Review Article

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Nanoparticles: A Revolutionary Approach To Battle Cancer

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1. Abstract

The increasing number of cancer cases in the world means that there is a need to search for innovative treatments that are more effective and have fewer side effects than conventional therapies. Recently, scientific research has focused on metallic nanoparticles (MNPs), which are particles ranging from 10 to 100 nm in diameter composed of magnetic materials such as iron, cobalt, and nickel. These particles can deliver drugs directly to tumour cells and serve as contrast agents for early cancer diagnosis.
In this review, several articles concerning the production of MNPs using various techniques and their role in clinical studies and drug delivery for various types of cancer have been analysed.

2. Keywords: Nanoparticles, Cancer

3. Introduction

According to the World Health Organization (WHO), cancer is the second cause of death in the world [1]. A tumour is composed of tumour cells; “unhealthy” cells characterized by an higher growth rate compared to healthy cells. This is because the healthy cells are spineless, so they are unable to compete with the tumour cells for nourishment [2]. The most commonly used technique for cancer treatment is cytotoxic chemotherapy, a therapeutic treatment based on chemical substances that interfere with the cell multiplication mechanism. This therapyis highly effective on rapidly reproducing tumour cells. Unfortunately, it is also effective on healthy cellsthat reproduce rapidly, such as those in hair follicles, skin, or mucous membranes chemo. When these cells are damaged by these chemical substances, undesirable side effects occur, such as skin discoloration, hair loss [3]. Furthermore, chemotherapy is not recommended during the first three months of pregnancy as it may lead to changes in the developing embryo. It is also not advised for patients with low red blood cell or white blood cell levels or those who already have kidney or liver problems [4]. A hope for the future is represented by nanoparticles.

4. Chapter 1: The Metallic Nanoparticles (MNPs)

Metallic nanoparticles (MNPs) are particles of very small dimensions, generally less than 100 nanometres (nm). MNPs are made up of metals such as gold, silver, platinum and many others.
MNPs can deliver drugs in a targeted manner, can be easily absorbed inside cells, and furthermore, their shape and size can be easily controlled. These properties make these particles very advantageous in cancer treatment (5.)
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5. Chapter 2: Synthesis Of Nanoparticles

There are two group of techniques for the preparation of nanoparticles:

- Top- down techniques;
- Bottom-up techniques.

In the top-down techniques, appropriate raw substance is crushed to small nanoparticles using processes such as sputtering, milling [6]. Instead, in the bottom-up techniques nanoparticle are created by assembling atoms or creating new nuclei that eventually develop into particles of Nano-scaled dimension [6]. Both technique have advantages and disadvantages. Bottom up techniques are economical procedures, based on adjustable parameter. However chemical purification was required and cannot be used for the large-scale production on nano-material. Top down technique can be used for the large-scale production of Nano materials, but they are complex and expensive. Moreover controlling the parameters of deposition is hard [6].

5.1. Chapter 2.1: Analysis And Application Of Two Bottom Up Techniques

In precipitation the reactants are mixed in a solution, which is then precipitated by adding a precipitant.The precipitant causes the formation of nuclei that grow in size until they form Nano scale particles. After being separated from the solution, these particles are calcined to remove any impurities present and to optimize their properties. In 2020, M. Liu et al. [7] conducted a study on the potential applications of MSN particles produced using this technique, for the treatment of breast cancer.

MSNs have a porous structure with Nano scale-sized pores within their silica matrix. MSNs exhibit the following characteristics:

- They have a controllable particle morphology and size;
- They have good thermal and mechanical stability;
- They are hydrophilic in nature.

The preparation of the particles was carried out starting from 0.5 g of CTAB (Cetyltrimethylammonium bromide) and 0.14 g of sodium hydroxide, which were dissolved in 240 ml of deionized water.Later, the solution was heated to 80°C and stabilized for 30 minutes. After stabilization, 2.5 ml of TEOS (Tetraethyl orthosilicate) were added to promote the formation of silicon-based nanoparticles. Finally, the solution wascooled, and the white precipitate was collected and calcined for about six hours at 550°C to remove the cetyl-trimethylammonium bromide. However, the nanoparticles obtained in this way could have had limited applications due to the uncontrolled drug release. Therefore, M. Liu et al. coated these particles by chondroitin sulfate (ChS). After coating, the particles were loaded with paclitaxel (PTX), a chemotherapeuticdrug that acts by inhibiting the division of tumour cells, and with the P-glycoprotein inhibitor (PQ) (MSNs- ChS@PQ)

P-glycoprotein (P-gp) is a membrane protein found in many types of cells, including tumour cells. They can be transport molecules across the cell membrane. However, this protein often transports a wide range of chemotherapeutic drugs out of the cellular tissues, reducing their therapeutic effectiveness. The injection of these particles was performed at the laboratory level in female mice. During the treatment,the tumour volume and body weight of the mice were monitored to assess the possibility of developing toxicity. No lesions were found in the heart, liver, spleen, or other organs of the mice. Instead, what was observed was a better persistence of the anti-tumour drug in the cells, leading to an improvement in the anti-cancer effect [7].

Another bottom-up technique is the sol-gel technique. Sol-gel, as the name suggests, consists of two different kinds of materials, and has several benefits, including the fact that it is often formed at low temperatures during the process, as well as reduced energy use and emissions. In a sol-gel process, “sols” are formed in a liquid and subsequently connected to form a network or some subunit capable of building aporous network. It is possible to generate powders, thin films, or even a solid that is monolithic bydehydrating the liquid. In general, sol-gel synthesis entails hydrolysis of ingredients, condensation accompanied by poly condensation to create particles, gelation, and drying in different ways [6].

G. Gasparotto et al. in 2017, using this technique, synthesized zinc oxide (ZnO) and gold (Au) nanoparticle nano-hydrates. This group of researchers prepared a solution in a ratio of 1:4:16 of zinc citrate, citric acid, and ethylene glycol. Subsequently, this solution was used to create a thin film through coating on a glass substrate, which was further coated with gold traces via sputtering. The thin film was then treated at 400°C to remove organic materials and promote the formation of the crystalline phase of ZnO [8]. The ZnO nano-hydrates were then grown on the seeding layer using microwave-assisted hydrothermal synthesis. Zinc nitrate hex hydrate, $Zn(NO3)2•6H2O$, and hexamethylenetetramine, HMTA - $C6H12N4$, were mixed in an equimolar aqueous solution. The reagents and the glass substrate were placed in a Teflon cup, and the hydrothermal process was carried out at 90°C for 1 hour. Subsequently, the substrates were removed from the solution, washed with deionized water, and then air-dried [8].

In order to form Au-coated ZnO nano-hydrates (ZnO-NPs), the obtained nanostructure was coated with Au using a Bal-Tec SCD 050 model via sputtering for 2-5 seconds. After this step, the nano-hydrates were treated at 400°C for 1 hour. The particles obtained were loaded with CA-125, a protein found in many ovarian tumors [8]. The purpose of this study was to create a sensor for potential future detection of ovarian cancer in patients.

5.2. Chapter 2.2: Analysis And Application Of One Of Top-Down Technique

For the top-down techniques for producing nanoparticles, we have laser ablation, a method that uses a laser beam to produce and manipulate nanoparticles. During this procedure, the laser is focused on a targetmade of a solid material, such as metal, semiconductor, or ceramic. The high-energy laser beam strikes the target, vaporizing and ionizing the material. This process generates high-temperature plasma which rapidly expands and leading to a series of chemical and physical reactions that result in the formation of nanoparticles [6].

In 2020, Khashan et al. [9] utilized this technique to produce nanoparticles of ZnO (zinc oxide) and AlZnO (an alloy of aluminium, zinc, and oxygen). A Nd:YAG laser was applied to irradiated the surface of the zinc target that was impressed in 3 mL of deionized distilled water (DIW) contained in a small glass container with continuous rotation. The height of water above the target was 2 mm, while the laser beam was focused at the surface of the target by a convex lens with a focal length of 100 mm and focus energy at 700 mj and different numbers of pulses (25, 50, 75, 100 and 125). The interaction between the laser pulses and the solid target in the liquid environment allowed achieving target ablation and the desired suspension of nano material [9].

At a constant concentration of zinc oxide nanoparticles, doping occurred by replacing the zinc target withan aluminium target and irradiating its surface with a constant laser energy and different pulse numbers (20, 30, 40, 50) . These particles were used to treat MDA MB-231 human breast carcinoma cells [9]. The study demonstrated that treating tumour cells exclusively with ZnO nanoparticles resulted in an initial morphological modification of the tumour cells. Conversely, treating MDA MB231 cells with AlZNO nanoparticles caused mitochondrial damage in the latter. ZnO nanoparticles in contact with cancer cells, release Zn+ ions, which increase the release of reactive oxygen species (ROS). ROS cause mitochondrial damage and apoptosis of tumour cells. The presence of aluminium ions further enhances the release of these ROS [9]. The study also showed that laser ablation is a simple and effective technique for the production of magnetic nanoparticles (MNPs) [9].

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6. Chapter 3: Cancer Treatment During Pregnancy

Cancer is diagnosed in 1 out of 1000 pregnancies, and it is expected that this statistic will increase as an average. The precise impact of chemotherapy on pregnancy depends on the gestational age. As demonstrated by various studies, chemotherapy entails a high fetal toxicity, especially during the first trimester. Therefore, patients with cancer at the beginning of pregnancy must decide whether to terminate the pregnancy or delay treatment in the subsequent months [10]. However based on other studies, it is also known that taxane-based chemotherapies cross the placenta and enter in the fetal compartment even during the second and third trimesters of pregnancy.

The use of metallic nanoparticles and other nanoparticles to deliver antitumor drugs during pregnancy can avoid exposing the fetus to these drugs and direct therapy to maternal tissues. The potential of nanoparticles for cancer treatment during pregnancy was demonstrated by Zhang et al. in 2018 [11]. Zhang et al., working in vitro, used polymeric nanoparticles to deliver doxorubicin for the treatment of "chorio carcinoma", a rare tumour. The nanoparticles were coated with specific peptides of chondroitin sulfate A (CSA) and absorbed by chorio carcinoma cells. The drug (doxorubicin) only targeted the tumor cells without crossing the placenta. Figueroa-Espada et al. [12], furthermore, started from the aforementioned study, demonstrated that by controlling the engineered properties of nanoparticles, such as their material, surface modifications, and sizes, these technologies can be specifically designed to enable the treatment of a wide range of maternal diseases, in addition to tumours, while avoiding fetal exposure.

7. Conclusion

From the gathered information, it has been highlighted that in the last two decades, nanoparticles in general, and metallic nanoparticles (MNPs) in particular, have shown a promising role in cancer treatment and diagnostics at the laboratory level. The goal for the future is to continue investigating nanoparticle production to identify the most efficient techniques for their manufacturing. This will enable effective medical use of the drug, including in oncology patients, even those who are pregnant, ensuring its safe and beneficial application in the medical field.

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