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Anti-melanotransferrin and apolipoprotein E on doxorubicin-loaded cationic solid lipid nanoparticles for pharmacotherapy of glioblastoma multiforme

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ABSTRACT

Cationic solid lipid nanoparticles (CSLNs) with surface anti-melanotransferrin (AMT) and apolipoprotein E (ApoE) were used to carry antimitotic doxorubicin (Dox) across the blood–brain barrier (BBB) for glioblastoma multiforme (GBM) treatment. Dox-loaded CSLNs (Dox-CSLNs) were prepared in microemulsion, grafted covalently with AMT and ApoE, and applied to human brain-microvascular endothelial cells (HBMECs), human astrocytes, and U87MG cells. An increase in the weight percentage of stearylamine (SA) and a decrease in the stirring rate enhanced the particle size and the absolute value of the zeta potential of AMT-ApoE-Dox-CSLNs. In addition, the encapsulation efficiency of Dox in CSLNs decreased with increases in the weight percentage of Dox and the order in the encapsulation efficiency of Dox was 10% SA > 20% SA > 0% SA. However, the reverse order was true for the release rate of Dox, suggesting that AMT-ApoE-Dox-CSLNs containing 10% SA had better characteristics of sustained release. Moreover, AMT-ApoE-Dox-CSLNs fabricated at 10 μg/mL of ApoE could slightly reduce the transendothelial electrical resistance and increase the permeability of propidium iodide. AMT-ApoE-Dox-CSLNs did not induce serious cytotoxicity to HBMECs, and AMT-ApoE-Dox-CSLNs fabricated at 10 μg/mL of AMT and at 5–10 μg/mL of ApoE could significantly enhance the permeability of Dox across the BBB. The order in the efficacy of inhibiting U87MG cells was AMT-ApoE-Dox-CSLNs > AMT-Dox-CSLNs > Dox-CSLNs > Dox. Hence, AMT-ApoE-Dox-CSLNs have appropriate physicochemical properties and can be a potential colloidal delivery system for brain tumor chemotherapy.

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Abbreviations

AMT	anti-melanotransferrin
AMT-Dox-CSLN	doxorubicin-loaded cationic solid lipid nanoparticle with surface anti-melanotransferrin
ApoE	apolipoprotein E
ApoE-AMT-Dox-CSLN	doxorubicin-loaded cationic solid lipid nanoparticle with surface apolipoprotein E and anti-melanotransferrin
ApoE-Dox-CSLN	doxorubicin-loaded cationic solid lipid nanoparticle with surface apolipoprotein E
BBB	blood–brain barrier
CNS	central nervous system
CSLN	cationic solid lipid nanoparticle
Dox	doxorubicin
Dox-CSLN	doxorubicin-loaded cationic solid lipid nanoparticle
HA	human astrocyte
HBMEC	human brain-microvascular endothelial cell
HBMEC/HA	HBMECs regulated by HAs
MT	melanotransferrin
PI	propidium iodide
SA	stearylamine
TEER	transendothelial electrical resistance

1. Introduction

Solid neoplasm in the central nervous system (CNS) has been commonly classified into two types, primary and metastatic tumor, according to its original occurrence tissue site [1]. Recent epidemiological statistics reported that the incidence rate of primary neoplasm in the CNS increased gradually and the incidence rate of glioma was about 33–45% [2,3]. Among glioma, glioblastoma multiforme (GBM) is the most malignant cancer with very high fatalities [4]. With regard to the lethal cause of GBM, the early stage

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Nomenclature

C_{AMT}	concentration of AMT for grafting on Dox-CSLNs (μg/mL)
C_{ApoE}	concentration of ApoE for grafting on AMT-Dox-CSLNs (μg/mL)
D	average diameter of AMT-ApoE-Dox-CSLNs (nm)
E_{AMT}	grafting efficiency of AMT on Dox-CSLNs (%)
E_{ApoE}	grafting efficiency of ApoE on AMT-Dox-CSLNs (%)
E_{Dox}	encapsulation efficiency of doxorubicin in CSLNs (%)
P_{Dox}	weight percentage of doxorubicin in Dox-CSLNs (%)
$P_{Dox,BBB}$	permeability of doxorubicin across the BBB after treating with AMT-ApoE-Dox-CSLNs (cm/s)
$P_{PI,BBB}$	permeability of PI across the BBB after treating with AMT-ApoE-Dox-CSLNs (cm/s)
P_{SA}	weight percentage of stearylamine in Dox-CSLNs (%)
$P_{V,H}$	viability of HBMECs after treating with AMT-ApoE-Dox-CSLNs (%)
$P_{V,U}$	viability of U87MG cells after treating with AMT-ApoE-Dox-CSLNs (%)
R_{Dox}	cumulative percentage of doxorubicin released from AMT-ApoE-Dox-CSLNs (%)
t	time for releasing doxorubicin from AMT-ApoE-Dox-CSLNs (h)
ω	stirring rate during preparing Dox-CSLNs (rpm)
ζ	zeta potential of AMT-ApoE-Dox-CSLNs (mV)

detection of GBM in clinical practice is difficult, and also phenotypic GBM has an intrinsic nature of strong tissue aggression with poor prognosis and high recurrence [5]. Thus, a salvage pharmacotherapy and/or adjuvant medication is a critical challenge in GBM management. In traditional chemotherapy for brain carcinoma, the obstruction of the blood–brain barrier (BBB) could significantly reduce the efficiency of antitumor drug [6]. To enhance the permeability of therapeutic agent across the BBB, applying bioactive molecules with targeting ability can be a useful strategy.

Melanotransferrin (MT), a homologue of transferrin, can be an important membrane-anchored syaloglycoprotein for permeating the BBB [7]. MT has a molecular weight of 95–97 kD and was first found in human melanoma cells [8,9]. Therefore, MT was named melanoma-associated antigen p97 and was localized on membrane by the linkage of glycosylphosphatidylinositol [10]. It was intriguing that MT could be independent of transferrin in transport and metabolism of iron [11,12]. A truncated form of membrane MT also exhibited an antineoplastic ability to retard glioblastoma growth through inhibition of angiogenesis [13]. In addition, low density lipoprotein (LDL) receptor played an essential role in facilitating penetration across the BBB and apolipoprotein E (ApoE) could conjugate LDL receptor and protect drugs from lysozyme decomposition [14,15]. Moreover, lipoproteins containing ApoE could be an essential pathway in transporting cholesterol into the CNS [16,17]. Hence, an incorporation of anti-MT (AMT) and ApoE in pharmaceutical formulation can be feasible for delivering drug to the brain and treating GBM.

Charged colloids are commonly encountered drug carriers in pharmaceutics and can have interesting interactions with cells in biomedical application [18,19]. Solid lipid nanoparticles (SLNs), for instance, are a potent colloidal delivery system for entrapping drugs and genes due to their good biocompatibility [20,21]. In a suspension, the surface charge of particles is primarily acquired from dissociation of ionogenic species and/or absorption of surrounding potential determining ions [22]. By attracting counterions and repelling coions, diffuse layers next to the charged colloids (electrical double layers around interfaces) are established in the medium [23]. In SLNs, solidified lipids, ionic and/or nonionic surfactants, and co-surfactants were the major components of the colloids [24,25]. Hence, in particle fabrication, the emulsified concentration of surfactants could affect specific surface area and surface tension of SLNs. The characteristics of lipids, including hydrophobicity and chain length, could also alter the particle size, shape, charge, drug encapsulation, and drug release [26,27]. In addition to the chemical ingredients, a physical operation condition such as stirring rate might modify the physicochemical nature of SLNs [28]. Cationic SLNs (CSLNs) are emerging biocolloids, having unique electrical properties in colloidal science and biotechnology. For example, a gene therapy related to cell receptor binding revealed that a strong attraction occurred between biotinylated ligands and a charge-stabilized preparation of CSLNs, DNA, and streptavidin [29]. Moreover, CSLNs containing cetylpalmitate could have an effective gene loading capacity and gene transfection efficiency [30]. An encapsulation of antipsychotic clozapine and antiviral saquinavir in CSLNs also enhanced the bioavailability and brain distribution of the two drugs [31,32]. These studies suggested that CSLNs can be proper biomaterials to formulate lipophilic doxorubicin (Dox), a typical reagent used to treat carcinoma, and to control its delivery.

The aim of this study was to prepare Dox-loaded CSLNs (Dox-CSLNs) with surface AMT and ApoE (AMT-ApoE-Dox-CSLNs) for GBM pharmacotherapy. The complex components of AMT-ApoE-Dox-CSLNs, including positive surface charge, AMT, and ApoE, may be functional in interaction with cells. In addition, the release of Dox from internal lipids of AMT-ApoE-Dox-CSLNs can be crucial and needs to be regulated because an abrupt change of dissolution rate may induce a strong cytotoxic effect of Dox. We investigated the distribution of average particle diameter, zeta potential, morphology, encapsulation of Dox, grafting of AMT and ApoE, release of Dox from AMT-ApoE-Dox-CSLNs, integrity of tight junction, permeability of Dox across the BBB, toxicity to the BBB cells, and inhibitory efficacy against the growth of GBM cells.

2. Materials and methods

2.1. Materials

Beeswax (BW), cholesteryl hemisuccinate, D-mannitol, Dox hydrochloride (D1515), Dulbecco's phosphate buffered saline (DPBS), ethylenediaminetetraacetic acid (EDTA), palmitic acid (PA; hexadecanoic acid), phosphotungstic acid (PTA), sodium azide, sodium taurocholate, Tween 80 (polysorbate 80), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC), QuantiPro bicinchoninic acid (BCA) assay kit, gelatin, propidium iodide (PI), formalin, and 4′,6-diamidino-2-phenylindole (DAPI) were purchased from Sigma-Aldrich (St. Louis, MO). Stearylamine (SA) was obtained from Fluka (Buchs, Switzerland). Ethanol was purchased from Tedia (Fairfield, OH). Tris hydroxymethyl aminomethane (tris) was obtained from Riedel-de Haen (Seelze, Germany). 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-N-[carboxy(polyethylene glycol)-2000] (DSPE-PEG(2000)-CA) was purchased from Avanti Polar Lipid (Alabaster, AL). *N*-hydroxysuccinimide (NHS) and Triton-X-100 were obtained from Acros (Morris, NJ). AMT was purchased from Santa Cruz Biotechnology (Dallas, TA). $ApoE_{131-169}$ was obtained from AnaSpec (Fremont, CA). Sodium bicarbonate was purchased from J. T. Baker (Phillipsburg, NJ). Regenerated cellulose membrane was obtained from Spectrum Laboratories (Rancho Dominguez, CA). Acetonitrile was purchased from BDH (Poole, UK). Ultrapure water was obtained from Barnstead (Dubuque, IA). Filter paper was purchased from Toyo Roshi Kaisha (Tokyo, Japan). Dimethyl sulfoxide (DMSO) was obtained from J. T. Baker (Phillipsburg, NJ). Human brain-microvascular endothelial cells (HBMECs) were purchased from Biocompare (South San Francisco, CA). Human astrocytes (HAs) were obtained from Sciencell (Corte Del Cedro Carlsbad,

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