in water, and therefore functionalisation is carried out. This process is based on the deposition of various functional groups on their surface. As a consequence, these nanoparticles can be used, for example, in as drug carriers and biosensors.

Application of nanoparticles – quantum dots in the marking of neoplastic cells

According to the latest statistical research, cancer is one of the most dynamically developing diseases on a global scale. The number of actions taken in the fight against various types of cancer is constantly expanded with more and more modern solutions. An example is the use of nanoparticles in anti-cancer therapy, mainly in aspects of radiation therapy.[24] An example of the use of nanomaterials for imaging and combating various types of cancer cells are quantum dots as a representative of a zero-dimension system. A quantum dot is a small volume completely limited by a semiconductor with a larger band gap, constituting a barrier. The principle of the material idea is based on the knowledge in the field of quantum mechanics concerning the motion of a particle closed in a potential well. Regardless of whether a particle is confined in an infinitely high potential well or in a finite height well, its energy and momentum are quantized. This means that they only accept strictly selected permitted values. More importantly - the values of allowable energy and momentum depend on the width of the L potential well. In such systems, the processes of absorption and emission of electromagnetic radiation energy are important. Absorption, i.e. absorption of the photon's energy, occurs when the charge carrier at a certain energy level E_i absorbs the radiation quantum hν, whose energy strictly corresponds to the distance between a given level of E_i and some higher E_j. The emission process is the reverse process and is accompanied by the release of previously absorbed energy ΔE, while the charge carrier moves from a higher energy level E_j to a lower energy level E_i:

$$\Delta E = E_{higher} - E_{lower}$$

In the material system which is a quantum dot, the movement of the carrier is quantized in all three directions, there is no free movement. Most importantly, the allowed energy of the carrier in such a system is fully quantized, it depends on the size of the system with three components L_x, L_y, L_z and the effective mass of the carrier. Similarly, all the components of the carrier's momentum are also quantized. The most important methods for producing such thin films are Molecular Beam Epitaxy (MBE) and Chemical Vapor Deposition (CVD). The most important for the processes of light emission in such systems is the form of the density function of the energy states of the charge carriers of the system, because the intensity of the optical transition depends on its value. In addition, in electron transport, the density of states determines the number of states available for carrier movement, and their scattering time depends on the number of states into which they can dissipate. In the processes of light emission and absorption, two principles must be met: the principle of conservation of energy and momentum. Since the momentum of the carrier has 3 components for the 3D system, in order for the energy to be emitted at the transition of e.g. an electron from a higher energy level (in the conduction band) to a lower one (in the valence band), such a state of the carrier must be additionally available (e.g. holes in the conduction band). valence), which has identical components px, py pz as in the higher state. In other words, the components px, py from the recombining electron and the holes must be identical. Along with the reduction of the size of the system, the number of momentum coordinates that must be adjusted to each other decreases, thus the number of available carriers for the emission process increases. In the 0D system, we no longer need to reconcile the components, so each excited electron can recombine with the hole at a lower energy level. So the light emission due to the 0D recombination of electrons and holes is huge. From the point of view of the huge possible applications of such systems, the most important thing is bioimaging used in today's science in biology and medicine. Because there is the possibility of precise introduction of quantum dots into specific places of living organisms, e.g. into the nucleus of a cell by injection through a nano-needle, and observation of the expansion of the material along with the growing cell (e.g. cancerous). Moreover, by light emission, it is possible to obtain a precise image of the examined cell structure fragment. It should be emphasized that the possibility of maneuvering the wavelength of light emitted by a quantum dot means that its application potential in the field of physics, chemistry and biology is constantly expanded.

The main purpose of quantum dots is to label diseased cells. A quantum dot in combination with a properly selected atom or molecule (ligand) and precisely placed inside a tissue or cell is a very good marker of cell surface and intracellular structures in in vitro and in vivo tests. Due to the properties of quantum dots, long-term monitoring of labeled cells is essential. Such possibilities are guaranteed by the use of a fluorescent probe based on nanocrystals. The process that is determined by fluorescent probes is called bioconjugation or bioconjugation.[25] Molecules that can be attached to the surface of quantum dots include nucleic acids, various types of peptides and antibodies. In order to make the so-called coupling, cross-linkers and biomolecules are used, which are attached to nano-

structures by covalent bonds or electrostatic interactions directly to the material made of nanostructures. In this method, linker molecules connect given quantum dot functional groups with conjugated biomolecules. In this way, a covalent bond is created between the linkers and groups such as: amino, carboxyl or thiol groups. Proteins and antibodies are attached directly to the surface of quantum dots using a polyhistidine tag to zinc or other metal atoms on the surface of a given nanocrystal. conjugated polypeptide.[26] The attachment of peptides to the surface of the nanocrystal increases the solubility of quantum dots in aqueous solutions, and also introduces functional groups to the surface. So they can be used for further transformations. The bioconjugation method based on the principle of interaction of oppositely charged molecules is also known.[27] At the time of ligand exchange, the quantum dot has a negatively charged surface, which means that a protein with a positive charge is attached to its surface. For example, such a protein can be and is avidin. Avidin is an animal protein consisting of four polypeptide chains, weighing approx. 70 kD.[28]

Most importantly, avidin exhibits one of the most powerful unconventional interactions observed in nature. Therefore, the resulting strong binding of avidin with e.g. biotin enables various functional molecules, e.g. antibodies, to be attached to the surface of quantum dots. Due to the emerging difficulties in the preparation of fluorescent markers, the bioconjugation of molecules with quantum dots is largely limited. One of the main barriers is the inability to control the direction and orientation of attached molecules to the surface of the quantum dot. As a result, the molecule does not sufficiently fulfill its function. In addition, molecules can uncontrollably attach to the surface of nanocrystals, which means that the fluorescent probe may not accurately count the number of particles attached.

On the other hand, the use of quantum dots as a material acting as a contrast agent in in vivo research is also associated with various types of problems. It is known from the general principles of physics that tissues located in deeper states absorb only a part of the fluorescent radiation emitted by quantum dots, which makes the obtained quantum data not fully reliable. The ideal solution is to mark quantum dots with β^+ particle-emitting radionuclides, thanks to which they can be used in combined imaging methods, in biology and chemistry as bimodal agents. Thanks to this, they can function in a similar way to iron oxide nanoparticles.

Another example of the use of quantum dots is the transport and observation of drug carriers to specific locations in the cell. Based on the structure and functioning of quantum dots, systems are created that deliver chemical compounds (including e.g. drugs) with the simultaneous observation of distribution in the body. According to the research of numerous research centers, one of the main examples of the use of quantum dot materials as drug carriers are experiments on the delivery of doxorubicin to prostate cancer cells. Additionally, on the basis of numerous publications, quantum dots are also used as one of the elements of the system that monitors the extinction of gene expression with small interfering RNA.[29-31]

Conclusion

The fundamental element of medical diagnostics is in vivo imaging of cells, tissues or pathological organs. The combination of a conventional imaging method with optical imaging with the use of fluorescent markers based on the quantum dot model is a great hope in further research and an invaluable tool in the treatment of pathological cells.

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Author contributions

Conceptualization, K.D. and D.A.; Writing – Original Draft Preparation, K.D. and D.A.; Writing – Review & Editing, K.D. and D.A.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

Data supporting the results of this study shall, upon appropriate request, be available from the corresponding author.

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