Nano-carriers as a Selective Treatment for Cancer

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Abstract:

Among many therapeutic treatments for cancer, nano-carriers are the focus of our review to illustrate the update usage of this drug delivery approach, the most likely side effects and the reality of their potential application with minimum adverse effects. Here, we demonstrate the types of these nano-carriers based on their nature with detailed recent studies about their use. The variation in the skeleton of these nanoparticles enable the selection of the suitable type with higher specifications than others. However, the poor in vivo testing is the main stumbling block for completion of their manufacturing. This review will help the researchers to find the road map for further investigation to finally aid the pharmaceutical companies in manufacturing these nano-carriers in appropriate dosage forms to save the life of millions of people in the world.

Key words: Oncology, Micelles, Nanoparticles, Cancer treatment, Nano-carriers

الناقلات النانوية كعلاج انتقائي للسرطان

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الخلاصة:

من بين العديد من العلاجات العلاجية للسرطان ، فإن ناقل النانو هو محور مراجعتنا لتوضيح استخدام التحديث لإيصال هذا الدواء ، والأعراض الجانبية المحتملة وحقيقة تطبيقها مع الحد الأدنى من الآثار الجانبية. نوضح هنا أنواع ناقلات النانو هذه بناءً على طبيعتها من خلال دراسة حديثة مفصلة حول استخدامها. يمكّن التباين في الهيكل العظمي لهذه الجسيمات النانوية من اختيار النوع الأفضل بمواصفات أكثر من غيرها ستساعد هذه المراجعة الباحثين في العثور على خارطة الطريق لمزيد من التحقيق لمساعدة شركة الأدوية في تصنيع هذا الشكل الجرعي لإنقاذ حياة ملايين الاشخاص في العالم.

الكلمات المفتاحية: علم الاورام , المذيلات المعكوسة , الحبيبات النانوية, علاج السرطان, الناقلات النانوية

Introduction

Nowadays, cancer invading millions of people around the world since its rapidly expanded with a more than one million cases per year which made it the second cause of death in the world [1-4]. Despite the fact that there are many options for the treatment of oncological diseases; chemotherapy, radiation and sugary represent the appropriate choice among other therapies [5,6]. Chemotherapy is complex due to the variation in the pathogenesis and symptoms [3]. In addition, drugs cannot differentiate between the healthy and cancer cell which results in triggering undesirable effects to the patients such as mucositis, suppression

of bone marrow activity, nausea, secondary neoplasms and infertility [2, 5]. Furthermore, low selectivity and possibility of recurrence are common [3]. For these reasons, the chemotherapeutic drugs were developed to be delivered either passively or actively by nano-carriers [2, 7]. Passive type enables the chemotherapeutic drug to accumulate within tumor cells. While, active one involves a conjugation of nanocarrier containing chemotherapeutic drug with an antigen or receptor on the cancer cell [2]. Nano-carriers possess an advantage over their free drug counterpart such as preventing the drug form biological degradation, ensure better absorption than free form and improving pharmacokinetic route [2].

Types of nano-carriers for cancer targeting:

The size of particles range form 100-200 nm [8]. They are varied in their structure such as lipids [3, 9-12], polymers and PLGA [13-19], carbon structure [20-22], proteins [23, 24], inorganic metals [25-27], silica based [28, 29], viral [30-33]. As well as they are varied in their shape including spherical, rod, geometrical and wire [34].

Lipid based nano-carriers

They have a vital role in the enhancement of the solubility of lipophilic materials [35, 36]. Lipid based formulations (LBFs) have a great impact on improving the solubility of class II and IV type drugs (poorly water-soluble drugs) [5,37]. These “grease ball” type of drug can enhance both oral and parenteral bioavailability [37-39] and have advantages on delivery of ophthalmic drug by enhancing their bioavailability, targeting and controlling drug release [40]. Lipid-based nano-carriers, including nanoemulsions, liposomes, cubosomes and niosomes [41].

Liposomes are spherical in shape that consist of phospholipid in which a phosphate is the hydrophilic head and fatty acid is the hydrophobic tail. When they are introduced into water, they are self-assembled into vesicle that consist of bilayer [42, 43]. The vesicle has the ability to envelop either hydrophilic and hydrophobic drugs in which the hydrophilic drug can be entrapped inside the vesicle while the hydrophobic drug incorporated into the lipid bilayer [44]. Liposomes are varied with their permeability, charge density and steric hindrance [45].

Liposomal nanocarriers can protect the chemotherapeutic drugs from degradation, improving their bioavailability by accumulation in the tumor cells and consequently reducing the side effects [46]. Cytarabine (cytosine arabinoside) is an example of chemotherapeutic drug that interfering with DNA synthesis thus inhibit cancer growth [42]. For example, liposomal vesicles act as carrier and intact carrier enters the SC carrying drug molecule then vesicles worked as penetration enhancers and modify SC intercellular lipid lamellae and thus facilitate the penetration of free drug molecules into and across the SC. In addition, elastic liposomes can effectively protect the drug against undesired skin clearance into cutaneous blood vessels and are capable of retaining the drug long enough on, in and below the skin barrier [47].

Doxil is another example of liposomal formulation of doxorubicin for treatment of Kaposi sarcoma and multiple myeloma. Doxil can passively be targeted to the tumor cells with a lower concentration of doxorubicin achieved in healthy cells [10, 45]. The mechanism of action for DOX is to bind to DNA, and therefore, following passive diffusion into the cell cytoplasm, the DOX was clearly able to accumulate within the nucleus [48]. However, the conventional liposomes have many problems such as low drug loading, and rapid elimination form blood stream due to rapid uptaking by reticular- endothelium system (RES) [49]. Therefore, the surface of the liposome can be modified with different moieties such as polyethylene

glycol (PEG), ligand such as antibody, carbohydrate, protein and theranostic liposome (diagnostic and treatment liposome) [42, 50].

Large unconjugated liposomes are eliminated more rapidly than small, neutral, or positively charged one [49]. The pegylated liposome is sterically-stable type to prevent rapid uptake by RES which offers a better circulating time. Other limitations include the immunological response [51] which can be reduced by methylation of the PEG type of a nano-carrier. Increasing the liposomal activity can be achieved by the addition of a postive charged lipid to the liposome to increase the muco-adhesive and bio-adhesive property by ionic interaction [52] such as targeting of liposome to the GIT [49, 53-55]. Despite the fact that there are many formulation and chemical modification resolutions but there are many obstacles such as pharmaceutical, governmental rules and intellectual property [56]. Regarding to the pharmaceutical aspect, the cost and the stability of a new liposomal product restricts its production [49,57]. The number of the control group required for this type of study limits the manufacturing of such type of liposome [49].

Polymer based nano-carriers and micelles

Depending on the incorporation mechanism, polymeric-based carriers can be divided into three main types which are: Polymer–drug conjugates via covalent conjugation, polymeric micelles through hydrophobic interactions and polyplexes or polymersomes by encapsulation [5, 58, 59].

Polymer-drug conjugate (PDC): The combination of the chemotherapeutics drug with macromolecules is the oldest method for oncological delivery among other methods [60-62]. Enhancement of the drug solubility and bioavailability, retarding drug releaseand reduction of toxic effects of the chemotherapeutic drug produced by this type of conjugates rendered it the favorable type for delivering drug to the site of action. In addition, the nano-size ensure accumulation of drug at the site of action due to increasing the permeability and retarding drug at tumor site [63, 64]. This type can be prepared by PEG, polyglycerol, poly (2-methoxy-2-oxoethyl methacrylate) (MEMA), poly (L-amino acid) and poly(N-(2-hydroxypropyl) methacrylamide) (HPMA) though pH-triggered system [65]. N-(2-hydroxypropyl) methacrylamide copo-lymer conjugated with both amino-gluthetimide and doxorubicin (HPMA-AGM-Dox) to act as aromatase inhibitor for the treatment of chemotherapy-resistant breast cancer with reduction in the toxicity [66, 67]. Other example for this type is the combination therapy of paclitaxel (PTX) and cyclopamine (CYP) which work synergistically. PTX and CYP conjugated to the carboxyl groups of polys (ethylene glycol)-block-poly (2-methyl-2-carboxyl-propylene carbonate) (mPEG-b-PCC) [64]. These drugs are highly hydrophobic so that this polymer-conjugates is the better choice [68, 69].

Micelles are polymer aggregates with a size of (10–200 nm) consist of hydrophobic core and a hydrophilic corona which are self-assembled to be thermodynamically stable. The outer hydrophilic chains cover the hydrophobic core which inhibit direct contact with water thus reducing the probability of polymer-water system formation [70]. The linear amphiphilic molecules arranged via a self-assembly process. For this reason, the stability of the micelles is affected by the concentration, flow stress and interactions with serum proteins [71].

In cancer, two phenomena are existed, the 1st one is the increased vascular permeability and 2nd is the defective lymphatic drainage that allows the leakage of both blood plasma components and micelle ranges from tens-thousands nanometer into tumor tissue to be retained in tissues. This phenomenon is termed

enhanced permeability and retention (EPR). [72-74].

Polymeric micelles attract many researchers to use them for the delivery of hydrophobic drugs due to the hydrophobicity of the core that enhances the solubility of slightly soluble drugs with hydrophilic shell that stabilizes the colloidal system, hence long circulation time [75]. In addition, to the EPR effect due to the nanosize [72]; Furthermore, the shell could be modified with ligand such as antibody, peptide, folate, and biotin for specific targeting [76]. Finally, the release behavior, drug loading and stability can be adjusted form the architected micelle such as addition of pH sensitive property [75]. Endocytosis in polymeric micelle happened without any surface ligand for targeting [77].

Paclitaxel (PTX) is a chemotherapeutic drug used for the treatment of solid tumors. However, its neurotoxicity and hypersensitivity limit its use [78]. A polymeric micelle, Genexol®-PM significantly improves PTX solubility and decreases its toxicity both in vivo and in vitro [79]. The amphiphilic carboxymethyl chitosan-rhein conjugate (CR conjugate) could self-assemble in water and form CR PMs and encapsulate PTX [80]. An amphiphilic copolymer with poly (lactic acid) (PLA) block and poly (2-ethyl-2-oxazoline) (PEOz) block which represent a hydrophobic core for (PTX) [81]. The PEOz is used due to lower toxicity and better solubility than PEG [82]. Furthermore, PEOz has a an attractive pKa value that donates proton at a pH of (4.5–6.5) with the release is being pH sensitive [83].

However, there are some limitations of polymeric delivery and micelles regarding to the stability issue which might result in leakage of the drug, diffusion of protein, absorption of protein and dilution below critical micelle concentration. Furthermore, the high cost of high drug loading while lower drug loading results in faster drug release in addition to fast clearance form RES [84]. Poor transfusion, high toxicity and poor solubility in aqueous solution are other disadvantages of some polymeric micelles [85].

Dendrimers

The size of the dendrimer used for cancer targeting is between 5-50 nm [86]. A three-dimensional treelike structure with a core molecule which is mainly composed of three main composition which are initiator core, branches and terminal functional group [87-89]. They are varying from low to high molecular weight and they are either natural or synthetic [87]. The dendrimer can be modified and conjugated to the drug through hydrogen bonding, hydrophobic interaction and chemical bonds [90].

They have a definite size, structure and molecular weight that provide a flexibility for various applications. The large surface area of dendrimer offers a suitable recognition for the receptors [91]. Additionally, it has a low immunological sensitivity with appropriate solubility and potential selectivity with low systemic side effects.[92]. [93].

Functionalization of dendrimers with monoclonal antibodies (mAbs) which have the ability to bind with the surface of the cancer cell via covalent bonding to produce immunodendrimers [94] An example of this type is the conjugation between monoclonal antibody K1 (mAbK1) and half-generation poly (propylene imine) (PPI) dendrimers for the treatment of ovarian cancer. By introducing paclitaxel (PTX) to the hydrophobic part to produce mAbK1-PPI-PTX, it was found that there is an extension in animal survival significantly by increasing drug uptake into the cancer cell [95]. The efficacy PTX in the treatment of pancreatic cancer increased by coupling with peptide conjugate dendrimer that results in accumulation in pancreatic cancer cell [96-99]. Doxorubicin is another example of chemotherapeutic drug that encapsulated to the peptide dendrimer by covalent bonding [100].

Metal based and magnetic nanoparticles

These are particles that result from the binding of a drug into magnetic particles (MNPs). Their size ranged from 10-100 nm with ability to deliver radionucleotide with aim of targeting tumor cell in addition to diagnostic purpose [101-106]. External magnet can be used for the delivery of nanocarriers into the tumor cells for the reduction of side effects. Furthermore, in this condition, particle agglomeration risk is excluded [107-109]. Many factors affecting application of magnetic nanocarriers such as colloidal stability, cytotoxicity and duration [110]. Iron oxide NPs (IONPs) was approved by FDA because of their biological compatibility, low toxicity and easy synthesis. Superparamagnetic (IONPs) can be obtained from size below 27 nm which is called (SPIONs) [111]. SPION was successfully translated for the treatment of glioblastoma multiforme in Europe [112].

Carbon-based nanoparticles

Carbon nanotubes (CNTs) are delivering molecules into cytoplasm by using ‘‘needle-like penetration’’. They enter to the tumor cells by endocytosis to be protected from the cellular pump [20]. Its size is varied form 1 nm to 1 µm with high surface area which results in introducing of the drug into the cancer cells with high loading by passive diffusion [113]. The shape of the carbon-based nanoparticles looks like a tube rolled with sheets of graphene which enable penetration of the material into the cell. They are either single or multi-walled. There are several types including garphenes, fullerenes, carbon nanotubes or carbon quantum dote. They could form either a covalent or non-covalent interaction. A covalent interaction involves introducing a hydroxyl, carboxyl and amino group into the surface of the molecule with further protection using PEG. One the other hand, a non-covalent interaction is formed through amphiphilic molecules to the surface of the cell [113]. They have many applications, besides their use in cancer drug delivery, they have been applied in tumor imaging and diagnosis. Example of carbon-based type is doxorubicin can be loaded up to 400% by weight [5]. They have been applied in gene therapy to fight the cancer cell via gene delivery without any limitation to the size by carrying the plasmid and interfering with RNA of the tumor [20].

Although carbon-based nanoparticles have many advantages for the eradication of cancer cells. Some disadvantages are existed related to their toxicity due to high uptake form liver with low clearance [113]. In addition, DNA damage perhaps results from the high dose of this type that might result in mitochondrial damage [20]. For this reason, coating this nanotube carriers with polymers may prevent their retention in the organ, improve their ability to circulate in the blood and enhance their clearance [20].

Genral Limtations of nano-carriers

Despite the fact that nano-carriers are a promising strategy for cancer therapy, many limitations might be observed which restrict their application. The first limitation is the resistance of the drug due to the sustained action at the site of action. For this reason, multifunctional targeted nano-carriers have been developed, distribution of the endosome to ensure a quick drug release in the cytoplasm and using of multiple drug or drug-nucleic acid. In addition, to that changing the physicochemical properties of the drug such as changing the particles size, agglomeration behavior and initial drug release.

Novel materials that form nano-carriers such as organic and inorganic materials can have a toxic effect such as gold and carbon nanotubes. For this reason, factors such as particle size, encapsulation efficacy and desired release profile and cost will solve this problem.

Nanoparticles in the systemic circulation are recognized by reticular-endothelial

system with accumulation in the spleen and liver that might results in toxic effects. For this reason, particles size should be selected carefully for targeting without this side effect.

Slow development of the nano-carriers to be approved by the FDA is due to the absence of testing these nano-carriers in vivo at the real time. Consequently, few products such as DaunoXome®, Doxil®, Myocet® and Onco-TCS ® have been approved.

Conclusions

Many formulation strategies such as liposome and carbon based naanocarrier can solve the problems of nano-carriers used for cancer treatment besides focusing on the extensive in vivo testing to make these products are available in the market within a short period of time. The slight physicochemical modification may help to solve some problems related to the side effects and fate of these products. This will help pharmaceutical industry to produce chemotherapeutic drugs to treat millions of people in the world with fewer adverse effects.

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