Xi'an Shiyou Daxue Xuebao (Ziran Kexue Ban)/
Journal of Xi'an Shiyou University, Natural Sciences Edition
ISSN: 1673-064X
E-Publication: Online Open Access
Vol: 67 Issue 07 | 2024
DOI: 10.5281/zenodo.12794324

EXPLORING INNOVATIVE APPROACHES FOR TARGETED DELIVERY OF ANTHRACYCLINES TO CANCER CELLS THROUGH LIPOSOMES, EXOSOMES, AND POLYMERIC NANOPARTICLES

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Abstract

Nanomedicine is the use of nanotechnology in the medical domain. Our decades-long contributions to this emerging field of inquiry have yielded substantial advances, especially in the treatment of cancer, which have sparked the curiosity of researchers. Applications of cancer nanomedicine include medication administration, nano formulation, and nanoanalytical contrast agents. Nanotechnology may be able to get around many of the limitations of conventional methods by increasing tumor medication accumulation, reducing side effects, and improving therapeutic efficacy. The last 20 years have seen a significant advancement in nanotechnology, which has made it possible to include a variety of medicines, sensing, and targeting agents into nanoparticles (NPs) to create new nanodevices that can identify, stop, and cure complicated illnesses like cancer. The primary drug nanoformulations based on organic NP types are discussed in this review, along with the benefits of the novel formulations over their free drug equivalents and the ways in which nanodrugs have enhanced clinical care. Polymeric NPs, liposomes, micelles, and exosomes, a tiny subgroup that has just lately been employed in clinical trials were the four primary categories into which we separated them.

Keywords: Anthracyclines, Daunorubicin, Doxorubicin, Idarubicin, Epirubicin, liposomes, Polymeric exosomes, Nanoformulations.

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1. INTRODUCTION

Common methods for treating cancer include immunotherapy, radiation, chemotherapy, and surgery [1]. Daunorubicin (DAU), Doxorubicin (DOX), Idarubicin (IDA), and Epirubicin (EPI) are common representatives of a broad spectrum of anticancer activities. There are several FDA-approved cytotoxic and targeted anticancer medicines that belong to the anthracyclines group that may be used in chemotherapy. Over the past 20 years (2000–2020), DAU has drawn more attention than DOX, IDA, and EPI. After localizing in the nucleus, these medications integrate between neighboring base pairs of DNA, which allows them to affect DNA transcription processes, replication, and topoisomerase II activity [2]. Reactive oxygen species (ROS) are produced by anthracyclines in the microenvironment of cancer cells when oxidoreductive enzymes such cytochrome P450 and NADH dehydrogenase undergo redox reactions [3]. Damage to biological macromolecules and lipid peroxidation result in further cytotoxicity. Furthermore, apoptosis is triggered by the formation of an adduct by a covalent interaction between the exocyclic amino group of guanine and the 3-amino of daunosamine under anthracycline stress [4]. Nevertheless, there are two significant disadvantages that follow: increased adverse effects and medication resistance in cancer cells.

Cardiotoxicology and myelosuppression are the primary dose-dependent adverse effects of anthracyclines [5]. Since innate and acquired pathways in drug resistance overlap, more complexity must be considered in order to overcome drug resistance in tumor cells. Multidrug resistance (MDR), which refers to a tumor's resistance to a variety of anticancer medications, described by both cellular and non-cellular processes. When a tumor is non-cellular, aberrant circumstances in the extracellular milieu of the tumor, such as inappropriate tumor vascularization, hypoxia, and low pH due to lactic acid production, might make it more difficult for the tumor cells to absorb medications.

Anticancer medications pumped out of malignant tumor cells by MDR associated protein (MRP) and P-glycoprotein (P-GP), members of the ATP-binding cassette (ABC) family. Apart from the increasing drug resistance observed in cancer cells, physiological barriers like the blood-brain barrier (BBB) might impede the uptake of therapeutic medicines with molecular weights above 400–600 Da. But such drugs can be delivered in suitable lipid formulations with suitable shape and within a constrained size range. Since nanoparticles (NMs) have special properties, new and effective formulations are required to overcome these problems, such as augmentation by nanotechnology-based formulations. For example, a high ratio of surface area to volume allows for easy functionalization and modification by other active materials. Using appropriate NMs in this context, greater therapeutic, biocompatibility, and biodegradability features are anticipated under physiological settings. The three types of nanometer-sized particles (NMs) are zero (nanoparticles and nanovesicles), one (nanotubes and nanowires), and two (nanofilms and nanoplates). Additionally, organic and inorganic nanomedicines (NMs) have been identified based on the origin of the materials, and the types and stages of cancer encourage the selection of these NMs [6]. Also, based on origin of materials, organic and

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inorganic NMs have been recognized and their selection is promoted by cancer types and cancer stages. In this mini review, recent progress and challenges related to polymeric and liposomal nano-formulations of four common anthracyclines namely DAU, DOX, IDA and EPI are presented to obtain optimum formulations.

Additionally, NMs classified as organic or inorganic have been identified based on the origin of the materials, and the types and stages of cancer influence their selection. This brief overview discusses the difficulties and latest developments in polymeric and liposomal nano-formulations of the four widely used anthracyclines DAU, DOX, IDA, and EPI in order to provide the best possible formulations [4].

Table1: Illustration of type, advantages, and disadvantages of Nanocarriers

Type	***Advantages***	***Disadvantages***
Liposomes based Nanocarriers		
Conventional liposomes	Reduced adverse drug effects	Rapid clearance via RES Toxicity
Stealth Liposomes (PEGlyated)	Reduction in toxicity More circulation times Passive targeting	EPR effect dependent Compromised efficacy Toxicity
Solid Lipid Nanoparticles (SLNs)	More drug capacity Low-cost production Easy in scale-up Toxicity reduction	Polymorphic transition risk Stability challenges Eventual particle increase
Polymer based nanocarriers		
Polymeric Micelles	High drug entrapment Bio-stability	Undefined microstructure Unclear tissue distribution
Dendrimer	Abundantly involve in surface functional groups Monodispersed Long drug retention time Low side effects Convenient for use	Complex preparation process Toxicity and immunogenicity Poor biological barrier escape ability
Nanoparticle of Albumin bound (Nab)	Natural carrier of hydrophobic molecules Enhanced Endocytosis	Side-effects Immunogenic Poor metabolic stability
Polymeric Nanoparticle	Chemical versatility Complete drug protection High drug-loading capacity Sustained reduced release Good highly stability Low level of toxicity Long body circulation Targeting	Limited carrier materials Limited industrial preparation Poor long-term stability Poor effectiveness Poor safety
Exosomes based Nanocarriers		
Feasibly used of drug Nano delivery	Inert Safe-profile Control of the porous size to introduce drugs Active-targeting Low-density Large specific surface area	Toxicity of synthetic process Ambiguous tissue distribution assembly Potential toxicity

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	High adsorption Unique permeability Favorable in optical performance	
Physiological fluids	Extremely specific	Coupling-strategies Specific targeting necessary
Biomarkers	Gene-therapy High efficacy	Immunogenic Safety problems (Viral spread to unaffected organs) Expensive

2. ANTHRACYCLINE DRUGS WITH THEIR DIFFERENT FORMULATIONS

2.1. Daunorubicin (DAU)

2.1.1. Liposomes

Functionalized liposomal and polymeric formulations of anthracyclines have been shown to have a number of benefits, including effective drug loading and encapsulation, sustained and controlled drug release, avoiding significant therapeutic roadblocks like MDR and the blood-brain barrier in brain tumors, and universal targeted drug delivery. The trade names Daunomycin ($C_{27}H_{29}NO_{10}$) and DOX ($C_{27}H_{29}NO_{11}$) are derived from the wild-type and mutant strains of Streptomyces peucetius, respectively [6].

Without taking into account a strategy to transport anticancer medications across the blood-brain barrier (BBB) and remove the vasculogenic mimicry (VM) channels, it is impossible to eradicate the malignant brain glioma by chemotherapy [7]. Thus, the malignant brain glioma has been targeted by honokiol liposome encapsulating DAU that has been modified by lactoferrin (Lf). In this formulation, a high-affinity binding of Lf receptors in endothelial cells with BBB improved the cellular absorption of honokiol liposome. The downregulation of VM protein markers including matrix metalloproteinase-2 (MMP-2) and the activation of the apoptotic enzyme caspase 3 resulted in antitumor effects [8].

2.1.2. Polymeric carriers

When creating suitable formulations, the biocompatibility and biodegradability of both synthetic and natural polymer sources is considered. These polymers have the ability to reduce toxicity and inflammation in non-targeted cells [9]. Common biodegradable synthetic polymers include poly (amino acids), poly (lactide-co-glycolide) (PLGA), poly (lactide) (PLA), and poly (ε-caprolactone) (PCL) [10]. Natural polymers like cellulose, chitosan, and alginate have been employed in a variety of medicinal contexts, including medication administration and wound healing. Determining the physicochemical characteristics of the polymers for DAU formulations as well as the absorption, bioavailability, biodistribution, metabolism, and excretion of these materials through the body are crucial factors to acquire appropriate formulations, the pharmaceutics and pharmacokinetics of drugs [11].

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2.1.3. Exosomes

In order for exosomes to be a feasible drug nano delivery platform for cancer treatments, they need to be highly pure and isolated in large quantities. Since fungi and plants are the original hosts of these particles, exosomal synthesis is not exclusive to the animal kingdom. One of the drawbacks of employing exosomes in cancer treatment and medication administration has been the difficulty in locating a source for the mass separation of these nanoparticles, even though exosomes have several natural sources. Exosomes are thought to carry their endogenous payload as they communicate from one cell to another. We and others have employed exosomes to carry exogenous payloads, such as small compounds and biologics, based on this idea [12].

2.2. Doxorubicin (DOX)

2.2.1. Liposomal formulations

Wide-ranging anticancer effects of DOX against lymphomas, solid tumors such lung, ovarian, breast, thyroid, and liver carcinomas have been reported. An external trigger, such as light with near-infrared (NIR) wavelengths (the range of 750–2,500 nm), can release the drug into liposome's while having no negative side effects and an appropriate tissue penetration ability [13]. A range of photosensitive linkers, such as vinyl ether, vinyl disulfide, amino and thiopental, can be employed to create formulations possessing embedded photosensitivity. These connections can become unstable due to the singlet oxygen that NIR produces. For instance, reactive oxygen species (ROS) produced by porphyry phospholipids under near-infrared radiation (NIR) have the ability to damage liposome membranes [11].

2.2.2. Polymeric formulations

Making polymeric NPs is a common process that involves reversible addition-fragmentation chain-transfer polymerization, or RACT polymerization. In this case, PSMA-targeted hyperbranched polymer NPs containing DOX were created using this technique to specifically target prostate cancer cells that express PSMA, and they also had the ability to release the medication 90% of the time over the course of 36 hours under endosomal conditions [14]. In a different study, the RAFT polymerization process was used to create a nano-prodrug with an average diameter of 21 nm that contained DOX and N-(1,3-dihydroxypropan-2-yl) methacrylamide (DHPMA) copolymer. This polymeric NPs not only increased blood circulation time but also achieved a 54% 4T1 tumor growth inhibition value in comparison to free DOX [15].

2.2.3. Exosomic formulation

Exosomes can be found in many bodily fluids and in cell culture medium. It is established that most cell types, both in healthy and diseased states, secrete them. Exosomes have also been found to be present in physiological fluids such as serum, urine, breast milk, cerebrospinal fluid, bronchoalveolar lavage fluid, saliva, and malignant effusions. These

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have been found to be released by all studied cells, including B cells, dendrite cells, T cells, mast cells, epithelial cells, platelets, stem cells, and cancer cells [12].

2.3. Epirubicin (EPI)

2.3.1. Liposomal formulations

One notable benefit of EPI ($C_{27}H_{29}NO_{11}$) over DOX is that it has less of a cardio toxic effect; yet, both molecules have similar anticancer activity. As was previously indicated, the two primary strategies for liposome-based anticancer drug delivery are passive and active targeting. An example of active targeting was shown when liposomes decorated with sialic acid (SA) were intended to bind to the over expressed SA receptors on the surface of tumor-associated macrophages. After 30 days of incubation, modified EPI-loaded liposomes by SA showed a significant reduction in tumor volume in comparison to PEGylated liposomal EPI [16]. The primary obstacles are intrinsic and extrinsic drug resistance resulting from changes in ATP-binding cassette and apoptosis-related gene expression.

2.3.2. Polymeric formulations

When treating glioblastoma multiforme (GBM), the blood-brain tumor barrier is a significant obstacle to effective chemotherapy. Through their enhanced permeability and retention (EPR) impact, polymeric NPs can provide a workable solution to this issue. The cRGD peptide can be used to create polymeric NP This method produced polymeric nano-formulations of the EPI medication that, after 48 drug exposure, had IC50 values of 0.32 µg/ml [17].

To load EPI with pH-sensitive property, 647-conjugated-poly (ethylene glycol)-b-poly (β-benzyl L-aspartate) (PEG-b-PBLA) was applied that specifically targeted the αvβ3 and αvβ5 integrins on the GBM endothelial cells. This formulation significantly reduced triple negative breast cancer (TNBC) axillary lymph node metastasis (ALNM) during treatment [18].

Sonodynamic treatment (SDT) using high-intensity focused ultrasound (HIFU) can result in thermal ablation of cancerous tissue. For this reason, under trigger-pulsed HIFU, polymeric micellar nanoparticles (NC-6300) loaded with EPI showed notable anticancer action against human pancreas adenocarcinoma (BxPC-3) cells [19].

2.3.3. Exosomes formulation

Exosomes are essential for the identification of cancer biomarkers because of their ability to load cargo selectively and their similarity to the generating cell. Scientists are using exosomes to more effectively identify molecules for cancer targeting and to apply more individualized techniques for detection, diagnosis, and prognosis. This is achieved by optimizing the protocols for isolation from cell culture and patient body fluids, performing advanced characterization, and improving isolation protocols. Mass spectrometry is utilized to characterize proteins (Kreimer et al., 2015), and immunoprecipitation methods

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are employed to detect and measure peptide and nucleic acid (miRNA, mRNA, etc.) profiles. It is possible to load drugs into exosomes exogenously or endogenously [20] .

2.4. Idarubicin (IDA)

2.4.1. Liposomal formulations

The molecule with formula $C_{26}H_{27}NO_9$ has a higher hydrophobicity than DAU, which makes it suitable for oral prescription. Combining hyperthermia (HT) with thermosensitive liposomes (TSL) as a stimuli-responsive strategy could be a quick way to target cancer cells. Here, the clever liposomal formulation of IDA demonstrated reduced cytotoxicity at 37 °C and IDA release at 42 °C [21].

Aptamers, which are oligonucleotide or peptide compounds, have the ability to target specific receptors found on cancer cells. In this regard, elongation factor 1A (eEF1A), which is linked to the promotion of hepatocellular cancer, was targeted by liposome surface modification using an A75 nucleotide long aptamer bearing GT repeat (GT75). HepG2, JHH6, and idarubicin-containing modified liposomes demonstrated notable therapeutic effects [22].

2.4.2. Polymeric formulation

Research on the anticancer properties of IDA drug polymeric nanoformulations is encouraging. IDA was encapsulated in poly(lactic-co-glycolic-acid) (PLGA) and newly created maleate-polyester (MPE) nanoparticles in order to prepare cell-mediate delivery via polymeric NPs. This formulation was absorbed into human T cells that had been ex vivo stimulated in the second stage [23].

As was previously mentioned, loading anthracyclines with different NP sizes and shapes can provide various therapeutic effects. For instance, star polymers made from methyl methacrylate (MMA) and tert-butyl acrylate (tBA) as the hydrophobic arms and β-cyclodextrin (CD) as the hydrophilic core section showed enhanced IDA loading and absorption [24].

2.4.3. Exosomes

In breast cancer cells, the human epidermal growth factor receptor 2 (HER2) is overexpressed. Targeting HER2 with an exosome containing the monoclonal antibody trastuzumab and the encapsulated IDA medication showed a greater, dose-dependent decrease in SK-BR-3 cell viability as opposed to MCF-7 cells [22]. Nanotechnology-based therapeutics is highly used in cancer therapy for enhancing drug solubility, stability, and decreasing multidrug resistance as well as to enhance the safety and efficacy of cancer treatment. Nanoparticles, dendrimers, polymeric micelles, liposomes, polymeric drug conjugates, exosomes, and polymersomes are some of the efficient carriers in nanotechnology-based drug delivery systems; which are presently investigated extensively for augmented cancer therapy [25].

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3. CONCLUSION

The efficacy of traditional chemotherapy may be diminished by the ability of cancer cells to withstand drugs. To create formulations that are acceptable, it is important to consider the physicochemical properties of the materials used in anthracycline medications as well as their absorption, bioavailability, bio-distribution, metabolism, and excretion through the body. To improve a medication's oral bioavailability, anthracycline encapsulation in biocompatible and biodegradable polymers like alginate and chitosan stabilized by a particular surfactant may be used. Numerous changes pertaining to PEGylations, electric charge surfaces, targeting, and stimulus responsiveness can be made to achieve polymeric formulations. To create formulations with the right drug loading capacity, mean size, PDI, and zeta potential, MW should be considered.

Imidazole, amino acrylate, vinyl ether, vinyl disulfide, and thioketal are good linkers to use when creating formulations that react to produce reactive oxygen species (ROS) at certain light wavelengths. An effective method to increase the anticancer activity of liposomal or polymeric formulations is to encapsulate secondary metabolites of medicinal plants that contain a variety of flavonoids, terpenes, and alkaloids and are bound by anthracyclines. Considering this, treatment of MDR cancer tissues will require a clever mix of photodynamic, sonodynamic, and chemotherapy based on innovative liposomal and polymeric anthracycline formulations.

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