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POLY ALKYL CYANOACRYLATE NANOPARTICLES AS DELIVERY VEHICLE IN COMBATING DISEASES

Science

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ABSTRACT

The major problems in drug delivery to specific diseased sites possess drug-resistance, drug-toxicity, biological barriers and non-specificity to the target-cells observed among patients worldwide. To overcome these barriers, the biodegradable poly alkyl cyanoacrylate (PACA) nanocarriers have been used, while a core made up of PACA is functionalized with biologically active ligands such as cargos, biotin and antibody for enabling specific targeting, and stabilized with outer polyethylene glycol or surfactants in combating cancer, neurodegenerative and infectious diseases. The review demonstrates mainly the synthesis, functionalizations and the biomedical applications of PACA nanoparticles against various diseases to consider them as potent delivery vehicle.

KEYWORDS

Diseases; Poly alkyl cyanoacrylate nanoparticles; Functionalizations; Potent delivery vehicle

Introduction

Many people suffer from severe diseases such as infectious, cancer or neurodegenerative disorders every year throughout the world [1-12]. The diseases generally develop when oxidative stress generated by toxicants dominates over the antioxidant defense mechanism and the protective innate and acquired immunity of the host body [13]. Infectious organisms generally survive in the host phagolysosomal compartment and spread throughout the host cells in the diseased state [14], while uncontrolled proliferation of cells without apoptotic cellular death make the disordered cells cancerous followed by in some instances metastasis. Alzheimer's disease (AD) represents the progressive productions and the toxic aggregations of β-amyloid peptides 1-42 (Aβ1-42) and the intracellular accumulations of the hyper-phosphorylated tau proteins in the brain neurons affecting acetyl-cholinestarase activity, while Parkinson's disease (PD) represents the deficits of dopaminergic neurons within the substantia nigra pars compacta and the dopamine decrement in the striatum accompanied with reactive oxygen species (ROS) generation.

In many of the cases, the conventional treatment of the diseases cannot cure the patients completely showing their aggravations of the disease state as drug resistance due to over-expressions of efflux proteins such as P-glycoproteins and multidrug resistant proteins, biological barriers such as blood brain barriers that restrict the exchange of solutes between the blood and the brain extra-cellular fluid where brain endothelial cells and peripheral endothelia are joined by tight junctions, systemic enzymatic drug degradations, non drug specificity to cells, drug toxicity, non drug-stability and non drug targeting efficiency become prominent. To overcome these obstacles, it is needed a delivery system to target cargos to specific site of interest for treating diseases having insignificant side effects. In this concern, nanotechnology, a multidisciplinary area, consists of engineering functional systems at the molecular level covering material science, applied physics, colloidal and interface sciences, and supra-molecular chemistry as well as electrical, mechanical and chemical engineering for the applications in the medical and pharmacological fields as nanoparticulated, nanomedicinal drug delivery. Therefore, the ideal nanomedicine platforms should represent their appropriate features such as (i) biodegradability / biocompatibility to permit secure administration, (ii) exhibition of stealth properties for escaping the immune responses, (iii) functionalizations with radioactive / fluorescent probes to trace / localize them, and (iv) suitability for surface-functionalizations with ligands for achieving active targeting to specific cells. In this context, different polymers have been utilized to transfer active compounds to target sites for getting better therapeutic index as delivery vehicles, while biodegradable nanoparticles have been emphasized more for biomedical applications as they provide better encapsulation efficiency, longer bioavailability, sustained release and insignificant side toxicity.

Targeted treatments are utilized for blocking the specific biological transduction signaling or diseased proteins involved in for their progressive development i.e. the molecular targets such as growth factors, receptors, kinase cascades, and apoptotic and angiogenic molecules that are available in normal cells, but are mutated or over-expressed in diseased cells. The objective of these treatments is to occlude the signals that induce the malignant cells to expand and split frantically, and to create the diseased cells-deaths with the induction of apoptosis, stimulation of the immune system or targeting the delivery of cargos especially to diseased cells, diminishing normal cells-death and preventing the unwanted concomitant effects [15,16]. Active targeting is achieved with the attachment of distinct ligands to the nanoparticles-structures to allow a discriminating identification of various antigens or receptors over-expressed in the diseased cells-surfaces to increase the cytotoxic actions of the cargos with the insignificant side effects, as the exposures of cargos to healthy cells are minimized [17]. The functionalizations of the polymer nanoparticles-surfaces, not only provide their active targeting activities, but also improve the therapeutic efficacies of the cytotoxic active compounds to overcome also the multi drug resistance (MDR) [18,19].

In this concern, biodegradable colloidal poly alkyl cyanoacrylate nanoparticles (PACA NPs) have attracted attention for nano-biomedical applications as they have exhibited their significant preclinical outcomes in several pathologies such as severe microbial infections and cancer as well as in few autoimmune and metabolic diseases [20-22]. Presently, in phase III clinical assessments, doxorubicin-stuffed PACA NPs have exhibited their upgraded safety and survival compared to the usual treatments in patients with MDR-hepatocarcinomas [23], and their overlay with polyethylene glycol (PEG) not only turned them into long-circulating nano-vectors but also enabled them to traverse the blood-brain-barrier (BBB) [24-26]. To accomplish particular disease targeting, biotin and folic acid were used as ligands with PACA NPs to target selectively different cancer cell lines as receptors-mediated cancerous cells-uptake therapy [27-30]. For the treatment of AD, PACA NPs were functionalized either with drugs or with a distinct antibody through the biotin / streptavidin attachment to bind not only the cerebral Aβ1-42 monomer, but also Aβ1-42 fibrillar aggregates [27-29]. This review demonstrates the therapeutic efficacies of PACA NPs for the treatment of cancer, neurodegenerative disorders and microbial infections to consider as suitable delivery vehicle.

Synthesis and preparation of poly alkyl cyanoacrylate nanocomposites

Alkyl cyanoacrylate monomers are generally reactive highly owing to their combination of ester and nitrile electron-withdrawing groups bonded to the same carbon atom leading to polarization of the C=C bond susceptible to be attacked by anions and compounds having nucleophilic groups such as amines.

Alkyl cyanoacrylate monomers are utilized for their anionic polymerization in water to synthesize polymers (Fig.1). The hydroxyl groups present in water initiate reaction by attacking on the extreme methylene group of the alkyl cyanoacrylate monomers. The resultant carbanions behave as nucleophiles and react with other alkyl cyanoacrylate monomers for producing the growth of carbanion chains resulting in the generation of PACA, while polymerization becomes ceased by mobile protons present in water. In general, 1mL monomer is adjoined in one shot to 15 mL water to carry out

polymerization for 1.30 h at 40◦C under magnetic stirring at 1200 rpm. After that time, a milky suspension is acquired for the poly isohexyl cyanoacrylate (PIHCA) and poly butyl cyanoacrylate (PBCA). For the case of poly isobutyl cyanoacrylate (PIBCA), poly propyl cyanoacrylate (PPCA) and poly ethyl cyanoacrylate (PECA), a milky dissolution containing polymer-aggregates is obtained. The milky suspensions are freeze-dried whereas the aggregate polymers are liquefied in acetone, and dried under vacuum at room temperature. The polymers, thus derived, are utilized for the preparation of nanoparticle-composites.

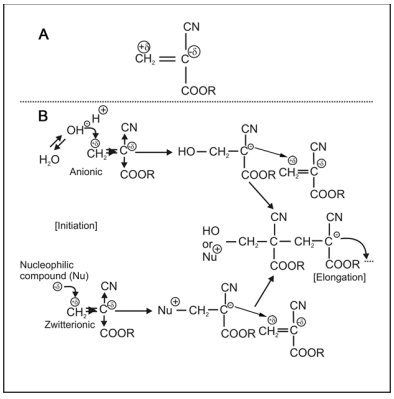

Fig.1. Chemical structure (A) and scheme of anionic and zwitterionic polymerization (B) of monomeric alkylcyanoacrylates.

For the preparation of nanoparticle-moieties (Fig.2) utilizing nanoprecipitation and emulsification-solvent evaporation modified methods [31,32], an organic solution (acetone) (2 mL) of PACA (20 mg or 10 mg) is mixed with drug (2 mg) in acetone / chloroform (0.5 mL). The mixture solution is then added drop-wise to an aqueous solution (5 mL) of surfactant such as 0.5-1% w/v pluronic F-68 / polysorbate 80 / poloxamer 188 or another stabilizer such as dextran 70,000 / poly ethylene glycol (PEG) in 0.001N HCl (pH 1-2.5) under vigorous mechanical stirring (1200 rpm) for 2.5 - 3 h at room temperature. The resultant dissolution is nullified with 0.1N sodium hydroxide (NaOH) solution to finish the polymerization reaction. The organic solution is then evaporated under reduced pressure and nanoparticles are purified by centrifugation and filtration. The final pellet is resuspended in deionized water to yield a nanoparticle suspension which is lyophilized after addition of 3% mannitol as cryopreservative for future use.

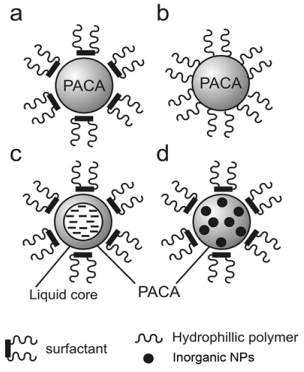

Fig.2. Schemetic presentation of various types of produced polyalkylcyanoacrylate nanoparticles.

For the preparation of nanocapsules composed of a liquid core with a surrounding polymeric envelope, interfacial polymerization techniques may be applied [33-38], while the reactions are accomplished either in microemulsions or in oil-in-water or in water-in-oil emulsion systems resulting in the creation of oil or water - containing respective nanocapsules. To prepare oil-possessing nanocapsules by the polymerizations of alkyl cyanoacrylates at the oil / water interface of oil-in-water emulsions, an organic phase containing 1 mL oil, 0.125 mL alkylcyanoacrylate, and drug liquefied in 25 mL acetone or ethanol is added into the 50 mL aqueous-phase containing 0.25% hydrophilic surfactant under strong magnetic stirring. The development of milky suspension implies the formation of nanocapsules, while an ideal 2% oil/ethanol ratio in the organic phase is maintained [38]. The organic solvent is then evaporated out and the residual suspension is ultracentrifuged to get pellet of nanocapsules. The aprotic solvents such as acetonitrile and acetone, and protic solvents such as ethanol, iso-propanol, n-butanol are used to induce the generation of nanocapsules and additional nanospheres with nanocapsules respectively. On the other hand, water-containing nanocapsules are prepared by the interfacial polymerizations of alkylcyanoacrylates in water-in-oil microemulsions. In this process, water-swollen micelles of uniform and small sized surfactants are disseminated in an organic phase. The monomers are then adjoined to the microemulsion where they may polymerize at the surface of the micelles to form polymers at the water-oil interface and may precipitate to yield the nanocapsule shells [34,36,37]. These water-containing nanocapsules may encapsulate water-soluble molecules e.g. nucleic acids, antisense oligonucleotides and peptides [37,36], which are useful for the intravenous administration, as the aqueous-core-containing nanocapsules may be converted into an aqueous continuous phase by ultra-spinning of the oily dissolution over a layer of pure water possessing Span®80 [36].

Poly alkyl cyanoacrylate nanospheres may also be prepared by emulsion polymerization method [39] used to synthesize colloids with a matrix structure of nanosphere (Fig.2). In this process, the polymerization is actuated by the hydroxyl ions of water, and then elongations of the polymer chains occur on the basis of anionic polymerization mechanism (Fig1) controlled in an aqueous medium by the adjustment of the pH with the concentration of the anionic polymerization inhibitor in the monomer and strong mineral acid [40]. In brief, 100 µL monomer is dispersed in 10 mL acidified water (pH 2.5) containing a colloidal stabilizing agent or a surfactant (0.5-1 % pluronic F68 or dextran 70) to allow polymerization for 3 to 4 h under strong magnetic stirring, while drugs may be entrapped in PACA nanospheres or coupled covalently to the surfaces of nanospheres [41,42].

Characterizations of poly alkyl cyanoacrylate nanocomposites

Microscopic techniques such as Scanning Electron Microscopy, Transmission Electron Microscopy and Atomic Force Microscopy determine the morphology of the nanocomposites along with their size, distribution analysis and roughness of the material-surface. Dynamic Light Scattering is used to determine the size of the Brownian nanoparticles in colloid suspension along with zeta potential measurements as stability studies. Fourier Transform Infrared Spectroscopy is used to get information about the confirmative structural details of proteins such as their nature of modifications in folding, chemical bonding in lyophilized nanoparticle-suspension.

Poly alkyl cyanoacrylate nanoparticles as delivery carrier

Few potential utilities of PACA NPs as drug delivery device in controlled cargos-targeting have been demonstrated in Table 1 [43].

Table 1. Different therapeutic applications of poly alkyl cyanoacrylate nanoparticles.

Applications	Materials	Purposes
Intracellular targeting	Nanoparticles with antiviral or anti –parasitic cargos	To target reticulo-endothelial intercellular infections.
Cancer therapy	Nanoparticles with oligonucleotides, anti-cancer cargos	To target cells for enhanced uptake of antitumor cargos. To reduce toxicity and improve *in vitro* and *in vivo* stability of cargos.
Ocular therapy	Nanoparticles with steroids, anti-microbial and anti-inflammatory cargos for glaucoma	To improve retention of cargos and to reduce wash-out.
Other usages	Nanoparticles with peptides	To cross blood-brain barrier, and to improve absorption and permeation for transdermal application.
	Copolymerized peptide nanoparticles of activated peptides	To deliver peptides orally.
	Nanoparticles with radioactive or contrast agent	For radio-imaging
	Nanoparticles with adsorbed enzymes	For enzyme-immunoassays

For Infectious Diseases

Generally, pathogens cause severe intracellular infections by

developing their different survival mechanisms [44,45]. The entrapment of antibiotics in the nanocarriers to improve the therapeutic index by targeting drugs to infected cells have been performed [6,20,44-48], while opsonized nanoparticles containing antibiotic are entrapped in the phagolysosomal compartment through endocytosis or phagocytosis to release their bioactive ingredients into the cells [44]. The application of ampicillin entrapped poly isohexyl cyanoacrylate nanoparticles in experimental salmonellosis increased the antibiotic efficacy by 120 fold [20,49], while other antibiotics were incorporated in different PACA-based nanovehicles [44,46-48,50-54]. Ciprofloxacin entrapped PBCA nanoparticles were found active as pH-controllable drug release against bacteria [55]. The exposure of ampicillin entrapped PIBCA nanoparticles into the infected macrophages showed their reduced viability to 99% after 30 h of incubation [56]. The *in vivo* experiment with mice showed the high efficacy of antibiotic entrapped PACA nanoparticles against intracellular infections [44,20,56]. The similar natures were also monitored for the applications of antiviral agents -loaded nanovehicles [57-61].

For cancer

Cancer therapy suffers from its non-selective damage especially to normal cells with additional multi-drug resistance of cells due to over-expression of P-glycoprotein. To overcome these obstacles, different bioactive compounds such as cytostatics, peptides, nucleic acids and hormones have been entrapped in PACA nanocarriers with / without PEGylation as delivery systems to target cancer cells by passive or active targeting through phagocytosis or receptor mediated endocytosis accompanied with tumorial EPR effect [6,44,62-71]. Drugs entrapped nanocarriers, thus, penetrate the leaky tumor vasculature to accumulate in the tumor interstitiums and to liberate the loaded drugs, creating their high concentrations as anticancer agents. To achieve active targeting, ligands are anchored to the surface of nanocarriers to target tumor endothelial cells that impart nutrients and oxygen to the tumor cells [72-74]. The main target specific ligands for cancer cells indicate the folate receptor, the transferring receptor, the glycoproteins and the epidermal growth factor receptors, whereas for the tumoral endothelial cells the integrins, the vascular endothelial growth factor receptors, the matrix metallo-proteinases and the vascular cell adhesion molecule-1. Recently, PACA-based nanoparticles have been functionalized to their surfaces with different targeting ligands through azide-alkyne 'click' chemistry as anticancer delivery system [74].

For cerebral diseases

A physiological blood-brain barrier may limit the transports of many bioactive compounds such as cytostatics and antibiotics to the brain tissue. This limitations may be further augmented by the BBB- related enzymes e.g. g-glutamyl transpeptidase for the degradation of the drug molecules [75]. Surface functionalized PACA NPs have shown their capabilities to deliver cargos not only into the brain but also to protect them from the enzymatic degradations [76-78,32]. In general, to target brain tissue, PACA NPs become reformed with PEG for escaping from the uptake of macrophages, or with surfactant to increase the BBB-penetrability and to obstruct ABC efflux protein -activity on the BBB. Moreover, the ligand-specific nanocarriers may adsorb apolipoproteins E from blood plasma to pass through the brain endothelium through receptor mediated endocytosis and then transcytosis [78].

For acquired immunodeficiency syndrome

Human immunodeficiency virus-1 (HIV-1) causes acquired immunodeficiency syndrome (AIDS) resulting in reduction of CD4+T cells as the virus generally targets few cells such as CD4+ monocytes / macrophages, CD4+T cells, microglial cells, dendritic cells and macrophages which act as reservoir site to reproduce virus [79]. Therefore, the common strategy for combating AIDS is the killing of the HIVs in cell and tissue reservoirs. However, targeting to HIV-infected cell is not a simple issue as CD4+T cells do not persist for long time as well as lack infection markers on the infected CD4+T cells, though these cells may accumulate highly in lymph nodes. Therefore, higher therapeutic efficiency may be achieved by delivering nanocarriers loaded with anti-HIV cargos to lymph nodes for their smaller sizes suitable to be internalized by lymphocytes as well as act as intracellular cargos reservoirs [80]. In this perspect, nanocarriers may be prevented from their opsonizations by mononuclear phagocyte system by minimizing their sizes to nano range and modifying their surfaces with hydrophilic materials. Moreover, PACA NPs may also be modified with the ligands of the pattern recognition receptors (PRRs) associated in the immune response for targeting cargos into the immune system, while the PRRs e.g. Toll-like receptors, C-type lectin receptors, scavenger receptors, nucleotide oligomerization domain-like receptors and retinoic acid inducible gene-like receptors can recognize few conservative elements expressed on pathogens, called pathogen-associated molecular patterns [81].

Biodistribution, pharmacokinetics and elimination of poly alkyl cyanoacrylate nanoparticles

The pharmacokinetics of drug concentration loaded in different PACA NPs formulations vary on their different routes of administration [82,83]. After oral administration of free and different nano-formulated drug at a single dose of 50 mg/kg body weight in rats, showed that maximum plasma concentrations of quercetin loaded PACA NPs and quercetin loaded PACA NPs coated with polysorbate-80 were enhanced ~1.4 and ~1.7 folds respectively compared to free quercetin, whereas their $t_{1/2}$ s were increased to ~14 h and ~19 h in comparison to 6 h of free quercetin. Quercetin-loaded PACA NPs and their coated-NPs showed higher concentrations of quercetin in the liver and spleen compared to free quercetin, whereas their distributions were less to the heart and kidney in comparison to free quercetin. The maximum concentration of quercetin into the brain was observed by the oral delivery of quercetin-loaded PACA NPs-coated polysorbate-80 compared to the quercetin-loaded PACA NPs and free quercetin, probably owing to their receptor-mediated endocytosis through the anchorage of polysorbate-80 for apolipoprotein-overcoated PACA NPs.

Doxorubicin (Dox) solution and Dox-loaded PACA NPs, synthesized by emulsion polymerization (EP) and dispersion polymerization (DP) techniques, were injected intraperitoneally (i.p.) into rats to study *in vivo* pharmacokinetics. Dox-loaded PACA NPs showed higher drug concentration in blood than Dox solution. The $t_{1/2}$ of Dox was enhanced by DP and EP -NPs while their elimination rate constants (0.2 h^{-1} and 0.16 h^{-1} respectively) were lower than Dox solution (0.43 h^{-1}). The area under the curve and area under moment curve of nanoparticulated Dox were significantly enhanced compared to Dox solution, while the bioavailability of Dox was augmented by DP and EP (1.9 fold and 2.12 fold respectively).

The Dox-loaded DP NPs exhibited an initial quick clearance from the blood following slow clearance after 2 h of intravenous (i.v.) injection to rats, while the Dox-concentration for injected DPNPs was higher than the Dox solution after 2 h i.v. post injection. Both DP and EP -NPs increased the $t_{1/2}$ and mean residence time of Dox significantly in blood rather than administered Dox solution. The area under the curve and area under moment curve were also enhanced for Dox delivered through EP and DP -NPs, while the elimination and clearance rate constant became lower compared to Dox solution. EP NPs showed the lower Dox clearance (0.13 mL/min) in blood compared to DP NPs (0.21 mL/min), while the area under the curve and area under moment curve became higher.

Dox solution and Dox delivered through EP and DP -NPs after i.p. injection exhibited lower drug concentration in tissue compared to after i.v. injection. After i.p. injection, Dox-distribution delivered via DP NPs was fast to liver and spleen and followed to lung after 1 h of administration. EP NPs, after their administration, showed lower concentration of Dox in organs of RES in comparison to DP NPs and Dox solution, while NPs showed their greatly reduced Dox-distribution to heart.

Degradation and toxicity of poly alkyl cyanoacrylate nanoparticles

The biodegradation mechanism occurs through the hydrolysis of the side chain ester bonds of the PACA NPs producing the alkyl alcohol and polycyanoacrylic acid, while the latter being water-soluble is excreted by renal filtration (Fig.3) [84-88]. This hydrolysis of PACA NPs proceeds in a couple of hours and depends on the alkyl side chain –length i.e. the longer the chain, the slower the hydrolysis catalyzed by esterases from lysosomes, plasma and pancreatic juice [89,87]. However, the full elimination of these materials may occur for PACA polymers having lower molecular weight below 10,000 g mol^{-1}. It is also postulated that the unzipping depolymerization initiated by a base may take place in the PACA biodegradation pathway in a biological media induced by amino acid of protein followed by instant repolymerization forming lower-molecular-weight polymers [90].

PACA polymers may also degraded on the basis of inverse Knoevenagel condensation reaction producing alkyl cyanoacetate and formaldehyde through hydrolysis of the polymer chains having α-hydroxyl functions if hydroxyl ions are utilized initially as an initiator [91].

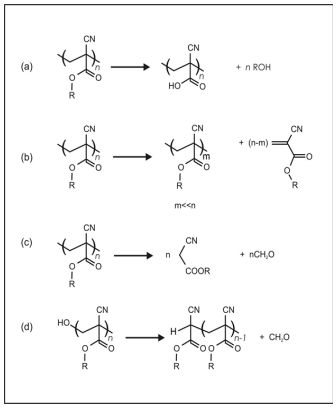

Fig.3. Possible degradation pathways of polyalkylcyanoacrylate polymers: (a) hydrolysis of ester functions, (b) unzipping depolymerization reaction, (c) the inverse Knoevenagel condensation reaction, and (d) liberation of formaldehyde from the α-hydroxyl hydrolysis.

The cytotoxicity of PACA NPs has been correlated with the biodegradation rate of polymer backbone, while higher toxicity comes from higher biodegradation rate related to the alkyl side chain length [85]. The PACA NPs having longer alkyl chain degrade slowly and exhibit less cytotoxicity [89]. The adhesion of PACA NPs to the cell membranes may also enhance the cytotoxicity by the local liberation of higher biodegradation yields [92]. It was experimented that poly butyl cyanoacrylate NPs showed no cytotoxicity to cells at their concentration of 75 µg/mL whereas membrane injury appeared at their concentration of 150 µg/mL [93].

Conclusions and future perspectives

Conventional chemo and antimicrobial therapies have been protecting lives from infectious diseases and cancer to some extent for many decades. However, occurrences of drug resistance and new toxic agents are causing serious health-hazards. The development of new drugs and chemical modifications of existing drugs may be the approaches in combating these threats, but they may lead to limited and temporary success. In this aspect, nanotechnology based PACA NPs, due to their ease and reproducible preparation, ease of storage and administration in sterile form, suitable drug-loading capacity, site-specificity, excellent biodegradability, low toxicity, controlled and sustained drug release capability, and feasibility for scale-up production, have attracted attention as suitable drug delivery device to overcome the biological obstacles, though the selection of specific monomers to polymerize and prepare PACA NPs is very important to get their maximum efficiency against various diseases. As PACA NPs are toxic to some extent as higher dosages, their PEGylated forms, surfactant coating and ligand binding may make them unique to be utilized for site specific drug targeting at lower dosages and to get maximum biological effectiveness.

Though PACA NPs have currently entered Phase II clinical trials expecting for the treatment of resistant cancers, this drug delivery system requires more investigations regarding their pharmacokinetics, choosing of appropriate monomers, suitable surface functionalizations with surfactants, ligands, bioactive cargos and proper polymer-coating to overcome biological barriers and polymer cytotoxicity for their specific targeting to diseased cells to get translational more efficient nanomedicines.

Disclosure statement

No potential conflict of interest was reported by the author.

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