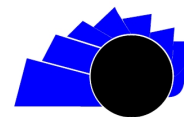




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Evolution of the use of nanoparticles in cancer diagnosis and treatment

Evolución del uso de nanopartículas en diagnóstico y tratamiento del cáncer

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ABSTRACT

The use of nanoparticles in the health area is a research topic that has been increasing in recent years, from that perspective this work focused on making a characterization of nanoparticles, their evolution and interaction with blood, aspect addressed through the description of the biomagnetic fluid, focusing on characteristics such as viscosity and geometry. Also, the evolution of the applications or techniques in which nanoparticles have been used is presented, focusing the review on cancer treatments, for which the four progressive generations of this research field were considered, as well as the use of nanoparticles in diagnostic imaging. Finally, some fields of implementation and study in Colombia were identified. The review carried out allows concluding that the evolution of the use of nanoparticles in medical applications has made possible the realization of targeted cancer treatments; in this sense, the incidence of SPIONs in the advances achieved recently is recognized, as well as the importance of deepening the study of the movement of these particles.

RESUMEN

El uso de nanopartículas en el área de la salud es un tema de investigación que ha experimentado un crecimiento significativo en los últimos años, desde esa perspectiva, este trabajo se enfoca en hacer una caracterización de las nanopartículas, su evolución e interacción con la sangre, aspecto abordado a través de la descripción del fluido biomagnético, centrándonos en características como la viscosidad y la geometría. Además, se da a conocer la evolución de las aplicaciones o técnicas en las cuales se han venido empleando las nanopartículas, especialmente en tratamientos contra el cáncer, para lo cual se consideraron las cuatro

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generaciones progresivas de este campo investigativo, así como el uso de las nanopartículas en imágenes diagnósticas. Finalmente se identificaron algunos campos de implementación y estudio en Colombia. La revisión realizada permite concluir que la evolución del empleo de las nanopartículas en aplicaciones médicas ha posibilitado la realización de tratamientos de cáncer focalizados; en ese sentido se reconoce la incidencia de los SPIONs en los avances logrados recientemente, así como la importancia de profundizar en el estudio del movimiento de estas partículas.

1. Introduction

The term nanotechnology refers to a multidisciplinary field that deals with the research, design, synthesis, application of materials and functional systems by controlling substances at the nanometer level. The interest of nanotechnology is not only to manipulate matter on a small scale, but also to study the unique physical and chemical properties of nanostructures (e.g., surface properties, electrical conductivity and magnetic properties). In recent years, nanotechnology has had a major impact in areas such as biology and medicine [1]. With the aim of advancing in this field, a bibliographic review was carried out, oriented towards three topics: characterizing nanoparticles (np) and their evolution; describing the medium in which they move and therefore their interaction with it, and identifying the applications or techniques of nanotechnology in health sciences, specifically in cancer treatments (tumors), and the obtaining of diagnostic images through methods that use nanoscopic contrast agents or markers.

2. Characterization, description and evolution of the np

The np are particles with dimensions of the order of $1 \text{ nm} = 1 \times 10^{-9} \text{ m}$, which facilitates their application to different fields of nanotechnology, in medicine for example, they are used for the purpose of monitoring, control, construction or repair, defending

or improving the human biological system at the molecular level [2]. Some of the np used in cancer treatments have been dendrimers, being np with three-dimensional tree-like structures in the range of 1-100 nm, they can host a variety of carrier molecules, both hydrophobic and hydrophilic and are useful delivery agents for genes, drugs and anticancer agents; thanks to their size and geometry they can be specifically controlled in groups, in order to possess pre-designed and specific physical and chemical properties [3].

On the other hand, micelles are hydrophobic spherical structures that are grouped to form the central core of the sphere in a liquid environment [4], so they are useful for the administration of water-insoluble drugs with sizes in the range of 10 - 50 nm [5]. Nanospheres, on the other hand, are spherical structures composed of a matrix system where the surface can be modified by adding polymers and also biological materials, have a size in the range of 10 - 100 nm [4]. From the perspective of their use as carriers, nanocapsules are vesicular systems with a central cavity or core to which it is possible to confine a drug, their size is in the range of 10 - 500 nm [6]. Finally, we find the magnetic ones, on which we will go deeper, because their characteristics have made possible advances in the transport through the blood as a biomagnetic fluid.

2.1. Magnetic Nanoparticles (MNP)

They are np that are iron-based, therefore they can be manipulated by employing an external magnetic field (B) [7]. Magnetite (Fe_3O_4) is a black

ferromagnetic iron oxide of Fe(II) and Fe(III), which has been the most studied, due to the potential to act as an electron donor [8].

2.2. Ferrofluids

When talking about ferrofluids, we refer to a colloidal dispersion made by a special multidomain particles based on iron oxide and iron hydroxide by a wet chemical method, which facilitates the steering capability under the influence of a B [9]. Additionally, these colloidal magnetic np have unique surface properties that allow biocompatibility and biodegradability in addition to having minimal toxicity, they are suitable as drug-delivery vehicles that have excellent magnetic saturation [10].

2.3. Superparamagnetic

They are a unique type of MNP, because they have many desirable properties, from the point of view of biomedical applications, such as: biocompatibility, biodegradability and ease of synthesis, to which we must add their superparamagnetic nature. On the other hand, they do not produce hysteresis, since they leave a zero residual magnetization after an external B is removed, this feature helps to prevent coagulation, so compared to other MNP, it reduces the possibility of agglomeration in the body [8].

The size of these particles influences both their physicochemical and pharmacokinetic properties, so two groups are classified: Spions: (superparamagnetic iron oxides) are np that in particular are generally based on inorganic iron oxide coated with hydrophilic polymers, whose size is larger than 50 nm (including the coating). USpions: (ultra-small superparamagnetic iron oxides) are np that have a size smaller than 50 nm, being blood pooling agents they could be used for perfusion imaging enabling the diagnosis of cerebral or myocardial ischemic diseases [11].

3. Characterization and interaction of the environment

Currently there is a field of research associated with the interaction of B with living beings, and in particular it has gained relevance in nanomedicine, from this perspective we can consider two basic areas: magnetobiology and biomagnetism. The former deals with the effects produced by magnetic fields on organisms, ranging from the orientation capacity of some animals, to the controversial damage to health caused by exposure to low-frequency electromagnetic waves. Biomagnetism, on the other hand, focuses on the study of the B associated to the organism itself, in particular we refer to the biomagnetic fluid, which is found in organisms and reacts to the presence of a B. The results of these experimental fields are useful to obtain information that does not allow us to understand biophysical systems, to implement new clinical diagnostic techniques and to create new therapies centered on the use of np [13].

3.1. Blood as a transport medium for nanoparticles

The various applications of np as a means of transporting drugs or contrast chemicals, have led researchers to deepen both the knowledge of the blood, as the fluid through which these particles move, the interaction with the components thereof, and the incidence of external magnetic fields applied, in this sense, Bose and Banerjee [14] mention measurements made to estimate the magnetic susceptibility of blood and reported that this is between 3.5×10^{-6} and 6.6×10^{-7} for venous and arterial blood, respectively, also Bartoszek and Drzazga [15] show an experimental study of the magnetic anisotropy of blood cells at a B of up to 1.8 T for a temperature range between 75 - 295 K, employing torsional magnetometry.

In 2000, Ichioka and Ueno conducted *in vivo* experiments using rats as subjects, which were subjected to magnetic fields of 8 T, showing a reduction in blood flow and temperature of the animal. In the same direction, the *in vitro* experiments conducted by Haik, Pai and Chen [16], in which they used human blood samples subjected locally to a B of the same intensity, reduced by 30%, additionally established that as the biofluid enters and exits the gradient of B, In relation to the biomagnetic flux in narrow channels, Tzirtzilakis in 2005 found that these are affected by a constant and local B [14].

3.2. Simulating biomagnetic fluid (blood)

Liu, Zhu, Rao, Clausen, and Aidun [17] simulate the biotransport of np under a complex cell flow environment using a multiscale method based on the Lattice Boltzmann method (LBM), the basic components of which include liquid-phase LBM processing, the red blood cell spectrum linkage method (SLM), and the Langevin dynamics (LD) method to capture pauses of np motion. In addition, extensive bidirectional coupling schemes are established to capture precise interactions between each component and thus simulate np transport in cellular blood flow with high efficiency.

In turn, Lee, Ferrari and Decuzzi [18] present a general mathematical model to predict the transport behavior of particles with different physical properties: size (nano-microparticles) and shape, as well as the material in which they are immersed, considering a linear laminar flow. Their results show that non-spherical particles, under the concurrent action of inertial and hydrodynamic forces, can deflect laterally, an effect known as hydrodynamic margination, increasing the probability of interaction with the wall surface. Thus, in blood, np will periodically oscillate around their trajectory, thus reducing their distance from the vessel wall, while the particles may actually separate with a net lateral deflection.

On the other hand, Duncan and Bevan [19] generated a Monte Carlo simulation, measuring the net interactions between np "decorated" by ligands, which possess distinct chemical structures, providing multiple interactions in self-assembly, and membrane proteins on the surfaces of healthy and diseased cells. From their analysis they identify that these ligand-functionalized np are able to selectively bind to populations of diseased cells rather than healthy cells, proving attractive for improving the efficacy of drug therapies by using lower affinity ligands to target cancer cells with targeted membrane proteins.

Along the same lines, Müller, Fedosov and Gompper [20] performed simulations and attempted to study the marginal characteristics of carriers of different shapes and sizes using mesoscopic hydrodynamic simulations to explain the related physical mechanisms, finding that the properties of particle edges increase with increasing carrier size. The above results lead to the conclusion that addressing the various problems associated with drug delivery is a complex issue; its solution requires an interdisciplinary effort, including *in vitro* and *in vivo* experiments and realistic numerical simulations.

3.3. Viscosity

Blood viscosity and plasma viscosity are the best known parameters characterizing the properties of blood flow. Haik, Pai and Chen [21] conduct an investigation on the behavior of viscosity due to magnetic discharges in human blood, for which they carried out flow experiments on oxygenated blood *in vitro* and which is subjected to a B of up to 10 T. Additionally, they use a mathematical model to simulate biomagnetic fluid dynamics under similar conditions, which allows them to identify that the magnetization action will introduce a rotational motion to orient the magnetic fluid particles with the B [22]; however, the behavior and characteristics of the blood are unique to each patient. As a complement to the aforementioned computational experiments, Rukshin,

Mohrenweiser, Yue, and Afkhami [23] proposed a mathematical model describing the behavior of equations to visualize particle trajectories and calculate capture rates to assess the impact of various physical conditions on the success of magnetic drug targeting.

3.4. Geometry of the medium

Another element to take into account in the characterization of the medium is the geometry, muscle arteries have three major geometrical differences with capillaries, for example in microvessels, the anti-slip boundary condition reduces the velocity of blood near the wall relative to the centerline and improves the ability to trap particles by weaker magnetic force due to lower resistance compared to millimeter vessels [24]. In this case, the force required is well below the maximum allowable exposure, however, due to the higher blood flow rate in muscles and blood vessels, the particles require a higher magnetic force to resist the "tenacity" that occurs in the opposite direction of particle motion.

4. Evolution of applications in cancer treatments, using np

Cancer is a disease in which the cells of the human body acquire the ability to divide and multiply uncontrollably [26], this condition acquired by the diseased cells through mutations of the genome, as the cancer cells divide, leads to the fact that the new cells will inherit the same growth capacity and increase the number of cancer cells [27]. The treatments for this disease are diverse and in any case side effects must be considered, therefore, targeted treatments are an important option for patients. In this sense, the evolution in the use of np is presented, which is approached through 4 generations, identifying the main investigations and their results.

4.1. First generation

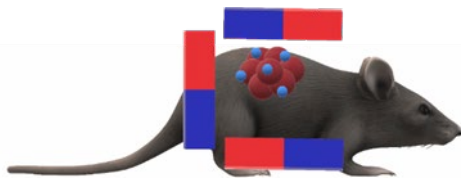
The first experiment was performed "in vivo" by Lübke et al [9], who developed a magnetic fluid to which drugs, cytokines and other molecules can chemically bind to allow these agents to be directed into an organism by an external high-energy B. They used male rats and mice, kept in a controlled environment. For which they used male rats and mice, kept in a controlled environment. For the design of the external B, using high-energy permanent magnets made of rare earths (neodymium), they consisted of disks or blocks with variable thickness, configured in the shape of a column or a block (see Figure 1). In this way, the magnets could be arranged more closely around the individual tumor configuration, with a B between 0.2 - 0.5 T (depending on tumor size). They tested two forms of therapy with the magnetic fluid: treatment of tumors by mechanical occlusion with the ferrofluid in high concentrations; and magnetic therapy, using small amounts of the ferrofluid as a drug carrier vehicle, which allowed epirubicin to be concentrated locally in the tumors.

The first part of the study focused on tolerance to ferrofluid and magnetically bound epirubicin. The results show that hematological and blood chemistry values did not change from baseline after injection of different amounts of ferrofluid. On the other hand, epirubicin caused changes in hematological parameters. Histological data showed that the magnetic particles accumulated in the liver and spleen, without causing significant hepatosplenomegaly, the latter two results were within predicted. After the sixth week of observation, one animal in each high-dose group died, possibly due to cardiovascular failure caused by sepsis. In those groups in which the high-dose epirubicin was administered, the animals died quickly; in the low-dose groups, they died somewhat later, around 4 - 6 weeks. In all other groups, including those receiving low levels of epirubicin, the animals survived the observation period [28].

The second part of this investigation focused on the mechanical embolization by the ferrofluid after its injection and concentration in the tumor by means of an external B, regardless of the type of tumor, there was a rapid and constant decrease in tumor volume within 14 days after treatment. It was impossible to reproduce this tumor response in the animals given only epirubicin, although the tumors responded to the high dose of this drug, this was only for a brief period and most of the animals in this group died shortly thereafter.

Subsequent experiments by Lübbe led to the conclusion that magnetic fluid is a good agent to decrease tumor volume and with further studies it can be used in different forms of local cancer treatment in conjunction with high energy magnetic fields, avoiding mortality of the subject [29].

Figure 1. Graphic illustration of placement of rare earth magnets in block form on the tumor to be treated.



Source: own

Thus, in the second experiment, Lübbe et al [29] chose their subjects with an eligibility criterion among them, seven patients with breast cancer, two with chondrosarcoma, two with parotid squamous cell carcinoma, one with Ewing's sarcoma and two with malignant tumor; with a life expectancy of at least three months and renal preservation. Continuing their line of research, they employed anticancer drugs that would reversibly bind to magnetic fluids, which were focused on locally advanced tumors through a B disposed on the tumor surface outside the body.

They tested for magnetite concentration in the tumor, and 10 of the 14 patients, had intact skin

covering the tumors, the other four showed wound healing and open superficial wounds. In the first four cases, since the B will obscure the shape of the magnetic block attached to the tumor, it is easy to observe magnetite absorption into the tumor, this discoloration lasted for 24 - 36 hours and then disappeared completely, these areas were not locally toxic and ensured that the discoloration could not be removed to rule out the possibility of iron deposition from the magnetic lumps in the superficial layer of the skin. So the targeted magnetic drug with epirubicin was well tolerated and mild tumor reductions were achieved at day 10 and some small responses at day 40 [10, 36].

4.2. Second Generation

Based on the results described above, Alexiou et al [30] used mitoxantrone-linked ferrofluid (FF-MTX) to treat rabbits with squamous cell carcinoma and concentrated it under a B. When the tumor reaches a volume of 3500 mm³, FF-MTX is injected intra-arterially or intravenously. When an external B is focused on the tumor, it is activated by an electromagnet with a maximum flux density of 1.7 T, producing a non-uniform B, both in direction and magnitude, a feature that is crucial for the use of magnetic drugs. Magnetic drug targeting is a means of keeping the chemotherapeutic agent at the desired site of activity, thus increasing efficacy and decreasing systemic toxicity.

Only when the MTX dose was increased to 75% and 100%, tumor remission was observed, but this resulted in severe side effects (hair loss, ulcers and leukopenia). However, this "magnetically targeted drug" provides a unique opportunity to locally treat malignant tumors without systemic toxicity. In addition, it is possible to use these magnetic particles as "carrier systems" for various anticancer agents such as radionuclides, antibodies and cancer-specific genes [31].

4.3. Third Generation

Under another line of research, Gitter and Odenbac [32] presented experimental results based on systematic "*in vitro*" quantitative measurements of a tube model simulating a Y-branched artery, in which they conclude that the success of particle orientation towards branching depends largely on the crossing point and the magnetic force at the site, elements that as previously mentioned must be evaluated.

For their part, Krukemeyer, Krenn, Jakobs and Wagner [33] performed a verification method on the effectiveness of cytostatic drugs coupled to ferromagnetic np and extracorporeal magnets, using 42 adult rats that were transfected with rhabdomyosarcoma. In the biodistribution assay, concentrations of mitoxantrone iron oxide and conventional mitoxantrone with and without 0.6 T magnets were measured *in vitro* in plasma and tumor tissue for one and two doses. During magnetic drug treatment, iron particles are rapidly removed and remain in the area where the tumor remained.

4.4. Fourth Generation

From the perspective of assessing patient safety, Attar et al [34] propose a configuration which investigates the thermal effect of superparamagnetic np on human cells, present a study considering general details on the design and construction of the configuration needed to generate a safe B to examine the thermal effect of superparamagnetic np on human cancer cells, then performed a series of experimental tests to study the effect of B on the cells for 30 minutes, which allowed them to calculate the temperature rise and specific absorption.

While it is true, hyperthermia treatment [35] is a mechanism to destroy malignant cells by increasing tissue temperature up to a range of 42 - 45 °C, temperatures above 45 - 56 °C, can cause necrotizing damage and subsequent tissue inflammation [36]. In this regard, ferromagnetic materials are commonly

used to treat hyperthermia and the general procedure involves the allocation of magnetic particles of various sizes depending on the type of treatment to the tissue, then, when the particles generate heat through two mechanisms (including hysteresis and eddy currents), the tissue is exposed to an alternating B.

Among the advances in this fourth generation, it is important to mention the work of Al-Jamal et al [37], who performed *in vivo* experimentation based on a solid theoretical foundation for the design of a magnetic nanocarrier, capable of magnetizing uptake after intravenous administration, in order to elucidate the parameters necessary for the detection of magnetic tumors. Because long-circulating polymeric magnetic nanocarriers are capable of encapsulating increasing amounts of superparamagnetic iron oxide np (SPIONs) in a biocompatible oil carrier, they were able to study the effects of SPION loading and applied B intensity on magnetic tumor targeting in tumor-bearing mice.

Another important element is the fact that the high loading of SPIONs eliminates the need to use highly magnetized np and the oil core promotes high hydrophobic drug loading, compared to polymer-coated SPIONs. The objective of this experiment was to evaluate the key factors influencing magnetic targeting efficiency, including the loadings of SPIONs on m-NC (polymeric oil-core magnetic nanocapsules) and the magnitude of the magnetic force applied at a distance. Under controlled conditions, they quantified magnetic targeting *in vivo* and found that it was directly proportional to SPIONs loading and B intensity, however, higher SPIONs loading resulted in reduced blood circulation time and stabilization of magnetic targeting.

5. Diagnostic imaging with np

Due to the physicochemical properties presented by nanomaterials, the development of nanodevices as

contrast agents in medical imaging has clear advantages over traditional agents used in the diagnosis of diseases, among which we can mention: better optical dispersion (absorption of light in the material, with a clearer visual spectrum), increased biocompatibility, decreased probability of denaturation and especially, their ability to bind to ligands, which turns them into devices with multiple functions that bind to cells, simultaneously allowing imaging for diagnosis and transport of drugs to specific sites, thus, achieving targeted and efficient treatment [38].

Nan, Suciu, Ardelean, Senila, and Turcu [39], report a simple reaction strategy for the synthesis of magnetic iron oxide np's stabilized with ethylenediaminetetraacetic acid (EDTA) followed by the chelation reaction of gadolinium (Gd) ions. These results show that these magnetic nanosystems represent a promising dual-mode contrast in agents for MRI applications with biomedical applications in mind.

Another type of contrast agent used for feature detection are SPIONs, due to their long half-life and small diameter, they provide a variety of possibilities to visualize intracellular targets, they can also be coupled with fluorescent dyes so that these particles can be detected in vitro and in vivo by optical fluorescence methods.

In this technique, SPIONs are inhibited by the binding of polyethylene glycol (PEG) chains that are anchored by peptide substrates shed by proteases, in diagnostic imaging, dextran-coated SPIONs provide stability for imaging, such as magnetic resonance imaging, computed tomography and optical fluorescence [40].

In this direction, Nahrendorf et al [41] performed a study, where single-crystalline fluorochrome-labeled SPIONs in the infrared were chelated with DTPA (diethylenetriaminepentaacetic acid) to allow binding of the PET radiotracer ^{64}Cu . While the iron oxide

core provided the MRI contrast, the fluorochrome served for fluorescence imaging (fluorescence microscopy, flow cytometry and fluorescence mediated tomography), and the ^{64}Cu radiotracer allowed PET (positron emission tomography) imaging, while the iron oxide core provided the MRI contrast.

The reported results show a trend towards the increasing use of SPIONs in various biomedicine applications.

6. Implementation in Colombia

Jaimez, Gonzales, Granados, Álvarez and Espitia [42] of the Pontificia Universidad Javeriana carried out a review article to see what advances and expectations there are in surgery to date, explaining what nanotechnology consists, its basic principles and some utilities in the field of surgery. On the other hand, Mendez and Muñoz [43] of the National University of Colombia wrote an article describing the clinical and molecular characteristics of premalignant lesions and oral cancer, as well as diagnostic methods using nanotechnology (nanochips, nanosensors, etc.) as an effective method for the early detection of cancer. Rodriguez, Moyano and Roa [44] from the Universidad Distrital Francisco Jose de Caldas, obtained a mathematical model and a computational simulation describing the trajectory of magnetic np injected near the target tissue. The magnetic np propagate along the blood vessel in the Z-direction and point to the target area through a cylindrical magnet located outside the body generating a constant B.

Likewise, Gallo and Ossa [45] from the University of Antioquia carried out a study where they evaluated two silver np synthesis processes, using, in addition, a biofunctionalization process with polyethylene glycol (PEG) to improve the anchoring properties and

biocompatibility of the np, for possible treatments against skin cancer.

In the master's thesis in engineering of Pantoja [46] of the Universidad Distrital Francisco José de Caldas, he has focused on proposing a mathematical model that can estimate the trajectory of NPM through the action of an external B and the blood flow is obtained through computational simulation. The model includes forces that significantly affect NPM dynamics, including magnetic fields generated by magnets, scattering forces, and drag. Molecular dynamics results show that NPM under the action of a B will be captured and attracted by it, so that they can be directed to the proposed target.

The reported results show that although there is no defined line of research on the use of np in Colombia, they nevertheless highlight the possibility of joining efforts to strengthen this field of knowledge.

7. Conclusions

The np seen as drug nanocarriers play a leading role and it is in this direction in which research has been carried out, from this perspective to characterize the np and evaluate its evolution, it is identified that currently the work is focused on superparamagnetic np. The review carried out provides clarity regarding the evolution of np, as well as the importance of understanding how their kinematics are through the blood, seen as a biomagnetic fluid, a characteristic that has allowed the evaluation of strategies for directing nanoparticles that move through this medium, in this direction the main advances are associated with SPIONs for their biomedical application. There are many challenges from the treatment of diseases, starting from an accurate diagnosis to achieve an effective treatment, which involves a reduction of the adverse effects that these may have on the organism of the treated subject, in this sense the np offer a viable

possibility both in diagnosis and therapy with low adverse effects, due to the possibility of targeting the treatment.

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