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Review article

Spatio-temporal control strategy of drug delivery systems based nano structures

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ABSTRACT

The drug instability, toxicity and the barrier to the target area necessitate a suitable drug delivery system with an external or internal control of the release. Spatio-temporal control using a surface functionalized nano-carrier seems to be the best alternative for guided drug delivery and release. This manuscript provides a broad spectrum about the drug carrier interface modification to cover the need for temporal drug delivery control under neglect side effects. On the other hand, recent advances related to the drug vehicle are highlighted, besides physical (Electric field, magnetic field, light) or mechanical (Ultrasound, mechanical strain), chemical (pH, redox gradient, enzyme) stimuli mediated DDS. Precisely, the paper focus on the NIR light as an effective external stimulus for remotely-triggered DDS. NIR responsive drug delivery systems are considered as novel drug modality that ensures an eco-friendly spatiotemporal control and an administrated meditation. This study also investigated the NIIR spectroscopy (NIRS) combined with partial least square (PLS) for quantitative analysis of a polyvinyl alcohol based prodrug (PVA-DOX) in order to reveal the high potential of NIRS for drug release monitoring and the extraction of concise calibration models.

1. Introduction

The incorporation of external or internal stimulus as a remote control to trigger the release of therapeutic payloads has received much attention in this recent years, where the drug instability, decreased toxicity, limited barrier to the target area and an enhanced therapeutic effect are the major factors.

The nano-particles has been involved widely in medicine for the treatment of considerable kind of diseases [1]. Generally, the design of novel therapeutic systems depends widely on the nature of the nano-carrier and its responsiveness to the intrinsic or extrinsic stimuli in the target site (abnormal tissues). Compared to the normal tissues, the infected or the abnormal tissues (such as tumor) present chemical or biological activity including the abnormal vascular agglomeration, blood vessel expansion, specific acidity (~ pH 6.8), abnormal temperature arise (due to the slow blood flow). Added to that, they present abnormalities in proteins and enzymes structure, inadequate oxygen supply (hypoxia) or an increase of reactive oxygen species (ROS) and high levels of metabolites. This abnormalities must be taken into consideration during the design of the DDS. For example, ROS are considered as a normal eukaryotic metabolism, but their presence in a high amount and their generation of redox gradient could be an index for some disease such as Alzheimer's, Parkinson's, cardiovascular disease and some cancers [2], thus the use of the listed infected cells

Abbreviations: AuNCs, gold nanocages; AuNPs, gold nanoparticles; AuNSs, gold nano-stars; AuNTs, gold nanotubes; AuNFs, gold nanoflowers; AuNShs, gold nanoshells; AuNRs, GNRs, gold nanorods; ATP, Adenosine-5′-triphosphate; BNs, carbon based nanoparticles; CA, contrast agent; COFs, covalent organic frameworks; CNTs, carbon nanotubes; CTAB, *n*-cetyltrimethylammonium bromide; DCA, dechloroacetate; DDS, drug delivery systems; DOX, doxorubicin; EF, electric field; FA, fluorescence agent; IONPs, iron oxide nanoparticles; ICPs, infinite coordination polymer particles; MCNs, mesoporous carbon nanoparticles; MMSSN, monodisperse mesoporous manganese silicate coated silica nanoparticles; MOFs, metal organic frameworks; MF, magnetic field; MWNTs, multiple walled carbon nanotubes; MTNs, multi titana nanoparticles; MSNs, mesoporous silica nanoparticles; NDs, nano diamonds; NPs, nano particles; NIRS, near infrared spectroscopy; NMOFs, nano-metal organic frameworks; ORP, oxidative and reductive potential; OPH, organophosphorus hydrolase; PTT, photothermal therapy; PDT, photodynamic therapy; PTX, paclitaxel drug; PTT, photothermal therapy; PDT, photodynamic therapy; PCL, poly(ε-caprolactone); PLA, poly-l-lactide; PLG, PLGA, poly lactide-*co*-glycolide; PEG, polyethylene glycol; PEA, poly ester-anhydride; PVA, polyvinyl alcohol; PPGDMA, polypropylene glycol dimethacrylate; PEGDMA, polyethylene glycol dimethacrylate; PPGDA, polypropylene glycol diacrylate; PEGDMA, polyethylene glycol dimethacrylate; PEG-DTT, polyethylene glycol -bpoly(aspartate diethyltriamine); PVA–HNT, polyvinyl alcohol–halloysite nanotubes; PDPA, poly(diisopropanol amino ethyl methacrylate cohydroxyl methacrylate; PSiNPs, porous silicon nanoparticles; PLS, partial least square; ROS, reactive oxygen species; RMSEC, root mean square error of calibration; SOD1, anti-oxidative enzymes; SP, propane-2,2-diylbis((1-(4,5-dimethoxy-2-nitrophenyl)ethyl)sulfane); SWNHs, single walled carbon nanohornes; SWNCs, single walled carbon nanocones; SWNTs, single walled carbon nanotags; SWNTs, single walled carbon nanotubes; TSL, temperature sensitive liposomes; UCNPs, upconversion nanoparticles

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properties to investigate the surface modification of nanocarriers by responsive coupling agents during the design of novel DDS is a straightforward way to get a guided drug uptake, delivery and release [3]. In this context, several physicochemical stimulations are under investigations to ensure an efficient monitoring of drug release including [4]temperature, enzymes, magnetic and electronic field, pH [5,6,7,8], Glucose, glutathione GSH concentration [9,10], mechanical compression [11,12], ultrasound [11,12–13], depolarisation [14], osmotic pressure [15], cell-surface receptors and circulatory biomarkers [2]. However, the smart nature of some diseases besides the relative toxicity and the control difficulties of the DDS leads to relatively limited therapeutic efficiency, thus the light actuated drug delivery systems are striking feature, but they remain under proof in order to limit mutagenicity, toxicity, and enhance biocompatibility [11]. Despite of their shortcomings, light-triggered drug delivery systems exhibit versatility in clinical applications for controlled release. The development of light responsive DDS based on NIR irradiation seems to be able to overcome the limitation of the UV light triggered release. This review presents several advanced organic-inorganic nanostructures used as drug vehicles in DDS, their responsiveness to the target physio-chemical change and the release mechanism of the loaded cargos. This article also emphasizes the major importance of the NIR light controlled DDS and the NIR spectroscopy combined with chemometrics for the monitoring of drug release and the extraction of a concise calibration model.

2. Drug delivery system

The problem of drug solubility, permeability, stability are the leading causes for normal cells damage, intensiveness and increasing of harmful side, thus, many researches trend to overcome those drawbacks and design novel drug delivery systems to ensure the drug transport until the infected site and trigger the release under selected conditions, which is known as drug delivery systems. A large amount of nanocarriers for drug delivery with different structure and materials has been investigated as DDS substrate, as follow a literature review about recent advances of nanostructures as DDS substrate.

2.1. Nanostructures for drug transport

Remarkable variety of anticancer drug delivery systems present high probability of chemotherapeutic agents' leakage, which might conduct to nonspecific delivery (harm the normal tissues), non-acceptable side effects with a lack of efficiency [16]. Therefore, nanocarrier for triggered drug release become the subject of recent researches, where the nanoparticles (NPs) were proved to have a high selectivity to accumulate into the target (e.g., tumor). The drug could be triggered exactly into the tumor site when the NPs contains microenvironment sensors, and therefore it prevents the nearby normal tissue damage [17]. The main aspect that should be considered during the fabrication of those kind of drug carrier is to ensure their neglect immune system reaction in the case of drug loading systems or to increase the immune response system in the case of vaccines loading systems by the selection of immunological agents (as adjuvants or antigen carriers), that has the ability to aid in the antigen uptake or the activation of the antigen presenting cells and restrains the side effects caused by the inflammation at the site of vaccination [1,18].

Generally for some systems the delivery of the payloads is the most important aspect without the need for any triggered release. Antigen-functionalized inorganic nanoparticles is good illustration of this kind of delivery systems due to their extra-immune responsiveness compared to microparticles [19]. The ability to protect the antigens from hydrolyse in harsh intracellular environments and the minimization of antigens leakage [19–20], the overcoming of the natural barrier and the ensuring of safe use of vaccines [21]. Caging is another concept to protect the payloads e.g., organophosphorus hydrolase 'OPH (Catalytic scavengers) [22] anti-oxidative enzymes 'SOD1' [23–24] by using semi permeable cages including polymers, liposomes or peptides linked proteins, which is known as nanozymes, their major role is to increase the permeability to the target site, protect the payloads from renal clearance or other active enzymes and keep their stability and biological activity.

The versatility of pharmaceutical payloads (genes, drugs, vaccines or enzymes) delivery vehicles represents a striking feature in DDS development. The major aspects to be evaluated during the selection of the nanostructures substrate for the delivery systems are: The biodegradability or bioresorbablity (Covalently linked polymer-drug conjugates to non-toxic monomers inside the body might be degraded under lysosomal or enzymatic cleavage [25]), hydrophilicity, surface and bulk properties, biocompatibility, smoothness, permeability (permeability to the target site [9]), a good distribution of the drug cargos, a high specific surface area, a good retention (the EPR effects electron paramagnetic resonance) [9,26], water sorption capacity (case of hydrogels) structural change under physio-chemical-biological stimuli, safety under preclinical tests and the possibility of surface functionalization, where the outside surface of the membrane could be modified with hydrophobic species to guide the drug to the desired location [5,27–29].

In case of polymeric nanocarriers the molecular weight is an important factor. It influences the drug release rate, while the number of monomers influences the rate of degradation (less monomer units ≥ high degradation rate), whereas the diffusion of the drug is inversely proportional to the polymer weight [30]; therefore the shape, the architecture and the geometry of the carrier are essential factors for cellular uptake and the kinetics of the release; but they are no longer widely examined due to the limitations in manufacturing [31]. Herein recent advances in several kinds of nanostructures for drug loading and their classification with the incorporation of stimuli responsive agent are presented (see Fig. 1). In addition, further explanations and comparison between organic, inorganic and hydride nano-vehicles for DDS are given in Table 1 with some characteristics, advantages and limitations. According to the presented nanostructures for drug delivery, it is obvious that every nanocarriers has one, two or set of drawbacks besides its advantages, so the selection of the suitable drug vehicle could be a confusing step. The organic NPs seems to be a good alternative as a substrate for drug delivery system due to its adequate physio-chemical properties, whereas the biocompatibility and drug safety remain a crucial issue during the selection of DDS substrate, this choice should not be based on which system has no side effects but on which system provides more therapeutic efficiency, less damages on living cells and protect the payloads from the intracellular environment. A suitable functionalization of the drug substrate illustrates the potential of stimuli responsiveness of the drug carrier for an easy control of drug delivery and release.

3. Triggered drug delivery and release

The triggered drug release is the important aspect for the design of novel drug delivery system, where the selection of the appropriate drug nanocarrier, the responsive functional group and the understanding of the drug release principal and process are primordial. Several factors contribute in achieving an efficient delivery of the drug to the infected cells, including *the substrate (the drug carrier), the drug and the stimuli-responsive agents.* (1) *The substrate*: Generally, nano particles with a large pore and high surface area present a suitability for the drug vehicle. They should present the ability to reach the infected site and deliver their payloads successfully to achieve the desired therapeutic effects [32]. This nano-carriers (particles' size ranging from 1 to100 nm) are considered as a profitable technology for drug delivery, because of their high loading capacity, less toxicity and the supra molecules impregnation ability on their surface [5,33,34]. The drug loading efficiency *DLE* (also known as the loading rate *DLR*) [35,36], the drug loading content