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Carbon Nanotubes-Doxorubicin Conjugates Molecular Dynamics and Bio-inspired Approaches for Clinical Toxicology

Contreras ML* and Rozas R

Environmental Sciences Department, University of Santiago de Chile, Usach, Chile

***Corresponding author**: M Leonor Contreras, Departamento de Ciencias del Ambiente, Facultad de Química y Biología, Universidad de Santiago de Chile, Usach, Avda LB, O'Higgins 3363, Estación Central, Santiago, Chile, Tel: +56 2 2718 1151; Email: leonor.contreras@usach.cl

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Abstract

Doxorubicin as a therapeutic drug is used in several human pathologies related to cancer. It has however some side effects that needs to be understood and controlled. This article discusses some applications using single-walled carbon nanotubes as carriers, making a molecular approach for a better understanding of clinical toxicological development. Finally, the general principles of nanoethics and its regulation as well as a bio-inspired design for a better control, is described.

Keywords: Defected Carbon Nanotubes; Encapsulated Doxorubicin; Toxicity Factors; Nanoethics; Bio-inspired Design; Regulation

Introduction

The real situation of the environment due to the human intervention in nature, and consequently the problems of health of the human body imply that new alternatives should be developed in order to keep equilibrium for a good interaction. In this reality, new knowledge such as nanobiotechnology, or the understanding of how nature has evolved after millions of years, are just two of the several alternatives that need to be learned and apply soon. This scheme is approached from a deep knowledge of molecular biology that may inspire a way to help in a good manner. So here we briefly review the application of Doxorubicin (DOX), transported by carbon nanotubes (CNTs) for good clinical toxicology, based on molecular dynamic (MD) methods, and the nanoethics that should be taken in account particularly using bio-inspired methods for an integral point of view.

Clinical Aspects of Doxorubicin

Doxorubicin (DOX) or hydroxydaunorubicin, is a drug widely used in cancer chemotherapy [1-3]. It is an antibiotic of the anthracycline family, being an intercalator of DNA [4]. It is commonly used in the treatment of a variety of forms of cancer. Doxil is a well-known drug (Johnson & Johnson) for administration of doxorubicin encapsulated in liposomes [5]. The main benefits of this form of administration consist of a reduction in cardiotoxicity.

Clinical Use

Doxorubicin is commonly used in the treatment of some leukemia and in Hodgkin's lymphoma, as well as in bladder, breast, stomach, lung, ovarian, thyroid, multiple myeloma [6].

Side Effects

Acute side effects of doxorubicin include nausea, vomiting, and arrhythmias. It can also produce neutropenia, as well as complete alopecia. When the cumulative dose of doxorubicin reaches 550 mg / m^2, the risk of developing cardiac side effects increases drastically. Cardiotoxicity due to doxorubicin is characterized by a dose-dependent decline in the number of mitochondria and in oxidative phosphorylation. Reactive oxygen species, generated by the interaction of doxorubicin with iron, can damage myocytes (cardiac cells), causing the loss of myofibrils and cytoplasmic vacuolization. In addition, some patients may develop palmo-plantar erythrodysesthesia or hand-foot syndrome, characterized by rashes on the palms of the hands and soles of the feet, with swelling, pain and erythema [5]. Doxorubicin presents a moderate toxicity; however the FDA (Food and Drug Administration) has approved its use [7-9]. DOX adsorption on suitably functionalized CNTs decreases its toxicity and increases its bioavailability [10].

Therapeutic Applications with Carbon Nanotubes

There are three modes of interaction between carbon nanotubes and the active components of pharmaceutical formulations. The first method of interaction is as porous absorbers to trap the active components within a mesh of nanotubes or nanotubes in the form of bundles. The second is the functionalization of carbon nanotubes by binding their outer walls to parts of the compound of interest. The third approach involves the use of nanotubes as nanocarriers [11].

The application of carbon nanotubes as carriers increases due to their ability to penetrate the cells. The functionalization of carbon nanotubes promises to be widely used in nanomedicine for the administration of drugs. For instance, the functionalization of carbon nanotubes with polyethylene glycol (PEG) fragments has been widely used to improve the solubility of the nanotube conjugates in aqueous solution, as well as the biocompatibility of the fractions. The PEG chains could be functionalized with terminal amine (PEG-NH2) and maleimide groups (PEG-maleimide), resulting in a positive interaction with a polar aqueous solvent.

It can be said that the administration and formulations of drugs have been revolutionized with the advent of nanotechnologies. The use of nanoparticles in medicine promises to solve the problems of drug administration in specific cells and facilitate the movement of these drugs through different barriers in the body. This would positively influence the treatment of diseases of the central nervous system, being able to control the passage, through barriers in the body of drugs that normally without the use of nanoparticles, would not cross them.

Nanopharmaceutical products based on carbon nanotubes require an understanding of their physical and chemical properties, with solubility being one of the most necessary properties to take into account. The biomedical applications of carbon nanotubes have guided, in recent years, the development of a new field in therapy and diagnosis. The majority of these applications consist of the use of functionalized nanotubes in patients. However, the use of carbon nanotubes in medicine is subject to the rigorous evaluation of its toxicity in the body.

Molecular Toxicology of Carbon Nanotubes (CNTs)

The molecular development of CNTs for biomedical and biotechnological applications is of growing interest, especially in delivery systems for molecules with an important therapeutic effect on target cells. However, the CNT-cell interaction may involve some toxicity. In this section, together with a brief review of the toxicological aspects of CNTs, the convenience of using these materials as drug carriers, in particular DOX, is described, based mainly on the ability of nanotubes to penetrate membranes and functionalize with different fragments that give it, on the one hand, solubility (for example polyethylene glycol groups, PEG) and, on the other hand, the ability to specifically target particular cells (for example through folate groups taking advantage of the interaction with folate receptors existing in tumors). In addition, molecular dynamics (MD) simulation studies useful in the prediction of DOX-CNT molecular interactions are shown. Finally the study is extended to show the use of CNTs with defects as potential useful components in the design of drug delivery systems (DDS).

The toxicological effects of CNTs refer to adverse effects that occur due to the presence of CNTs in living systems causing diseases. Due to their structure, the CNTs tend to associate with each other, mainly through van der Waals forces, forming insoluble bundles that can accumulate in the lungs. For example, if they are inhaled, the CNTs cause subpleural fibrosis in mice and in cases of chronic exposure, in humans, the CNTs damage the epithelial cells of the lungs leading to induce carcinogenesis [12,13].

The knowledge of the factors that affect the nanotoxicity of the CNTs undoubtedly is of great help to find mechanisms of mitigation and inhibition of their negative effects [14]. The CNTs once incorporated into the body, participate in an intracellular traffic or translocation. For example, when injected intravenously, they are taken by the liver and spleen and then excreted through the kidneys [15]. It should also be considered that some impurities that may be present in CNTs, such as Ni, Fe and Co, are highly toxic and alter the real toxicity of the CNTs [16,17]. On the other hand, it has been found that CNTs are biodegradable and, in the presence of enzymes such as plant peroxidases, generate fragments that do not produce an inflammatory response when they are aspirated into the lungs of mice [18,19]. This is especially important in the context of biomedical applications, as it suggests that individual nanotubes (or small bundles) are less toxic than larger aggregates.

The solubility of the CNTs is greatly improved by adequate functionalization of the side walls. Together with purity, they are the most important factors that affect the cytotoxic profile of CNTs. Experimentally, it was proved that ultrapure CNTs, totally dispersible, lack all toxicity at normal concentrations of 10-150 μg/ml [20,21].

When the CNTs are nitrogen-doped and the cell viability is analyzed both in mice and in amoeba cell, favorable toxicological effects are found indicating that the nitrogen-doped CNTs are less harmful and more biocompatible than the undoped CNTs [22].

As is known, the CNTs have a structure, called regular, constituted exclusively by six-member carbon rings (hexagons). During the formation process, other rings are also formed (incorporated in the regular structure), which can be 4, 5, 6, 7 and up to 8 members, called defects. Due to experimental difficulties, it is not currently known, the way in which these defects (for instance, their number, type and distribution in the nanotube), can affect the properties, including the toxicity of defected CNTs. In this context, theoretical calculations and simulation of molecular dynamics (MD) are of great help in the understanding of molecular interactions [23].

For example, by means of MD and density functional theory (DFT) studies it was found that CNTs containing Stone-Wales defects with rings of 5 and 8 members showed better hydrogen adsorption energies than CNTs having Stone-Wales defects with 5 and 7-member rings [24]. This is an important fact because it allows explaining the huge discrepancies reported in the literature regarding the ability of CNTs to store hydrogen as clean energy.

In relation to the DOX-CNT interaction molecular forces, it was found that DOX is quickly adsorbed on the outer walls of closed *zigzag* nanotubes. Using atomic force microscopy (AFM) and spin tunneling microscopy (STM) it was observed that the DOX formed stable conglomerates on the walls of the nanotube in such a way that it was possible to observe protrusions and depressions that account for the ability of the DOX to self-assemble [25]. Several studies have theoretically investigated the interactions DOX-CNT for regular nanotubes (without defects) [7,26-28]. The best interactions, mainly π-π stacking and hydrophobic, are established when the DOX is encapsulated inside the nanotube and not adsorbed on its surface.

CNTs with defects, for example, nanotubes that have five- and seven-membered rings of the bumpy type (which are formed by adding two carbon atoms for each defect) have been studied in this context. MD simulation research for *chiral* nanotubes (AMBER program, force fields ff99SB and GAFF, octahedron water box, TIP3P model) exhibit more favorable DOX-CNT interaction energy values of the Poisson-Boltzman and Generalized Born types, than for *chiral* nanotubes without defects [29]. *Armchair* and *zigzag* nanotubes doped with nitrogen improve DOX-CNT interactions compared to undoped nanotubes. When the nanotubes are functionalized with PEG groups, the presence of two PEG groups of eight units each one is more advantageous than that of four shorter PEG groups. Also, regardless of the chirality of the nanotube, the molecular simulation studies show that there is a certain curvature that allows optimal DOX-CNT interactions, which is produced for a diameter of ~14 Å [29]. These data suggest that there is a variety of structural modifications that can theoretically be predicted and that could be useful in the design of more convenient drug release systems provided that any toxicity risks are favorably resolved.

Nanoethics of Nanomaterials and Regulation

The use of nanomaterials that already exist on the market has continuously increased and the most important applications include biological devices and biosensors, implants, protective equipment, antibacterial materials, and the therapeutic administration of drugs and cosmetics. Nanoscale membranes and nanoparticles that have an extremely small pore size and a large surface

area are suitable materials for the removal of unwanted particles from drinking water, which has been a serious problem in developing countries. Some nanoproducts are highly toxic and can cause serious diseases to humans. Nanoethics deals with the harmful effects of nanotechnology to create a safer work environment for people involved in the research, development and education of nanotechnology, considering also the opinion of society as consumers of these products in the market.

Regulation in the United States

The FDA has formulated specific regulations relevant to nanobiotechnology products. The development of pharmaceutical products that contain nanoparticles and the methods of drug administration are regulated by the FDA as any other biopharmaceutical product, as well as food, and human medicine, where there is awareness of the consequences, good or bad, that are not yet well known. New technologies can have a disruptive influence on society, as has happened with the introduction of biotechnology in agriculture since the beginning of the 21st century. The FDA has not established its own formal definition, although the agency participated in the development of the nanotechnology definition of the National Nanotechnology Initiative (NNI).

Although nanotechnology has not posed any new ethical problems, it is convenient to take into account certain considerations when developing and applying nanobiotechnologies to medicine.

Several aspects of nanoethics that require better considerations are: 1) the restriction of ethics to prudence understood as rational risk management; 2) the reduction of ethics to cost / benefit analysis; and 3) the confusion of technique with technology, and of human nature with the human condition.

Nanotechnology patents: The USPTO has created a preliminary classification for nanotechnology, designated as a Class 977 Nanotechnology Cross Reference Art Collection. Its purpose is described on its website: (http://www.uspto.gov/web/patents/biochempharm/cross-ref.htm).

The nanoparticles have been patented for diagnostic use, as well as for combined diagnostic and therapeutic use. As there is no specific law on nanotechnology until now, it is necessary to use the existing regulations on the use of medicines and therapies as a model. But this field of technology requires a specific decision because many problems will arise in the future, which are not governed until now, and the security of the human being must be guaranteed as a main objective, which could be achieved through extensive legal regulation. An example is the application of a nanorobot for the control of health or interaction with the human being, since there is no similar machine, neither with the same function nor with the same objective.

Regulation in Europe

The regulation of the Member States of the European Union has the approaches of the European Commission (EC) and the European Parliament (EP) that regulate nanomaterials offering an overview of regulation in the field of nanomaterials. In 2004, the EC raised its strategy on nanotechnologies in a communication entitled "Towards a European Strategy for Nanotechnology". At that time, the strategy established that due to the nature of nanotechnologies, existing regulation should be examined and probably revised and that "a proactive approach should be adopted". However, the communications of the Commission of 2008 and 2012 on regulatory aspects of nanomaterials conclude that the current regulation (REACH) covers in principle the potential risks to health, safety and the environment associated with nanomaterials, as these are similar to normal chemicals.

The EC regulation No. 1223/2009 on cosmetic products includes specific provisions related to nanomaterials; incorporates the definition of a nanomaterial as an insoluble or bio persistent material on a scale of 1 to 100 nm. The regulation entered into force on January 1st, 2013. It establishes the notification requirement for cosmetic products containing nanomaterials. The notification must contain identification of the physical and chemical properties of the nanomaterial, the toxicological profile, safety data and exposure conditions. An explicit and publicly available catalog of all nanomaterials used in commercialized cosmetic products has been available since 2014.

Security Recommendations of the Royal Society of UK

The Royal Society of UK has published a report "Nanoscience and Nanotechnologies: Opportunities and Uncertainties" (http://www.nanotec.org.uk/report/summary.pdf), which contains a section on nanotechnology safety issues (NONS). This study is the first of its kind and responses are expected from organizations within the United

Kingdom and other countries. Some comments and recommendations in the report are:

- Most nanotechnologies present no new health risks and almost all concerns are related to the potential impacts of fabricated nanoparticles and nanotubes that are free rather than fixed to a material or within a material.
- It is very unlikely that new manufactured nanoparticles can be introduced in humans, in sufficient doses to cause the health effects that have been associated with nanoparticles in contaminated air.
- The release of manufactured nanoparticles and nanotubes to the environment should be avoided as much as possible.
- Chemical products in the form of nanoparticles or nanotubes should be treated as new substances according to the current regulations of "Notification of new substances (NONS)" and in the REACH system".
- In general, given the appropriate regulation and investigation according to the lines just indicated, there is no need for a moratorium, which some countries have advocated in the laboratory or the commercial production of manufactured nanomaterials.

Bio-inspired Design of New Materials

Bio-inspired design is a transdisciplinary approach that links biology and technology, generating knowledge beyond such disciplines. The most widespread terms are biomimicry and biomimesis [30,31]. Digital databases such as asknature.org provide access to several thousand biological inspirations [32]. The biologically inspired strategy can provide an analysis of a complete ecosystem, its components and equilibrium relationships. These approaches make it possible to conceptualize bio-inspired technical systems that are sustainable.

The bio-inspired design methods are based on different activities such as: the planning of a project in which biologists and engineers collaborate, taking into account the integration of their work; the abstraction, in which designers must abstract or allow the search for biological inspiration; the search for a biological inspiration of the technical project; make a careful analysis and comparison of the technical and biological systems to successfully apply the bio-inspired design; and transfer the more or less abstract analogies to develop a technical solution.

Procedure Based on TRIZ

TRIZ (Theory of Inventive Problem Solving) is a well-known innovation methodology that is based on the identification of design principles in the area of invention patents [33]. TRIZ is based on a procedure for extracting technology divided into two main phases: specification of objectives, and development of solutions. Its adaptation to bio-inspired design (BIOTRIZ) has the potential to lead technical designers to solutions different from other bio-inspired design procedures [34].

In comparison with other procedures, BIOTRIZ pays special attention to the specification of the objective, and it is maintained that the objective of the procedure is to specify the technical requirements in such a way that contradictory requirements become evident. The contradiction of the requirements as a central technical problem is important and must be resolved. The objective specification phase is focused on the technical system: it begins with the study of the market situation and the demands of the clients [35].

Clinical Bioassays with Bio-inspired Hydrogels

An interesting hydrogel bio-inspired on pufferfish (Tetraodontidae) device recently published, consists of superabsorbent hydrogel particles that allow the device to quickly imbibe water encapsulated in a mild but anti-fatigue hydrogel membrane that maintains the device's long-term robustness [36]. The hydrogel device can be ingested as a standard size pill which rapidly imbibes the water and is inflated (up to 100 times in volume within 10 minutes) in a large soft sphere (diameter up to 6 cm) and maintains the robustness under repeated mechanical loads for a prolonged time of two weeks *in vitro*. The *in vitro* data suggest that the hydrogel device can also be applied for a very long sustained drug delivery. In addition, the hydrogel device is able to shrink on demand to exit the body in response to a biocompatible saline solution. This ingestible and gastric-retentive hydrogel device has a series of advantages over conventional ingestible devices made of other materials due to its biocompatibility.

The hydrogel device consists of superabsorbent hydrogel particles (polyacrylic acid) encapsulated in a porous anti-fatigue hydrogel membrane (frozen and thawed polyvinyl alcohol and used for example as a miniature sensor (for movement, salinity, pressure, pH, gas or other specific biomarkers) integrated in the hydrogel device can allow long-term measurements of biological signals which could be developed as a sensing bionanorobot.

Conclusions

This manuscript has reviewed some molecular aspects related to clinical toxicology and to MD studies of the DOX-CNTs conjugates for determining critical parameters that are considered in the potential use of specific and new carbon nanotubes for transporting DOX.

The other point of view reviewed focused in the good results that can be obtained with the mayor stand point of bio-inspired design, where nature has some hydrogels of different material that can be used in the general field of natural solutions done in conditions of sustainability of different processes without having problems of toxicity.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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