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Doxorubicin hydrochloride liposome and albumin-bound paclitaxel in cancer: a nanotechnology perspective

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Abstract: Nanoparticles (1-100 nanometres in size), products of nanotechnology, offer a modern way to transport anti-cancer drugs by acting as transporters of drugs into tumor cells, hence quenching tumor cell proliferation. Such nanoparticles may be formulated to bind to the tumor cell membrane or inhibit specific reactions of tumor biosynthetic pathway by gene repression, or directly bind to the active sites of essential enzymes in the biosynthetic pathway. Consequently, drugs are completely delivered to the desired cancerous cells without system interference. Liposomal doxorubicin and albumin-bound paclitaxel are two examples of nanotechnologically developed drugs for treating cancer. Modern knowledge of nanotechnology opens up new opportunities for innovative research on cancer therapies and administration and helps minimize harm to healthy cells. This review focuses on the doses and routes of administration of these chemotherapeutic agents used in treating cancers.

Keywords: cancer; chemotherapeutics; drug delivery; nanoparticle; nanoparticle formulation; nanotechnology

Introduction

Nanotechnology has found effective use in almost all facets of life, including energy, electronics, biomedicine, environment, food, textile, etc. In this review, nanotechnology concerning its use in medicine will be looked into, especially related to materials used for formulating nanoparticles, their characteristic makeup, methods of formulation, drug delivery, and mechanisms involved and preventing anti-cancer drug resistance [1]. Thus, this will lead us to a proper understanding of what nanomedicine is all about. As per global data, nanomedicine is a promising area. The field of science and technology that integrates nanotechnology with medicines or therapeutic agents to enhance the ability to implement stricter cells or tissues is a conceptual study [2]. Nanomedicine attenuated adverse drug reactions in the patients, which improve the efficacy of drug treatment [3]. Nanomedicine is important in imaging, diagnosis, and drug delivery to target cells. This is a new method of treatment that relies upon alternate therapeutics and improving treatment effectiveness whereas minimizing harmful adverse effects to body cells, tissue, and organs [4].

Cancer cells, for instance, can develop drug resistance to conventional cancer therapies via a host of mechanisms, including alteration of drug target, and inactivation, repair damaged DNA, protection of cells, drug efflux, and the epithelial-mesenchymal transition, as well as the role of inherent tumor cell carcinogenicity [5]. Furthermore, cancer drug resistance is a primary reason for inefficacious cancer treatment [6], while Markman *et al.* identified that the most severe issues with cancer therapy are normal or resistance mechanisms [4]. The inability of cancer to react to a provided medication at first is referred to as natural resistance, while the unresponsiveness that emerges after initially successful treatment is regarded as acquired resistance. Yuan *et al.* reported that the occurrence of drug resistance in cancer therapy has also impeded the progression of new drug discovery, development, and research [7]. Furthermore, Dallavalle *et al.* investigated various conventional anti-cancer drugs concerning their efficacy in cancer treatment, and they reported that multidrug-resistance (MDR) seems to be the leading type of cancer chemotherapy failure [8]. Jiang *et al.* probed into the underlying molecular mechanism of the cause of long non-

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coding RNAs that have been involved as a predictor of tumor drug resistance, both inherent and developed chemotherapeutic resistance [9]. It concluded that targeting prolonged non-coding RNAs in cancer therapeutics could provide a solid foundation for overcoming chemotherapy drug resistance in the future.

Recent studies have shown that nanomedicine holds high hopes in reducing anti-cancer drug resistance and improving drug delivery to target cells. Anticancer-drug resistant reduction is possible in cancer management, especially in drug delivery designed through nanotechnological advancements due to a wide variety of formulated nano drugs, including liposomes, polymer conjugates, carbon-based nanoparticles, micelles, metallic nanoparticles, and dendrimers, etc. They can successfully get to the target cancer cells by overcoming various forms of drug resistance within the system. This advanced knowledge and the design of the alternative mechanism to drug delivery could serve as a valuable tool in cancer treatment [4].

Liposomal doxorubicin is administered as a doxorubicin hydrochloride liposome (DHL) injection for intravenous infusion, and this was approved in the U.S in 1995. It is used in treating ovarian cancer and AIDS-Related Kaposi's Sarcoma. For patients with ovarian cancer, DHL injection should be administered intravenously to adults at a dose of 50 mg/m^2 at an initial rate of 1 mg/min to minimize the risk of infusion reactions, and this should be given every four weeks for four courses minimum. Adult patients with AIDS-related Kaposi's Sarcoma should be given an intravenous injection of DHL at a dose of 20 mg/m^2 at an initial rate of 1 mg/min to minimize the risk of infusion-related reactions, and this administration should be given every three weeks. The LD50 of doxorubicin hydrochloride is established at 550 mg/m^2.

The mechanism of action of doxorubicin hydrochloride is thought to be related to its ability to bind to DNA and inhibit nucleic acid synthesis. DHL injection is DH encapsulated in long-circulating pegylated liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that is capable of encapsulating active drugs. The pegylated DHL injection is formulated with surface-bound methoxy polyethylene glycol (MPEG), a process often referred to as pegylation to protect liposomes from detection by the mononuclear phagocyte system (MPS) and to increase blood circulation time [10]. DHL injection is vital in that it offers a clinical advantage in the treatments of AIDS-related Kaposi's sarcoma compared with conventional therapy, recurrent ovarian cancer compared with topotecan, metastatic breast cancer compared with free DXR [11-15]. Overdose of DHL injection causes increased risk of severe mucositis, leukopenia, and thrombocytopenia, while common side effects include body aches/pains, headache, nausea or vomiting, constipation, diarrhoea, stomach upset, loss of appetite, and tired feeling [16].

Albumin-bound paclitaxel (ABP) is indicated for metastatic adenocarcinoma of the pancreas as first-line treatment combined with gemcitabine. It is administered intravenously to adults at the dose of 125 mg/m^2 over 30 - 40 min on days 1, 8, and 15 of each 28 - day cycle, while gemcitabine 1000 mg/m^2 intravenous (IV) is infused over 30 - 40 min immediately after paclitaxel protein bound on days 1, 8 and 15 of each 28 - day cycle. For non-small cell lung cancer, ABP is indicated for locally advanced or metastatic non-small cell lung cancer as first-line treatment combined with carboplatin in patients who are not candidates for curative surgery or radiation therapy. It is administered in adults in the dosage of 100 mg/m^2 IV infused over 30 minutes on days 1, 8, and -15 of each 21 - day cycle and carboplatin AUC 6 mg min/mL IV on day 1 of each 21 - day cycle immediately after paclitaxel protein bound fusion [17]. Montana *et al.* show that ABP is highly significant in phase II and III trials for metastatic cancer and lung and pancreatic cancer treatment. It was clinically efficient in treating these cancers [18]. ABP dose above 260 mg/m^2 could cause severe toxicity. The common side effects of ABP include nausea, vomiting, indigestion, diarrhea, dizziness, weakness, mouth sores, anemia, temporary hair loss, etc. [16].

Thapa *et al.* intended to develop a nano-drug using nanotechnology to manage and cure cancer-resistant cells [19]. Their results revealed that the developed hybrid nanosystem provided a foundation for successfully utilizing GOLDR therapy throughout the diagnosis and intervention of cancer or tumor forms that are immune to treatment. However, recent studies have shown that nanomedicine holds high hopes for reducing anti-cancer drug resistance and improving cancerous conditions. Chowdhury *et al.* identified that the leading cause of drug resistance in cancer treatment is increased efflux transporters such as ATP-binding cassette subfamily of proteins (P-GP and MDR-associated protein) which drastically limits intracellular drug absorption and drug efficacy [20]. Their nanoformulation approach with pluronic nano designs prevented drug resistance and minimized the dose required for treatment sessions, making it effective in a therapeutic setting [20].

Nanoparticle formulation methods

Nanoparticles are a form of target delivery device that includes an active component that is soluble, encapsulated, or adsorbed in a matrix substance [21] or merely characterized as a micro material with a size range of 1 to 100 nm, which, unlike bulk material, has a collection of quantum properties [22]. The nanoparticles formulation method hangs on the class and function of nanoparticles being formulated whether it is prepared for fluorescent biological labelling, delivery of drug and gene, pathogen or protein detection, DNA structure analysis, separation and purification of biological molecules and cells, tissue engineering studies, or for phagokinetic studies. One crucial factor to consider before selecting the formulation method is the physicochemical properties of the material. Another factor is the characterization of the nanoparticle, which is necessary to understand the synthesis and application of nanoparticles [23]. The third factor to consider is the type of material used for the preparation of nanoparticles. For

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example, polymeric nanoparticle (PNP) processing methods are a hot topic in biomedical research, especially in the drug delivery system [24]. It aids in the safe release of medications by control the release process, which exerts biocompatibility with cells and tissues.

Moreover, it improves the stability of active substances and helps drugs reach higher intracellular uptake than when the drugs are in free form. Finally, specific tissues can be targeted [25-27]. What should be of note is that various factors are to be considered while selecting matrix material for nanoparticle preparations. According to Kreuter, these factors include that material must not be toxic, immunogenic, and nanoparticle size must be suitable, the material should show desired drug release profile, permeability and surface charge of nanoparticle drug's solubility pattern and durability should never be affected, and biodegradability and compatibility must be at their highest levels [28]. **Table 1** shows the potential techniques selected for the preparation of nanoparticles.

nanoparticles can navigate tiny capillaries, access remote areas, and are easily absorbed. In contrast, delivery at specific sites can be achieved either by passive or active targeting and easily encapsulated for protection or controlled release [32]. There are numerous examples of nanoparticles which include polymeric, lipid-based, carbon-based, metallic, ceramic, and semiconductor nanoparticles. Polymeric nanoparticles and nano-capsules or nano spherical structures depend on the preparation method [23]. Polymeric nanoparticles have shown great potential for target drug delivery for the treatment of several diseases. In the nanosphere, the active compounds and the polymer are uniformly dispersed, whereas the active compounds in the nano-capsule are confined and surrounded by a polymer shell [33, 34]. Advantages of using polymeric nanoparticles in drug delivery systems include biocompatibility and biodegradability, increased stability of any volatile pharmaceutical agents, less toxicity, targeted drug delivery, non-immunogenicity, and non-

Table 1. Preparation of nanoparticles by using different types of polymers [29].

Type of polymer	Technique	Candidate drug
Hydrophobic Poly(alkyl cyanoacrylate)	Interfacial oil in water polymerization	Hydrophobic
Hydrophobic Poly(alkyl cyanoacrylate)	Emulsion polymerization	Hydrophilic
Hydrophilic Alginates and chitosan	water Cross-linking	Hydrophilic and protein affinity
Hydrophilic Dextran	Precipitation of polymerization with an organic solvent	Hydrophilic
Hydrophilic Albumin, Gelatin	Heat denaturation and cross-linking in oil in water emulsion	Hydrophilic
Hydrophilic Albumin, Gelatin	Desolvation and water cross-linking	Hydrophilic and protein affinity
Polyesters Poly(lactic acid) Poly(lactide-co-glycolide)	Solvent displacement	Hydrophilic and hydrophobic soluble in a polar solvent
Polyesters Poly(lactic acid) Poly(caprolactone)	Solvent extraction evaporation	

Characterization of nanoparticles

Nanoparticles are divided into different categories depending on their scale, form, and other physicochemical characteristics [30]. Nevertheless, the critical parameter for the development of nanoparticles is size calculation, and many strategies were being used to achieve this [21], such as dynamic light scattering, scanning or transmission electron microscopy (TEM), and photon correlation spectroscopy (PCS) [23]. Nanoparticles are more effective drug vehicles than microparticles [21]. The larger molecules diffuse out slowly because they have a larger core that fills more drugs [31], and surface area depends on particle size; therefore, the smaller the size, the greater the surface area and *vice versa* [21]. Furthermore, nanoparticles have some essential benefits in drug delivery systems, like toxicity [35], controlled-release [33], etc. Liposomes, nanostructured lipid carriers, stable lipid nanoparticles, and self-emulsifying drug delivery mechanisms are all examples of lipid-based nanoparticles [36], classified as generally spherical with a diameter ranging from 10 to 100 nm [33]. This type of nanoparticle has an outer core stabilized by emulsifiers or surfactants [37].

Lipid-based nanoparticles are helpful in RNA release in chemotherapy and drug carrier and delivery [29, 33]. Their success in the biomedical field is mainly due to their fascinating physical and chemical properties, which includes high bioavailability, easy administration via several routes, large-scale production, inherent ability to cross the blood-brain barrier, and the ability to implement macromolecules like DNA, proteins, oligosaccharides [38]

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as well as having potentials in decreased side effects and drug susceptibility to metabolism [39].

Carbon-based nanoparticles, contain two significant materials known as fullerenes and carbon nanotubes (CNTs). These nanoparticles are 100 times stronger than the steel used for structural strengthening [29]. The research of carbon-based nanoparticles has gotten a lot of interest because of their unique physicochemical properties, such as thermal, mechanical, electrical, optical, and structural diversity [40-42].

The physicochemical features and characteristics of nano drugs (NG) and tumor microenvironment, respectively, are paramount when considering how best to deliver a nano-drug to specific tumor cells. Two broad mechanisms of drug delivery exist, which are passive and active targeting mechanisms. These mechanistic approaches to anti-cancers have increased over the past few decades [43].

The concept of nano-drug targeting lies in the controlled biodistribution, especially of the intravascular administration, which involves the opsonization of the carriers [44, 45], meaning that the carriers are covered with protein molecules and recognized by the liver and spleen macrophages [39]. Thus, enhancing the targeting and the experimental treatment of pathogens such as hepatic metastasizes as well as leading to a substantial decrease of drug levels in unfavorable areas, thereby attenuating the toxic reactions of certain anti-cancer medications [39]. In tumor targeting, a tumor could be benign (non-cancerous), malignant (cancerous), may contain fluid or solid, and usually, treating it with traditional chemotherapy comes with serious side effects [46].

In passive amplification, the circulation time directly influences the success of the drug [44]. There are many approved passive tumor targeting delivery system as listed in **table 2**. This is achieved by wrapping the nanoparticles with nanomaterials such as polyethylene glycol (PEG), making the nanoparticle surface hydrophilic, therefore allowing the interaction of water molecules via hydrogen bonding interaction, oxygen is bonded to the PEG. The result of this is that an antiphagocytic substance is created. Sagnella and Gullotti, independently, identified that nanoparticles with sizes between 10 - 100 nanometers are found to circulate systematically for more prolonged periods [47, 48].

Table 2. List of approved passive tumor targeting delivery system.

Nanocarriers	Drug	Indications
Nanoparticles	Doxorubicin	Hepatocarcinoma
Liposomes (PEGylated)	Doxorubicin Doxorubicin	Breast cancer Ovarian cancer
Albumin	Paclitaxel	Pancreatic cancer, Breast cancer, Non-small cell lung cancer, Ovarian cancer

Necrosis and ulceration are characteristic of malignant tumors. They also invade surrounding tissues that are metastatic, initiating similar tumors in a distant organ. Tumors can be targeted and destroyed at a molecular level by interacting specific drugs with tumor receptors at tumor sites. These particular receptors are targets to deliver cytotoxic agents into tumors [43, 46, 49].

Passive targeting is all about using the typical dissemination pattern for the formulated drug delivery system; this is based on the drug accumulation around the tumors with leaky vasculature referred to as Enhanced Permeation and Retention (EPR) effect [46]. Active targeting, on the other hand, involves specific ligand-receptor type interaction. It is usually employed in the improvement of target cell signalling and target cell uptake. According to Golombek, the most common technique is ligand-mediated targeting, which uses ligands produced toward the receptor molecules or immunogenic predictors released on cancer cells or the vascular system as mentioned in **table 3** [46]. Since they do not rely on extravasation and penetration through pericyte, smooth muscle cells, and/or fibroblast-based cell layers, endothelial cell-targeted nanomedicines have a much higher potential for enhancing chemotherapeutic efficacy.

Table 3. Ligands for active nanoparticle targeted drug delivery.

Type	Ligands
Proteins	Antibodies, transferring hyaluronic acid
Polysaccharides, peptides	RGD, IL4RPep-1
Aptamers	AS-14II, GBI-10
Small molecules	Folate, Anisamide Phenylboronic acid

Also, they are not affected by high malignant cell volume or larger quantities of liquid pressure, which are detrimental to cancerous cell nanomaterials. Active-targeted nanoparticles act by ultimately depriving tumors of oxygen and nutrients, which result in tumor destruction. When they adhere to cancer blood vessels, they may be programmed to spill their materials into the cancer tissue allowing low-molecular-weight medicines to penetrate the tumor microenvironment [50]. As a result, EPR-based cancer therapy is becoming a popular technique for improving therapeutic agent distribution to cancers in the production of chemotherapeutic agents [46].

Conclusion

In summary, nanotechnology and the production of chemotherapeutic treatment should be of immense focus in

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the coming era. The quest for novel cancer drugs, their destinations, ligand-binding mechanisms, and molecular stability would enhance the chance to improve chemotherapeutic administration with minimal or no damage to normal tissues. This topic focused on two chemotherapeutic agents developed by nanotechnology to treat certain cancer diseases proven effective in cancer management. They get to the target cancer or tumor cells with minimal interference by the system, hence, exerting minimal damage to normal cells.

Declarations

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