Chapter

The Roles of Nanoparticle in the Treatment and Diagnosis of Ovarian Cancer

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Abstract

Ovarian cancer is the most common type of cancer worldwide among women, and it is usually diagnosed at an advanced stage. The initial treatment for ovarian cancer is surgical debulking, but this is only effective in the treatment of early stage disease. Surgery alone is insufficient for treatment of advanced disease and systemic therapies, in particular chemotherapies, are indicated. The main aim of this book chapter is to review the role of nano-therapy in treatment of advance ovarian cancer, in comparison to the use of traditional chemotherapies. Nano-therapies are thought to have advantages in terms of improving drug stability in the human body, chemotherapy toxicity profile, and drug delivery to the target cells thus enhancing drug penetration into the cancer cells. This book chapter also covers the development of nano-therapy and also the type of potential cargos. In summary, the types of nanocarrier, and their roles ovarian cancer diagnosis and treatment will be discussed.

Keywords: ovarian cancer, nanocarrier, Doxil, TPGS, PEG

1. Introduction

Although ovarian cancer represents only 5% of all cancer cases among women, it is ranked fifth for cancer deaths among women [1]. It is the most common among gynecological cancers and ranks third after uterine and cervical cancer, as it represents the highest, worst warning, and highest mortality rates [2]. Ovarian cancer, in particularly high grade serous subtype, is often regarded as systemic disease. I think you need to re-do this statement as up to 75% of OC is diagnosed at an advanced stage – stage III and IV. It is expected that in the next twenty years, the death rate of this type of cancer will increase significantly, the reason for the high death rate is that the disease grows secretly and without symptoms, the appearance of symptoms is delayed, and the lack of appropriate examination that detects the disease at certain stages, and this is why it is called the silent killer [3, 4].

Until recently, methods of prevention and early detection of ovarian cancer did not achieve satisfactory results, partly due to its heterogeneous nature [5]. In the past, ovarian cancer prevention methods were characterized by modifying risk factors and creating protective factors. Unfortunately, these modifications did not significantly reduce the incidence of the disease [6]. The initial treatment of ovarian- either with upfront cytoreductive surgery or chemotherapy (neoadjuvant) followed by interval debulking surgery, Almost the main reason behind recurring

ovarian cancer Is due to the aggressive nature of the disease and unfortunately all metastatic ovarian cancer will develop resistance to conventional systemic therapies, and it is known that cancer cells develop resistance especially through certain mechanisms such as reduced absorption, increasing elimination, inactivation/detoxification of drugs, and accelerating DNA repair [7, 8].

Currently, many new approaches have been developed to improve delivery of drug to the target cancer cells, including the use of nanotechnology, and may be one of the solution to overcome the obstacles in treating advance ovarian cancer, nanotechnology was found to have extensively investigated for molecular imaging, drug delivery, treatment and tumor targeting [9, 10]. In addition, this type of nano-based drug can overcome the systemic toxicity towards normal cells as well as the toxicological effects of conventional chemotherapy, In addition, it is possible through this technique to control the systemic toxicity of normal cells and reduce the toxicity of chemotherapy agents. Thus the new method can be followed by using multiple chemotherapeutic drugs with a suitable nanocarrier as a solution for the future of cancer treatment. Of course, this can be done by passive targeting and active targeting where both methods are used to ensure a certain and specific targeting of cancer cells [11, 12].

2. Nanotechnology application

Nanotechnology can be defined as a practical application that results in a process or product based on the single or multi-component nanoscale, which is a fairly recent field, nanoscale components having at least one dimension in the size range of 1–100 nm. This technology is referred to in the field of biology, nanobiotechnology and in the medical field of nanomedicine, and the main principle of nanotechnology is to increase the effectiveness of the techniques used in the diagnosis and treatment of cancer.

Due to the lack of early diagnosis and the vague and multiple methods in clinical procedures for detecting ovarian cancer, there are many attempts that would modify the course in this area, which is the use of nanotechnology and its platforms.

2.1 Nanocarriers

They are the same nanomaterials used in treatment and diagnosis, Nanocarriers are a multifunctional compound that can be loaded with several types of molecules through physical absorption and chemical conjugations reactions including drugs, imaging agents, targeting moieties such as ligands or antibodies, and polyethylene glycol. There are several types, including liposomes, micelles, and dendrimers (**Figure 1**) [13].

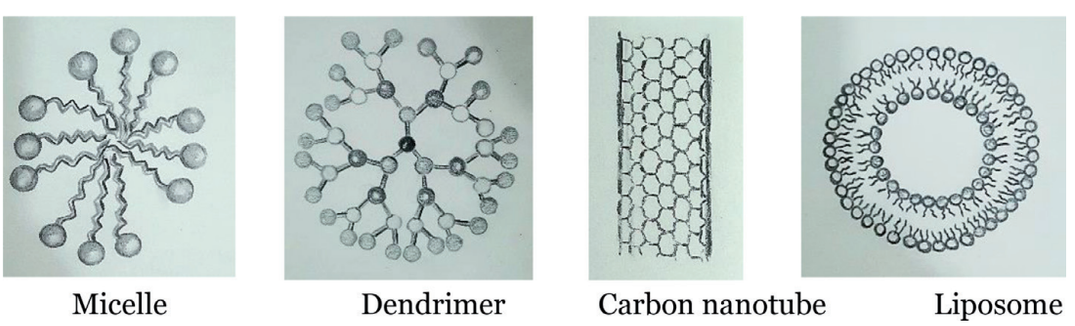

Figure 1.
Examples of some nanocarriers employed in therapy and diagnosis.

Nanocarriers can be used as an alternative to conventional chemotherapy for drug delivery because they have many advantages, including the delivery of poorly soluble drugs, as they surround them within the hydrophobic interfaces or act as carriers for them in the blood, reduce the systemic toxicity of chemical treatments, regulate the stability of drugs by prolonging their existence In the blood circulation and protecting it from disruption and reducing the renal clearance, reducing drug resistance by targeting cancer cells, where nanocarriers are taken up by the method of endocytosis [14, 15].

2.1.1 Liposomes

Liposomes have multiple properties as they are characterized by the presence of two parts, an inner hydrophilic part and an outer hydrophobic part, and of course in the form of a lipid bilayer, and it is also possible to modify the polar heads of these particles. This arrangement makes it easy to include various hydrophilic and hydrophobic drugs in the liposomes as well as to load various drugs.

They are delivery compounds that serve greatly in enhancing the efficiency of pharmaceutical components, as these compounds can hide from the immune system, simulate biological membranes, increase the chance of a drug remaining for a longer period until it reaches its destination, serve to help solubilize highly lipophilic drug molecules or, modulate the pharmacokinetics and biodistribution of the API—thereby helping to minimize side effects and enhance the product safety profile [16, 17].

2.1.2 Dendrimers

Dendrimers are radially symmetric molecules with a well-known structure that are homogeneous and monodisperse structure by tree-like arms or branches, they are hyperbranched macromolecules with a carefully tailored architecture, the end-groups, which can be functionalized, thus modifying their physicochemical or biological properties. Dendrimers have gained a broad range of applications in supramolecular chemistry, particularly in host-guest reactions and self-assembly processes. They are highly defined artificial macromolecules, which are characterized by a combination of a high number of functional groups and a compact molecular structure [18].

2.1.3 Micelles

This type of nanocomposite has gained very great importance as it has been well studied in the diagnosis and treatment of tumors. These interesting nanostructures comprise of spherically shaped, self-assembled amphiphilic block co-polymers made up of a hydrophobic core and a hydrophilic corona in an aqueous medium, with a diameter between 10 and 100 nm. The core of the micelle can accommodate hydrophobic drugs [19].

Polymeric micelles are gaining popularity as drug delivery systems because they not only provide increased solubility, but they also may enhance the stability of their drug cargo, in addition to providing in vivo pharmacokinetic advantages compared with the free drug [20].

2.1.4 Carbon nanotube

After discovering this nanotransmitter, it has enjoyed very great interest in the medical fields due to its unique structure and properties in terms of It has a

large surface area, large aspect ratio, nanoscale size stability and multiple chemical functions and they are especially important as carriers for transporting drugs and biomolecules. In this regard, this type has been used due to the functional properties it possesses as an important transporter for the delivery of anti-cancer drugs and many proteins and genes. Likewise, to directly kill cancer cells, it was used as a carrier for photothermal therapy (PTT) and photodynamic therapy (PDT) [21, 22].

3. Diagnosis and imaging

In recent times, there have been many improvements and major developments in the field of diagnosis and imaging with the help of nanotechnology, where it has been used the technologies of biosensors and point of care systems as well as the updated and improved imaging technologies as well as the integration of bioinformatics together with multiplexed assays. At present, there are many nanoparticle platforms and microelectromechanical systems to strengthen and improve diagnostic processes, largely as a means of diagnosing biomarkers and of course by enhancing the contrast agents used in imaging [23]. And the real mechanics of the imaging agent used to improve visualization and accumulation within the target cells in many imaging mechanisms on its subtype. There are different imaging methods that use imaging agents such as Optical Imaging, X-ray Imaging, positron emission tomography (PET), Magnetic resonance imaging (MRI) [24].

3.1 Targeted imaging agents

Targeted contrast agents are placed in a specific type of tissue or cellular receptors, including certain types, such as target agents designated for imaging fibrin, which are molecules associated with fibrin, which are molecules associated with fibrin, and other molecules to track stem cells from super magnetic iron oxide, and there are others for imaging angiogenesis, which are of the multimodal type of carbon fluorinated, liposomes are used to target the sclerotic components, and to visualize transplant rejection, microscopic bubbles were used in MRI and ultrasound [25].

3.2 Activatable imaging agents

There are many nanoparticles that are actually designed to have better performance and are imaging agents called operable molecular probes that can produce a signal or some kind of change that can be recorded or detected, for example, when enzymatic activity or a specific response to important chemical reactions, Two imaging technologies are combined into a single activatable lifetime imaging agent. This is applied by combining the high specificity of luminescence lifetime imaging with the high signal-to-background ratio of activatable fluorescence imaging [26].

3.3 Nano-liposomal imaging agents

Liposomes can encapsulate biomolecules that are hydrophilic and increase their internalization and solubility through the lipid bilayers of the cells, Among the drawbacks that can occur in the case of imaging by means of high elimination agents and low systemic retention degrees, and because the rapid removal process from the bloodstream or the body reduces the period and efficiency of imaging,

so it is necessary to add a molecule that increases the efficiency of imaging, and this is done by encapsulating the imaging agent with a liposome, can leverage the enhanced permeability and retention (EPR) effect seen in tumors [27, 28].

4. Fluorescent images and guided surgery

To increase the sensitivity, efficiency and strength of the imaging techniques used with surgery and increase their clinical efficiency, there is an actual need to develop new material, Therefore, many fluorescent nanoparticles essential for Image-supported surgeries were developed, tested and designed and tested in preclinical surgery there are some examples of that:

1. CF800 liposomes: This type is used to encapsulate iohexol contrast agent and is commercially available with clinically approved indocyanine green at ratio of 1000: 1 (iohexol to indocyanine green).

2. magnetic iron oxide nanoparticles: A HER - 2 particle that can be combined with optical magnetic resonance imaging. It is a targeting ligands. I learned a rare near-infrared dye called NIR-830 while magnetic iron oxide nanoparticles provide MRI contrast.

3. Porphyrin-lipoprotein mimicking nanoparticle: This type is based on the formation of a nanoscale in which several techniques are combined, photodynamic therapy, fluorescence imaging, positron emission tomography, where the size of the nanoparticle is 20 nanometers.

4. Fluorescent gold nanoparticles: This type is based on CT and fluorescent imaging platform an iodine based contrast agent is combined with aptamer with nucleolin specific targeting functions.

5. conjugated dendrimers: In this type activatable cell penetrating peptides are used Dendrimeric encapsulation and marker with gadolinium and Cy5 and sensitive in vivo to MMP-9 and MMP-2.

5. Nanoparticle therapeutics (anti-cancer)

Usually, nanoparticle treatments consist of therapeutic lines such as small-molecule drugs as well as peptides, nucleic acids, proteins, and other components or compounds that combine with them to form nanoparticles. As we previously knew that nanoparticles have a direct, targeted and improved anti-cancer effect compared to conventional treatments. This is owing to more specific targeting to tumor tissues via improved pharmacokinetics and pharmacodynamics, and active intracellular delivery. These properties depend on the size and surface properties (including the presence of targeting ligands) of the nanoparticles (**Figure 2**) [29].

5.1 Nanoparticle size

Naturally, the size of the anti-cancer nanoparticles should be between 10 and 100 nm. This measurement is based on the rates of glomerular sieving of the capillary wall of the kidneys. Research has indicated on size estimates where the

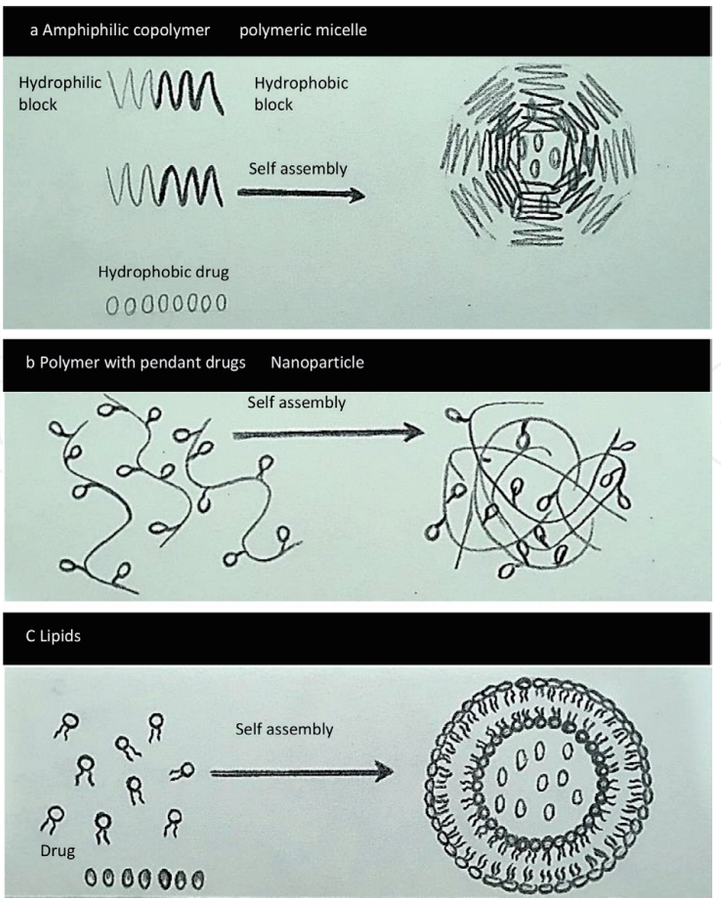

Figure 2.
Basic nanoparticles used in clinical trials. (a) Nanoparticles composed of therapeutic components. (b) the nanoparticles that are formed from polymer/drug. (c) Nanoparticles that are a liposome component.

minimum is 10 nanometers as a threshold for renal excretion and where it is known that vessels in tumor cases are subject to leak Macromolecules in a certain way, so the nanoparticles should not be able to circulate for a long time in the bloodstream and have a chance to reach the bloodstream through the vessels of the tumor tissue and enter the tumor tissue where the size of the nanoparticles is greater than 6–12 nm, which is the diameter of the sieve in the blood vessels of normal tissues and It is prevented from entering and not damaging the normal tissue, and it is known that the diameter of the sieve in the tumor blood vessels ranges from 40 to 200 nm (**Figure 3**) [30].

5.2 Nanoparticle surface

Nanoparticles have a very large surface area compared to the size of the nanoparticle and compared to normal particles, and this space provides a high degree of interaction with the molecule and its environment, and of course it is possible to almost determine the final fate of the nanoparticle inside the body through determining the strength of the interaction between the nanoparticle and its surroundings, and it depends largely on a mixture of size. And surface properties. Nanoparticles that are sterically stabilized polymers on their surface and have surface charges that are either slightly negative or slightly positive tend to have minimal self–self and self–non-self-interactions, Nanoparticles often have unexpected visible properties because they are small enough to confine their electrons and produce quantum effects. This provides a tremendous driving force for diffusion, especially at elevated temperatures [31, 32].

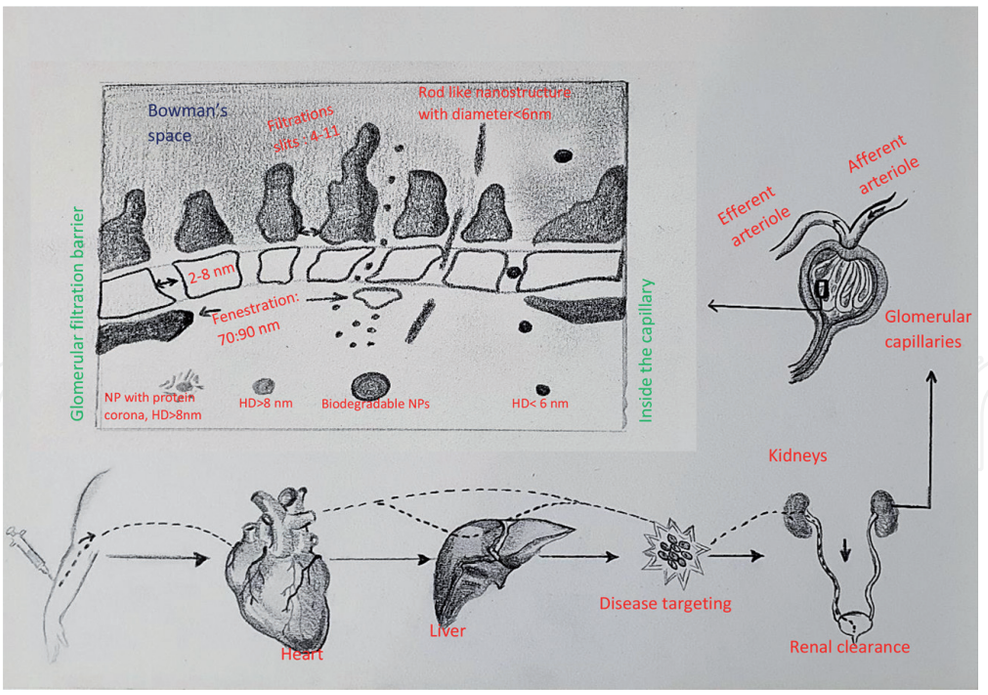

Figure 3.
The idea of special targeting of cancer cells to the nanoparticles that can be filtered through the kidney. As the nanoparticles target cancerous diseases, the residue that is not targeted is removed.

5.3 Nano-chemical therapeutics

The rare properties of nanoparticles have been exploited to present the science of chemical therapeutics in a unique way and as we previously knew that nanoparticles and the reason for their special composition can exploit the vascular infusion and absorption mechanisms associated with tumor cells to enter and implement a specific therapeutic effect where the particles accumulate in the tumor tissue, taking advantage of the enhanced permeability and retention effect, of course, when comparing the usual systemic chemotherapy by systemic administration with the science of chemotherapy coated with nanoparticles, where it can deliver the desired dose to the tissue environment of the tumor. In almost the same way, special bonds to cancer cells are added to nanoparticles to arrive in a uniform and targeted way to reduce the toxicity of systemic chemotherapy, we will mention the most common therapeutics [33].

A present example is a (PEGylated liposomal doxorubicin) formulation that has been.

U.S. Food and Drug Administration (FDA) approved for use in recurrent and platinum-resistant cancers (**Figure 4**) [34].

We previously knew that the liposomes remain less time in the circulatory system, and this affects the drug levels that reach the tumor tissue, and this can be bypassed by reducing the size of the carrier, but this may affect the levels of the drug and its required quantity, so to get rid of problems, the carrier is coated with polymers such as polyethylene glycol (PEG). As this system works to mask the immune system and increase circulation time [35]. The proposed mechanism of action and accumulation of DOXIL is as follows:

The liposomes coated with doxoribicin remain in circulation for 2–3 weeks after the injection process until the end of their estimated effective life, these particles enter the tumor tissue and settle in it through defects and gaps in the tumor vessels and then settle near the blood vessel, The extravasated liposomes release the drug

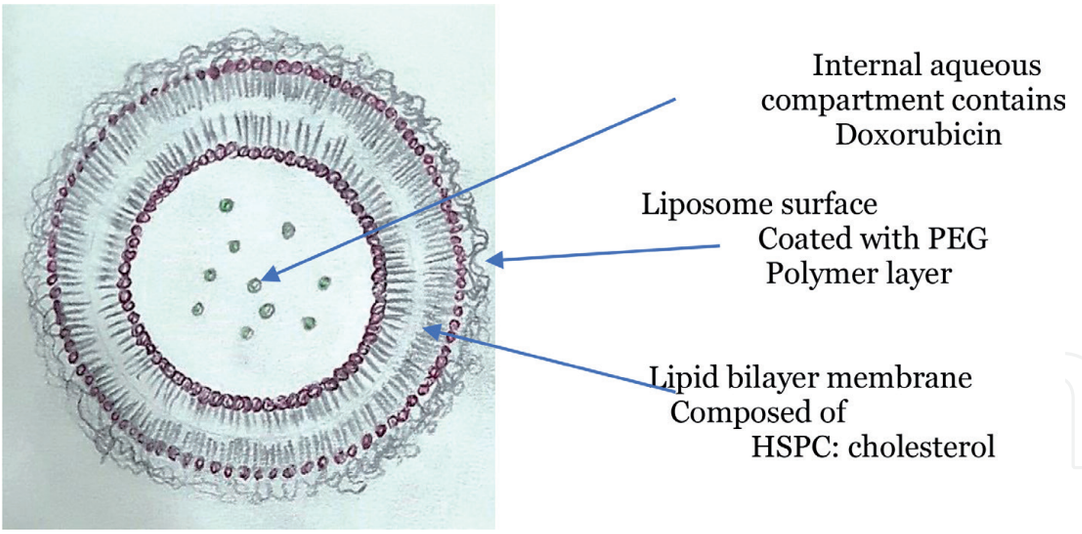

Figure 4.
This shape represents a Doxil liposome where doxorubicin is confined and encapsulated in the internal compartment where drug molecules are tightly packed.

components, and drug molecules enter deeply into the tumor tissue, where they reach and kill cancer cells. It is noted that this mechanism does not need a physical encounter and contact between the liposome and the cell, where the drug can reach and penetrate the barriers that intercept the particles [36].

There is another example of a nano-drug transporter (micelle) these structures typically contain a more hydrophobic component that helps solubilize/encapsulate therapeutic compounds, while a hydrophilic component provides stability of the assembly in aqueous environments and offers conjugation sites for eventual targeting ligands. This type of nanostructure has been widely used recently, an example being the D-α-tocopheryl polyethylene glycol (PEG) 1000 succinate (TPGS) (**Figure 5**) [37].

It is an amphiphilic water-soluble derivative of natural source vitamin E and PEG, that has been widely employed as a micelle-former biomaterial. Also, it has been reported that TPGS can inhibit the efflux pump that mediates multidrug

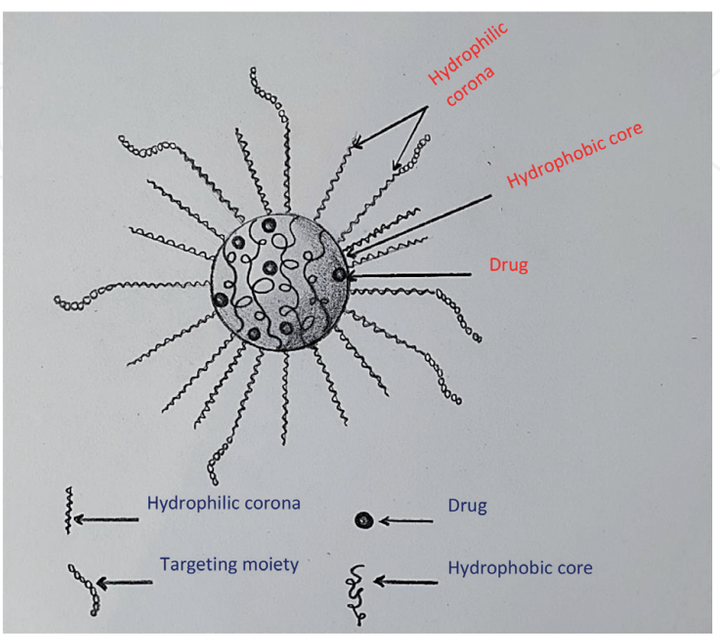

Figure 5.
A typical structure of polymeric micelle representing the drug encapsulated and targeting moiety attached.

resistance in tumor cells, known as P-glycoprotein (P-gp), In this context, TPGS has been employed for DOX encapsulation within polymeric micelles, Single polymers are the most acceptable type in recent times because they increase the solubility and stability of hydrophobic drugs, increase cellular absorption capacity, and to increase the susceptibility, two micelles were combined to obtain mixed micelles to increase strength. as enhanced thermodynamic and kinetic stabilities, higher drug loading (DL) capacity, more accurate size control and easier ways to modify their surface with different moieties [38, 39].

6. Conclusion

From the foregoing that nanoparticles are more efficient in the diagnosis and treatment of ovarian cancer as a basic alternative to chemotherapy and a highly efficient pre and postoperative adjuvant due to their great ability to reach the target tissue and high efficiency to stay in vivo for acceptable periods.

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