QUANTUM DOTS APPLIED IN HEALTHCARE – CBEB 2024

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ABSTRACT

This article addresses the applications of quantum dots in the health area, focusing on the applications of graphene and carbon dots. It also presents the explanation of what quantum dots are, and the motivation for using this technology in health. For this approach, research was carried out with several authors, in order to present to the reader the importance of fur- ther studies of this nanotechnology so that in the future it can be applied in the health network. It should be noted that only a portion of the studies already published on quantum dots and the health area have been addressed.

Keywords: Graphene quantum dots, Carbon quantum dots, Healthcare.

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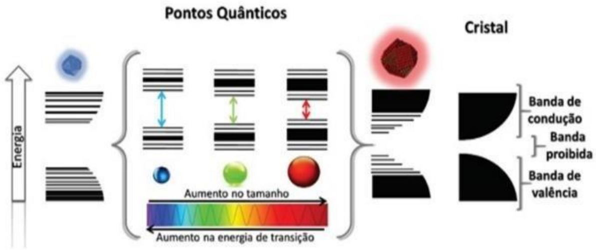
INTRODUCTION

In mid-1937 the French physicist Herbert Frohlich was discussing the existence of nanoparticles that are now known as quantum dots, at the time the discussion was nothing more than theoretical assumptions. Years later, three scientists prove that what was treated as a supposition was actually concrete and was called quantum dots. Because of these studies, the trio of scientists were awarded the 2023 Nobel Prize in Chemistry [1]. Although the most impactful development of quantum dots will be achieved after the Nobel Prize, the fascinating evolution of this area of study that correlates the physical, chemical and biological sciences begins, as previ- ously mentioned, in the mid-1980s on the effects of quantum size on colloidal nanoparticles. In the 2000s, notable ad- vances included Ekimov's synthesis of semiconductor quan- tum dots in a glass matrix, as well as Bawendi's development of optimal synthesis methods for quantum dots with well-de- fined size and resolution. By the middle of that decade, quan- tum dots showed promise in biomedical imaging, with sig- nificant improvements in brightness, stability, and tunable properties, as well as the development of biocompatible dots. Around 2010, this research marked an era of remarkable ad- vances in quantum dot applications, from integration into LED screens to improve color accuracy and energy effi- ciency to their use in electronics such as smartphones, tablets, monitors, and TVs. In the following decade, in 2020, we wit- nessed a substantial increase in the use of quantum dots in renewable energy, such as more efficient solar cells and greater energy capture and conversion, as well as in areas such as catalysis, nanomedicine, and high-speed communi- cation, highlighting their innovative potential in various sci- ences and technologies [2]. Quantum dots (QD) are consid- ered to be the trappings of a group of atoms in a place that is so small as to force a change in the position of the respective electrons. By this it is understood that the atoms are allocated in small places, where the electrons are according to their en- ergy level. When this space is moved and the quantum dot is allocated, there is then a separation of the energy levels and consequently there is a change in these levels. In this process of changing positions, when there are electronic changes in energy levels, the electrons emit a photon of a specific frequency, and this emission generates a coloration and this is one of the properties that can be observed [1]. The experi- ments carried out by the scientists showed that the particles had different optical properties, and that the size of the parti- cles influenced their coloration, with the larger particles ab- sorbing electromagnetic waves tending towards the red. Finally, quantum dots are small crystals that are composed of a certain number of atoms confined in a region [1]. It is con- sidered that quantum dots are outstanding materials due to their interesting optical and electronic properties, and this gives the material the capacity for technological application in several areas. These materials are endowed with capabilities that make them nanocrystalline semiconductors, they are made up of various atoms and have charge carriers, these car- riers being the electrons and holes that are the positive charges [3]. Another term used and of great importance is that of quantum confinement, which is nothing more than the physical size of this material being below the Bohr radius of the exciton, Bohr radius is understood as the average distance between the electron and the positive charge. What was ana- lyzed in the research is that the smaller the size of the mate- rial, the greater the confinement of the charge carriers, and thus a higher energy is in the prohibited band, as can be seen in figure 1.

Figure 1 Color of Quantum Dots [3]

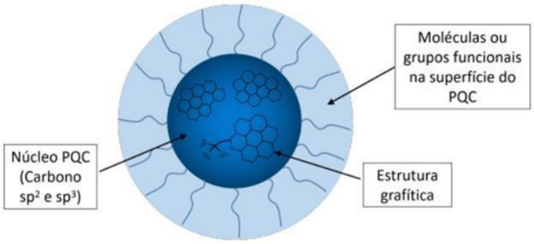


As can be seen in figure 1, the size is inversely propor- tional to the amount of energy, and the same chemical com- pound can produce different colors, it is only necessary to change the size of the nanocrystals. It is currently known that the dots have measurements from 1 nanometer (nm) to 10 nanometers (nm) [3]. QD can be manipulated through several elements of chemical groups II-VI, namely: CdSe, CdTe, CdS, ZnSe, ZnO, among others) or groups III-V such as InP and InAs. It should be noted that when handling Cd and Pb, there is difficulty in application due to the toxicity of the ma- nipulated materials. On the other hand, chemical compounds of groups II-IIIVI do not have toxicity, making these com- pounds more attractive for use [3]

CARBON QUANTUM DOTS

In 2004, while manipulating carbon nanotubes in order to carry out a purification process, the quantum dot of carbon was accidentally obtained. This material is based on carbon, has photoluminescence, quasi-spherical characteristics and has a zero dimension [4]. Since its discovery, numerous re- searches have been carried out, and from them it has been observed that this material is endowed with advantages, such as: Low toxicity, stable, it is considered low cost and abun- dant [4]. Carbon quantum dots (CQDs) are hydrophilic due to the presence of amino, carboxyl and hydroxyl functional groups. According to figure 2, the representation of the PQC point can be seen.

Figure 2 Representation of CQDs [4]



For the photoluminescence mechanism there are still doubts about its operation, and because of this there is no sin- gle explanation. Among these explanations are the factor of surface groups, size and even the presence of fluorescent molecules, so it is noted that there is not only a common un- derstanding of this issue, but several explanations. Because it is a quantum point, in general, it can be understood that flu- orescence comes from electronic excitations and exchange of its ground state.

GRAPHENE QUANTUM DOTS

Graphene is a material that is the allotropic form of car- bon, and its structure is two-dimensional and its thickness is that of a single atom. This material is considered of great value, due to its thermal, electronic, mechanical properties and also because of its chemical stability. It is observed that if when a portion of graphene is small enough to be under the influence of the quantum confinement effect, then it becomes a semiconductor and thus will exhibit special properties [5]. Graphene quantum dots (GQDs) are sheets with isolated na- nometric dimensions of graphene, these dimensions have a size smaller than 100 nanometers (nm), and due to their quan- tum confinement they generate intense photoluminescence, in addition to the confinement photoluminescence is gener- ated due to edge effects. They are part of the graphene nano- materials group [6]. GQDs have low toxicity, their disper- sions have stability when in water since their structure forms hydrophobic interactions, they have rapid interaction with chemical species, their optical properties have greater stabil- ity, and finally they have greater sensitivity to analytical re- sponses, all these advantages presented are related when compared to semiconductor quantum dots [6]. In this ele- ment, it is observed that some factors can influence the pho- toluminescence of the material, such as: structural defects, presence of oxygen-containing groups and finally the doping elements have generated influence on the luminescence, it is worth mentioning that there are doubts about the accuracy of the photoluminescence mechanism of the GQDs, and be- cause of this several theories have been generated [5]. These GQDs can have a range of colors ranging from ultraviolet, through blue, and up to red. These coloration bands can be observed when interacting with ultraviolet (UV) light.

There are different ways of preparing and synthesizing this mate- rial, but citation is not necessary due to the fact that it is not the scope of this work [5]. Some studies have shown that this material has the possibility of transporting drugs, as well as due to its size it is believed that it would have easy penetra- tion into the lipid layer and thus would not generate damage, thus facilitating the transport of drugs [7]. Thus, it is noted that quantum dots are nanomaterials of great applications and that they can promote a significant impact in several areas, including the health area. Its impact on health is broad and will be analyzed in further discussion, in addition to this ma- terial has economic advantages, which is positive for the health system.

MARKET

The market growth for quantum dots predicted from 2024 to 2029 is detailed in the report available by Mordor's Intel- ligence (https://www.mordorintelligence.com/pt/industryre- ports/quantum-dots-market-industry), a technical website for industrial growth and investment information, in this docu- ment several scenarios are considered for the applications of dots, in which possible biomedical applications are men- tioned. The market as a complex currently holds about 5 bil- lion dollars, concentrating the largest investment and expan- sion in the regions of Asia and Oceania, as shown in figure 3.

Figure 3 Quantum dots market

However, the report highlights the quantum applications related to imaging improvements, and their implementations in the market, in addition to their probabilistic applications such as biosensors and pathogenicity detectors, but does not corroborate for the applications related to drugs and treat- ment due to the toxicity effects of the compounds, which still have an experimental and investigative state.

BIOLOGICAL APPLICATIONS OF QUANTUM DOTS

CQDs are mostly relevant for biological applications due to their organic relationship based on the element carbon, which not only composes molecular structures, but is also intrinsically related to biological structures such as peptides, cells and tissues. Cells are complex structures composed of several mechanisms, which perform the most diverse and complex functions, from the absorption of water, to their rep- lication for tissue renewal or defense against invading organ- isms. Because they have the most diverse differentiations in organisms, they can be identified by means of more precise markers, that is, if they are made of more permeable materials or even more compatible with the environment. The relation- ship of quatum dots as biomarkers is evidenced due to the excitation capacity providing signals such as photolumines- cence, enabling the localization of mutations (carcinomas) and/or metabolic maladjustments. On the other hand, treat- ments are related to the ability to help biological structures to carry out the defense or restructuring of their metabolic ac- tivities in a coherent way after invasions, whether by micro- organisms, mechanical accidents or others. Thus, targeted therapies seek to relate the dots of various materials, includ- ing carbon, with the lowest possible toxicity for the formula- tion and activation of drugs, thus promoting their dispersion or absorption only by the organs, tissues or areas of interest for the defined treatment. In order for less invasive and more effective treatments to occur, the health sciences seek, over the years, to research more assertive materials and practices. For which more detailed examinations are necessary, ranging from the general functionality of an organ, the biological tis- sues, to the reproductions carried out gradually and steadily by these structures. Consequently, the greatest prominence and market expansion are those related to image resolution through quatum dots and their light emissions, enabling the visualization of the areas where the disturbances occur, so that their nanometric structure facilitates the identification of reactions and activities related to pathogenicities.

METHODS

To understand the vastness of quantum dots and their ap- plications in the biomedical sciences, a multifaceted method- ology composed of multiple steps was adopted. First, a thor- ough review of the scientific literature related to quantum dots was conducted. This review has ranged from the theo- retical beginnings discussed by Herbert Frohlich to the most recent discoveries and applications, which are presented in articles. A variety of sources, including papers, technical re- ports, and other relevant publications, were consulted to gain a comprehensive understanding of the development and evo- lution of this area of study. In addition, previous studies con- ducted by renowned scientists such as Ekimov and Bawendi were analyzed, and then sought to understand the advances and discoveries that contributed to the current knowledge about quantum dots. This analysis allowed us to identify the distinctive properties of quantum dots, especially carbon dots. Data collection played a key role in our methodology. Relevant information on applications in different sectors and market trends was gathered, with a greater focus on the areas of health. Ethical and safety considerations have been care- fully weighed throughout our research, especially with regard to the use of quantum dots in biomedical engineering. The challenges and ethical concerns related to the use of nano- technological materials in biomedical and therapeutic appli- cations were discussed, in accordance with international con- ventions on bioethics and animal welfare. Finally, a comprehensive market analysis was conducted, examining the growth trends, highlighted application areas, and eco- nomic and business considerations related to quantum dots. This methodology allowed a detailed and comprehensive analysis of quantum dots, from their theoretical bases to their practical applications, considering ethical, security and mar- ket aspects. The results and discussions obtained provided valuable insights into the potential of these materials in sev- eral areas, including health and technology.

RESULTS AND DISCUSSION

Quantum dots have several applications, as well as certain advantages already mentioned earlier in this article. It is therefore necessary to cite research that addresses the use of these materials in the health area, it is worth noting that the works cited here are only a sample of the potential of this material, thus not representing all the studies already carried out. It is presented from some authors that CQDs have been applied in bioimaging, quantum dots were prepared and after the preparation cancer cells from the human breast region were labeled, and human epithelial cells were used as con- trols. He then excited the cells to a certain length, and with this photoluminescence was presented. It was observed that this material is more biocompatible and that it was 80% higher in cell retention. In addition, cellular retention of quantum dots can be observed, and this retention has been observed using a common fluorescence microscope. After further testing, it was confirmed that the CQDs were inter- nalized into the cells and that this was accomplished by en- docytosis. It is concluded in this article that CQDs are inter- esting due to their low cost, they have a non-toxic character, demonstrating that they do not have problems for biological applications, demonstrating that their use will have a great impact [8].

Work was done to develop methods of analysis using gra- phene quantum dots, and these quantum dots would have the effect of a photoluminescent probe with the objective of de- termining a drug for cardiac patients. Graphene quantum dots were produced from aqueous dispersions and prepared by glutathione and citric acid pyrolysis, this dispersion gener- ated GQDs functionalized with amino groups. In addition, analyses were also performed with or without the presence or absence of Fe^{3+}. These GQDs were used in the study as probes to determine the use of the medication, the results ob- tained were significant and with this it was observed that re-gardless of whether or not there was Fe^{3+}, but that it is possi- ble to use these probes to measure the medication. In addi- tion, it was also observed that these probes have a competi- tive advantage in relation to others already used, this differential is the fact that no toxic reagent is used [6].

In 2018, a broader study was carried out on the use of GQDs as an analysis probe, where in addition to the use for observation of medication for 6 cardiac patients, its use in histamines and kanamycin sulfate was also analyzed. When in the presence of histamines, the study evaluated the photo- luminescent scattering reactions. For Kanamycin sulfate, gold nanoparticles were needed to measure the effect of pho- toluminescence associated with the GQDs. The study demon- strated that the probe for use in the analyzed cardiac drug had good results, so the proposal proves to be competitive when compared to peers already described in the literature. On the other hand, for the histamine probe, mediators in an aqueous system were needed, and with this a good correlation of the probe with Fe^{3+} for histamine analysis was again observed. Finally, in the probe analysis for Kanamycin concentrations, the study was successful for the determination of samples for- tified with yellow fever and for samples of pharmaceutical formulations. Therefore, it is possible to observe in this work a good use of GQDs for the analysis of certain substances [5]. In 2019 it published studies and analyses referring to as- says using quantum dots for biomedical purposes, however, only in vitro and ex vivo studies were included, due to the difficulties of bioethical approval related to long-term tox- icity associated with their administration. The study reaffirms the relevance of the applications of these methods for more assertive and specialized treatments, focused on the permea- bility and affinity of the tissues under treatment, making them a suitable tool for personalized treatments [9].

In 2020, a study was carried out using the graphene quan- tum dot for the treatment of leukemia, the quantum dots in this case would be in charge of loading chemotherapy drugs, in order to reduce the toxic effects of the treatment. In this study, carbodimide was functionalized so that it could later be conjugated to the drug imatinib. This drug was intended to be synthesized and conjugated to the GQDs, and this pro- cedure was successfully performed by the study. It was pos- sible to observe that this conjugate was able to induce the death of leukemia cells, and presented lower toxicity to healthy cells when compared to the use of the drug Imatinib alone. This work was able to demonstrate that drug carriers made from carbon nanoparticles have been effective in the treatment of cancer. In addition, they are less toxic, which is positive for the patient under treatment [7].

In addition to technical and scientific issues, it is critical to consider the ethical and safety implications associated with Quantum Dots studies in biomedical engineering. The bio- ethics conventions related to the studies in question are the Universal Declaration on Bioethics and Human Rights - UNESCO 2005, Oviedo Convention (Convention for the Protection of Human Rights and the Dignity of the Human Being with regard to the Applications of Biology and Medi- cine): - Council of Europe in 1997 and the Declaration of Helsinki, in which the need to inform patients about the risks of the research to which they are being submitted are high- lighted, the freedom in relation to the aggressiveness of the compounds or activities to be performed.

There are also conventions that cover animal welfare and protection, as well as the feasibility and authorization of their use in research, some of which are: European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes of 1986, Guide to the Care and Use of Laboratory Animals, Directive 2010/63/EU on the Protection of Animals Used for Scientific Purposes and Prin- ciples of the Three R's. These documents discuss the impli- cations of the well-being of individuals for the results and preservation of life in corroboration with the advancement of scientific research, predicting limits for pain, sleep depriva- tion, food, habitat area and other topics.

CONCLUSIONS

Quantum dots have been shown to have a high capacity for use in the health environment, in addition to their explo- ration capacity is still great, with this it is understood that over time this material will have greater use in the health area than it currently has. Through this article, it was demon- strated that the material is biocompatible, low cost and great applicability, these points are advantages that make this ma- terial have great potential for use in the health system. As a suggestion for future work, it was observed that there is a need for studies of this material for application in other ex- ams such as cardiac examinations, since there is a significant number of individuals who are affected by heart diseases, eventually using this material together with an image analysis device, it is possible to obtain clearer and better defined im- ages.

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