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Nano Drug Delivery System in Pharmacy and Chemistry Review Article

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Abstract: *Controlled drug delivery systems (DDS) have several advantages compared to the traditional forms of drugs. A drug is transported to the place of action, hence, its influence on vital tissues and undesirable side effects can be minimized. Accumulation of therapeutic compounds in the target site increases and, consequently, the required doses of drugs are lower. This modern form of therapy is especially important when there is a discrepancy between the dose or the concentration of a drug and its therapeutic results or toxic effects. Cell-specific targeting can be accomplished by attaching drugs to specially designed carriers. Various nanostructures, including liposomes, polymers, dendrimers, silicon or carbon materials, and magnetic nanoparticles, have been tested as carriers in drug delivery systems. In this review, the aforementioned nanocarriers and their connections with drugs are analyzed. Special attention is paid to the functionalization of magnetic nanoparticles as carriers in DDS. Then, the advantages and disadvantages of using magnetic nanoparticles as DDS are discussed. The efficient delivery of active pharmaceutical agents to specific organelles like mitochondria and lipid bodies, employing nanocarriers developed through the use of "click" chemistry, constitutes a continuing topical area of research. In this review, we highlight important contributions click chemistry in the nanosized drug delivery system and its future aspects.*

Key words: *drug delivery system, nanocarriers, nanoparticles, targeting therapy, click chemistry*

I. Introduction

Delivering therapeutic compound to the target site is a major problem in treatment of many diseases. A conventional application of drugs is characterized by limited effectiveness, poor biodistribution, and lack of selectivity [1]. These limitations and drawbacks can be overcome by controlling drug delivery. In controlled drug delivery systems (DDS) the drug is transported to the place of action, thus, its influence on vital tissues and undesirable side effects can be minimized. In addition, DDS protects the drug from rapid degradation or clearance and enhances drug concentration in target tissues, therefore, lower doses of drug are required [1]. This modern form of therapy is especially important when there is a discrepancy between a dose or concentration of a drug and its therapeutic results or toxic effects. Cell-specific targeting can be achieved by attaching drugs to individually designed carriers. Recent developments in nanotechnology have shown that nanoparticles (structures smaller than 100 nm in at least one dimension) have a great potential as drug carriers. Due to their small sizes, the nanostructures exhibit unique physicochemical and biological properties (e.g., an enhanced reactive area as well as an ability to cross cell and tissue barriers) that make them a favorable material for biomedical applications. Since then click chemistry has become one of the most common and reliable methods to link molecules covalently, and it finds applications in a variety of disciplines including the chemistry of nanomaterials, chemical biology, drug delivery, and medicinal chemistry.

Nanocarriers used in drug delivery system

According to the definition from NNI (National Nanotechnology Initiative), nanoparticles are structures of sizes ranging from 1 to 100 nm in at least one dimension. However, the prefix "nano" is commonly used for particles that are up to several hundred nanometers in size. Nanocarriers with optimized physicochemical and biological properties are taken up by cells more easily than larger molecules, so they can be successfully used as delivery tools for currently available bioactive compounds [2]. Liposomes, solid lipids nanoparticles, dendrimers, polymers, silicon or carbon materials, and magnetic nanoparticles are the examples of nanocarriers that have been tested as drug delivery systems.The way of conjugating the drug to the nanocarrier and the strategy of its targeting is highly important for a targeted therapy. A drug may be adsorbed or covalently attached to the nanocarriers surface or else it can be encapsulated into it. Covalent linking has the advantage over other ways of attaching as it enables to control the number of drug molecules connected to the nanocarrier, i.e., a precise control of the amount of therapeutic compound delivered. Cell-specific targeting with nanocarriers may be accomplished by using active or passive mechanisms. The first strategy relies on the attraction of a drug – the nanocarriers conjugate to the affected site by using recognition ligands, attached to the surface of conjugates antibodies, low molecular ligands, e.g., folic acids, peptides, etc. The active strategy can

be also achieved through a manipulation of physical stimuli (e.g., temperature, pH, magnetism). Once the drug-nanocarrier conjugates reach the diseased tissues, the therapeutic agents are released. A controlled release of drugs from nanocarriers can be achieved through changes in physiological environment such as temperature, pH, osmolality, or via an enzymatic activity .Nanocarriers used for medical applications have to be biocompatible (able to integrate with a biological system without eliciting immune response or any negative effects) and nontoxic (harmless to a given biological system). Undesirable effects of nanoparticles strongly depend on their hydrodynamic size, shape, amount, surface chemistry, the route of administration, reaction of the immune system (especially a route of the uptake by macrophages and granulocytes) and residence time in the bloodstream. Due to a number of factors which may affect the toxicity of nanoparticles, their estimation is rather difficult and, thus, toxicological studies of each new DDS formulation are needed.

II. Liposomes

Liposomes have been the first to be investigated as drug carriers. They are nano/micro-particular or colloidal carriers, usually with 80–300 nm size range [3]. They are spherical vesicles composed of phospholipids and steroids (e.g., cholesterol), bilayers, or other surfactants and form spontaneously when certain lipids are dispersed in aqueous media where liposomes can be prepared, e.g., by sonication [4]. Liposomes have been reported to increase the solubility of drugs and improve their pharmacokinetic properties, such as the therapeutic index of chemotherapeutic agents, rapid metabolism, reduction of harmful side effects and increase of in vitro and in vivo antiversible attachment of homing devices is useful especially in modified liposomal systems, whereafter they successfully perform the function of targeting at the specific site. Ligands, such as antibodies, are cleaved off in response to an environmental stimulus, e.g., pH [22]. In addition, cationic liposomes (CLs) can be used as a gene delivery carrier [5]. They are better than natural or anionic liposomes for gene transfer [5]. Kim and co-workers [72] studied modified cationic liposomes either by polyethylene glycol (PEG)-grafting or PEG-adding methods as transfection complexes of plasmid DNA. In a recent study, Biswas et al. [6] have examined polyethylene glycol-phosphatidylethanolamine (PEG-PE) conjugate with the TPP group as drug carriers. They used paclitaxel (PTX) as a model drug and studied them for their toxicity, mitochondrial targeting, and efficacy in delivering. As a result, they suggested that TPPPEG-PE can be used as non-toxic, mitochondria targeted drug delivery systems [6].

III. Dendrimers

Dendrimers are highly branched macromolecules, which are prepared by repetition of a given set of reactions using either divergent or convergent strategies.37Dendrimers consists of three basic architectural components, (i) the core, (ii) the interior and (iii) the end-groups. Generally, the reactions employed are high yielding without any side reactions. This then allows one to obtain defined and uniform structures. Well known processes, such as the Michael reaction, Williamson ether synthesis, amidations and reductions have been used extensively in pioneering work by Vögtle, Tomalia, Fréchet and Newkome.38Dendrimers and dendrons can be considered as unique quantized building blocks for nanosciece and have served as functional objects in nanotechnology and nano-materials science.7

The synthetic methods in dendrimer chemistry have recently been upgraded to allow easier access to high-quality dendritic products. These advances have taken advantage of widely-applied approaches such as the click chemistry.,7,8 This has allowed dendritic architectures to be incorporated into ever more elaborate nanostructures.9

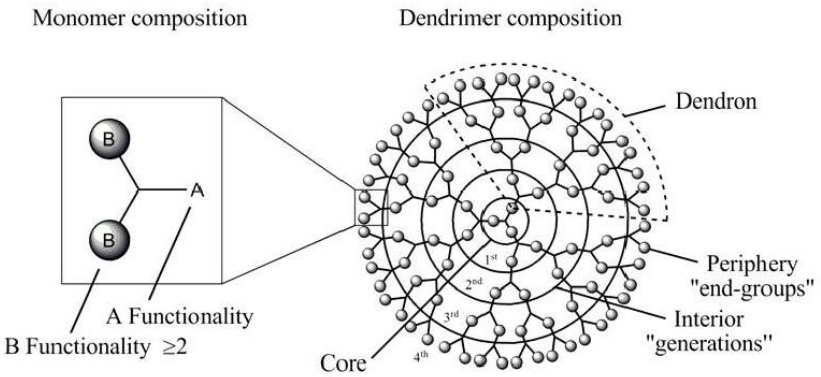

Fig.2:Basic architectural components of a dendrimer

IV. Click Chemistry In Nano Sized Drug Delivery

Tremendous effort has been devoted to the development of nanocarriers for the efficient delivery of therapeutic agents to the targeted site8. In this regard macromolecules have offered tremendous potential45, but such nanodelivery systems have to meet stringent requirements if they are to be employed for drug delivery9,10. The macromolecule based nanocarriers used for this purpose should be non-cytotoxic, remain intact prior to reaching the target site, and enhance the effectiveness of the selected drug. Although, significant efforts have been made in assembling macromolecule based nanocarriers using a variety of synthetic methodologies, challenges still remain in introducing multiple functions into a single platform. Click chemistry has offered new ways of developing nanomaterials11,12,13, particularly those with multiple functional groups and architecture51 . These moieties can be introduced within the nanocarrier architecture with high precision. Such nanoarchitectures have been exploited as suitable carriers for therapeutic agents and fluorescent labels to deliver them to specific cells, cellular organelle, to either prevent cell death52 or visualize them with or without drug delivery. A number of strategies to target cells with drugs had been adopted earlier, these include carbodiimide, thiol-maleimide and biotinavidin coupling to biomolecules53 . As already mentioned, recent progress in click chemistry has allowed coupling reactions to be carried out under mild conditions, and in an aqueous medium with negligible unwanted toxic byproducts1 . The use of 'click' chemistry to create dendritic modular systems has mainly involved dendrons. 'Click' chemistry is a particularly attractive coupling method because it can be performed with a wide variety of solvent conditions including aqueous environments. The stable triazole ring bridge, resulting from coupling alkyne with azide moieties, is frequently achieved at near quantitative yields and is considered to be biologically stable54-56 . Furthermore, the 'click' coupling chemistry is orthogonal to the coupling chemistries typically used to attach functional groups to the dendrimer. Lee and co-workers have detailed the synthesis of multi-module platforms using both un-functionalized PAMAM dendrons57-59 as well as unfunctionalized Frechet-type dendrons60 for each of the modules. In all of these systems, the focal point of the dendronpossessed either an azide or alkyne moiety. Wu and co-workers developed a 2,2-bis(hydroxymethyl)propionic acid (bis-MPA) based asymmetric modular dendron with 16 mannose units and 2 coumarinchromophores, and demonstrated binding in a hemagglutination assay61. Goyal, Yoon, and Weck have also developed a poly(amine) dendrimer that possessed a single aldehyde or azide moiety on the dendrimer periphery capable of orthogonal functionalization by small molecule functional groups62,63. These approaches appear promising but only the bisMPA dendron system has been demonstrated to have function as a targeted drug delivery platform. In all cases, the dendrons used were G3 or smaller. This has significant limitations for widespread therapeutic use because of the limited carrying capacity of low generation dendrons. To date, click chemistry has not been applied to a modular dendrimer system. Considering the focus of this review article, the following sections provide a few examples of nanodelivery systems targeting cell organelles, specifically mitochondria and lipid bodies (LBs). Mitochondria Mitochondria, cellular power plants, play pivotal homeostatic role in cellular functions such as cellular signaling, growth and differentiation, cell cycle regulation, electron transport, calcium storage and cellular death64,65. Mitochondrial dysfunction is implicated in a variety of pathological disorders such as aging, ischemiareperfusion, cardiac disorders, neurodegenerative and neuromuscular diseases, obesity, and genetic disorders66–69 . One of the major causes of damage in these conditions is the generation of mitochondrial reactive oxygen species70 . Some of the main disadvantages of selective drugs are their hydrophobicity, stability,bioavailability, inability to cross the membrane barriers and selective accumulation in the multi-membrane barrier organelles located in the cytoplasm, such as mitochondria. Targeting mitochondria with a variety of bioactive molecules and drugs is one strategy to overcome some of these hurdles66 . Unlike cellular targeting, the prerequisite for mitochondrial targeting includes the use of drug modifications or encapsulation into nanocarriers such as dendrimers. This would help not only cross several membrane barriers, but also have high accumulation in these organelles. The other advantage of using the nanocarrier systems is their ability for site specific targeting with improved efficacy and reduced toxicity71-74 . More recently an interesting new approach was taken by Dhar's group75. This study showed the versatility of biodegradable high density lipoproteinnanoparticles for detection of plaques by targeting the collapse of the mitochondrial membrane potential. The same study described a rationally designed mitochondria-targeted polymeric nanoparticle (NP) system and its optimization for efficient delivery of various mitochondria-acting therapeutics by blending a targeted poly(d,l-lactic-co-glycolic acid)-block (PLGA-b)-poly(ethylene glycol) (PEG)- triphenylphosphonium (TPP) polymer (PLGA-bPEG-TPP) with either nontargeted PLGA-bPEG-OH or PLGA-COOH. An optimized formulation was identified through in vitro screening of a library of charge- and size-varied NPs. A programmable NP platform for the diagnosis and targeted delivery of therapeutics for mitochondrial dysfunction-related diseases was also described75. The same group also showed how in situ light activation amplifies the host immune responses when NPs deliver the photosensitizer to the mitochondria, and opening up the possibility of using mitochondriatargetedNP treated, light activated cancer cell supernatants as possible vaccines76. An overview of strategies to target organelles by exploiting different nanotechnological tools was recently reported77

V. Anticancer Drug Delivery

The high toxicity of conventional cytotoxic anticancer drugs often forces these agents to be given at sub-optimal dosages and this can result in treatment failure88. To resolve this problem, delivery platforms that can discriminate between healthy and malignant cells have been developed88, 89. Actively targeted therapeutic delivery platforms consist of three different components: a targeting component comprised of targeting ligands with affinities for molecules expressed on cancer cells; a payload consisting of drug and/or imaging agents; and a nano-scale structure to which the targeting and payload moieties are attached. This platform targeting of anti-cancer drugs with cancer cell-specific ligands can dramatically improve a drug's therapeutic index. Conjugating multiple targeting ligands to a single platform molecule further increases the potential for specific targeting of cancer cells by allowing the possibility ofmultivalent interactions90, 91. The structural design of these types of delivery platforms is critical to the success of the delivery device. Numerous classes of targeted drug deliveryun desired cross reactions as well as degradation by hydrolysis. platforms have been developed that potentially meet the requirements needed to combine.

VI. Conclusion

Nanocarriers as drug delivery systems are designed to improve the pharmacological and therapeutic properties of conventional drugs. The incorporation of drug molecules into nanocarrier can protect a drug against degradation as well as offers possibilities of targeting and controlled release. Due to small dimensions, nanocarriers are able to cross the blood-brain-barrier (BBB) and operate on cellular level. In comparison with the traditional form of drugs, nanocarrier-drug conjugates are more effective and selective. They can reduce the toxicity and other adverse side effects in normal tissues by accumulating drugs in target sites. In consequence, the required doses of drugs are lower. Although there are several nanoparticle-based therapeutic agents which are currently being developed and are under preclinical evaluation, only a handful of nanoparticle drugs are available on the pharmaceutical market, e.g., liposomal conjugates: Doxil® (doxorubicin) or DaunoXome® (daunorubicin). It is due to the fact that nanoparticle based drug delivery systems do have a lot of drawbacks and limitations. Some of them arise from scaling up problems. For instance, small size and large surface area of nanoparticle-based targeting system can lead to an aggregation, making physical handling difficult. Nanocarrier-drug conjugates can be phagocytosed by cells whereas their intracellular degradation may cause cytotoxic effects. Other issues include low drug loading capacity, low loading efficiency, and poor ability to control the size distribution of carriers. Furthermore, there is a lack of technological methods, which will lead to nanodevices of approvable quality. Nanoparticles of diameter 10 nm can remain in cells and induct chronic inflammatory response and fibrosis of tissue. An additional problem is the lack of knowledge concerning the distribution of drug carriers and the unpredictability of the process. Thus, in our opinion, the magnetic targeted drug delivery system is one of the most attractive strategy target therapy. Magnetic nanoparticles have their unique magnetic properties and they can be attracted by magnetic fields, thus, acting as drug carriers in a target therapy. In addition, inorganic magnetic nanoparticles containing the iron and gadolinium serve as an excellent contrast enhancing agents in MRI (approved by FDA – Food and Drug Administration).The concept of dendrimers and dendritic structures containing an internal functionality is still a quite un explored area.Within this concept ,many new exciting materials and applications can be prepared

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