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REVIEW ARTICLE

Designing bilayer lipid encapsulated mesoporous Silica nanostructures: Review on structural and functional features of protocell

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Abstract

The word "protocell" refers to lipid bilayer-coated mesoporous silica nanoparticles (LB-MSNs) which have recently come to light as a new-generation cargo transport vehicle that combines the special features of both organic and inorganic components. LB-MSN can regulate biodistribution effectively due to the presence of bilayer encapsulation while high payload capacity was due to the presence of porous nature of silica core. The MSN can be fine-tuned to generate various sizes, shapes, and surfaces while multiple cargos can be easily encapsulated with physical interaction. The bilayer coating avoids the premature release of chemotherapeutics and enhances biocompatibility. The biofunctionalization of protocells provides high colloidal stability and extends surfaces for further modification. The inorganic core can accommodate and surface-engineered multiple classes of biorelevant surface tags for active targeting. The site-specific or organ-specific delivery enhances the reliability of the material while the engineered surfaces could pave a way forward in treating various diseases. The multifaceted review highlights the potential use of bilayer encapsulated MSN for therapeutic delivery and management of multiple diseases.

Keywords: *Lipid Bilayer Coating; Mesoporous Silica; Protobiont; Protocell; Surface Engineering; Surface Interaction.*

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INTRODUCTION

Nanotechnology is quickly emerging and radically altering drug delivery systems. Nanoparticles are excellent for combating life-threatening diseases because of their smaller dimensions, specific physicochemical attributes, high surface areas, and versatility. Surface engineering of the nanoparticulate system also improves the characteristics and therapeutic outcome. The prominent examination in surface engineering was Polyethylene glycol grafting (PEGylation) makes them multifunctional toward site targetability. The PEGylation improves the transport characteristics across the cellular barriers and avoids reticuloendothelial uptake [1].

Designing a nanocarrier for the prompt delivery of cargo has its limitation and challenges. The challenges start from the selection of material or precursor to stabilization in an aqueous environment with multiple setbacks observed during a clinical stage. The liposome-based nanocarriers have set an example to cross all the barriers and approved for drug

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delivery applications. Considering the poorly fabricated "Universal" liposomal nanocarrier may not be promoted for challenging fields like pharmaceuticals [2].

Despite their benefits, Mesoporous Silica Nanoparticles (MSNs) practical implementation has been hampered by several problems, including the possibility of toxicity from interactions between silanol groups on MSNs surface and healthy cells, as well as premature drug leakage from uncoated surfaces [3]. The MSNs have emerged as promising drug delivery carriers due to their large surface area (>1000 m^2/g), large pore volume (2–50 nm), tunable pore size, etc. The MSNs can be easily modifiable and their surface properties render them appropriate transporters for a variety of therapeutics [4].

MSNs particle size can be adjusted between 30 and 500 nanometers using precise synthesis methods, which allows effortless endocytosis by live organisms in the absence of cytotoxicity. Using different soft templates, the pore size may be regulated between 2 to 8 nm, and the pore structure could be 2-dimensional (2D) cylindrical structure or an interconnected structure. The presence of large interior and external surfaces on the MSN can be altered and functionalized with various moieties. The low toxicity potential of MSN distinguishes it from many other inorganic nanomaterials*. In vitro* research on healthy and malignant cell lines revealed the indication of low or no toxicity [5]. The MSN has been widely explored for biomedical applications, namely controlled drug/gene delivery, cell tracking, tumor targeting, photodynamic therapy biosensing, bioimaging, etc [6,7].

The functionalization of MSN using polymer encapsulates or suitable biomolecule coating possibly increases biocompatibility and enhances interaction at the bio-interface. The functionalization accelerates the active targeting mechanisms by coating using bioactive [8]. The functionalization prevents the premature drug release in an aqueous environment by enabling resistive polymer coat on the open pore structure of MSN. The polymer on the surface of MSN avoids direct diffusion of solvent molecules and extends the release rate of drug. The coating on the surface of mesoporous structure avoids direct exposure of actives and helps to improve the stability. The encapsulation can be processed either using natural or synthetic polymers or in combination with layer-by-layer techniques. Additionally, semisynthetic or synthetic rotaxane, metal oxides, or lipid bilayers were used as a capping agent for encapsulation on the surface of MSN. The encapsulation enhances stability, solubility, bioavailability, biodistribution, etc [9,10].

Lipids or phospholipids derivatives are one of the most frequently used polymers in drug delivery applications. The lipid structure contains hydrophilic and hydrophobic regions with tunable surface characteristics and prominent interaction with surfaces. Surface silanol groups of MSN interact with phospholipid membranes and forms strong bond. The encapsulates being protect in harsh environment. While lipids are haemocompatible in nature improved blood circulation time of designed protocell based nanocarrier [4]. Bilayer encapsulation containing lipids provides flexibility to MSN and improves stability, strength in exterior environment. The bilayer lipid encapsulated structures seems similar to cellular structure due to presence of bilayer lipids. The hydrophobic and hydrophilic ends of lipids forms structure similar to cell membrane while inner core containing MSN, has been appeared like nucleus. The fabricated structure looks like prototype cellular structure where MSN acts as a nucleus with loaded active while bilayer lipid encapsulates form a cell wall-like appearance. Surface tunning can be possible by combining trafficking or targeting ligands on the surface. In addition to targeting modalities, the surface-grafted polymers also enhance its biocompatibility and takes control over release of drug from the internal core.

The lipid bilayer encapsulates either promotes Van der Waals forces of attraction or stearic interaction at the interface. The lipid bilayer encapsulation provides an integrated drug delivery carrier with multifaceted modification within a single component system. Lipid bilayer encapsulation improvises the characteristics and properties of carrier than uncoated component. A supportive skeleton may act as a loading compartment for two or more drugs. The gatekeeper activity of lipid encapsulates, restricts the direct release of the drug, and avoids interaction with non-targeted components. The gatekeeper molecules also secure the elimination of MSN via endocytosis [11]. The protocell is newer advancement in the liposomal drug delivery system. The protocells show successful attempts

Table 1. Recent advancements in site-specific active delivery of actives using protocell.

Silica particle framework	Payload	Targeting Ligands	Application	Reference
Lipid PAA coated spherical MSN	Dual pH responsive co-delivery of Arsenic and Paclitaxel	F56	Tumor targeting for breast cancer cells.	[14]
Lipid Bilayer coated MCM-41	Berberine	Lactoferrin	Improved inhibition of acetylcholine and amyloid formation.	[28]
Lipid Bilayer coated spherical MSN	Co-delivery diacid metabolite of norcantharidin and ABT-737	Folic acid	Hepatic carcinoma	[29]
PEGylated lipid Bilayer coated MSN	Co-loading of Paclitaxel and Tanshinone II A	Folic acid	Acute promyelocytic leukemia.	[30]
Lipid coated porous MSN	Doxorubicin	None	Enhance efficacy and drug delivery of cancer therapy.	[31]
Lipid Bilayer coated porous MSN	Colistin	LL-37	Targeted delivery of antibiotic therapy to pseudomonas aeruginosa.	[32]
Lipid Bilayer coated MSN	Atorvastatin	None	Enhance the therapeutic efficacy of kidney injury.	[33]
Lipid Bilayer coated small pore MSN	Co-delivery of Levodopa and Curcumin.	Lactoferrin	Used for brain targeting to improve the efficacy of Parkinson's disease.	[34]
Monosized lipid Bilayer coated MSN	CRISPR Ribonucleoprotein	None	Release efficiency in cancer cells and mouse brain by in vitro and in vivo gene editing.	[35]
Core-shell structured lipid bilayer coated MSN	Paclitaxel	Angiopep-2	Glioma treatment.	[36]
Lipid bilayer coated hollow MSN	Glabridin	Polyarginine R8-6 histidine tag	Anti-pigmentation	[37]

not only in drug delivery but also in biosensing, enzyme protection, etc [10]. The protocell was advantageous over liposomes with multiple factors and produces stable colloidal aggregates compared to a liposomal carrier [9, 12]. The bilayer encapsulation not only increases release characteristics but also improvises the efficacy of the therapeutic agent. The use of protocell and bare MSN has improved the 10000-fold conjugation and affinity towards hepatocellular carcinoma [13]. The advancement increases the delivery characteristics of siRNA with 100 fold increase in loading capacity [14]. The membrane fluidity and rigidity can be tuned based on the composition of lipid bilayer encapsulates. The zwitterionic surface charges easy to invade the cellular barrier and permeated across the membrane [15]. The protocell-based active targeting ligands with the MSN framework were highlighted in Table 1.

STRUCTURAL FEATURES AND COMPOSITION OF PROTOCELL

Protobiont is an alternative to protocell used in recent times to highlight the self-organized, spherical aggregated containing lipid bilayer MSN. The protocell has combined features of liposomes

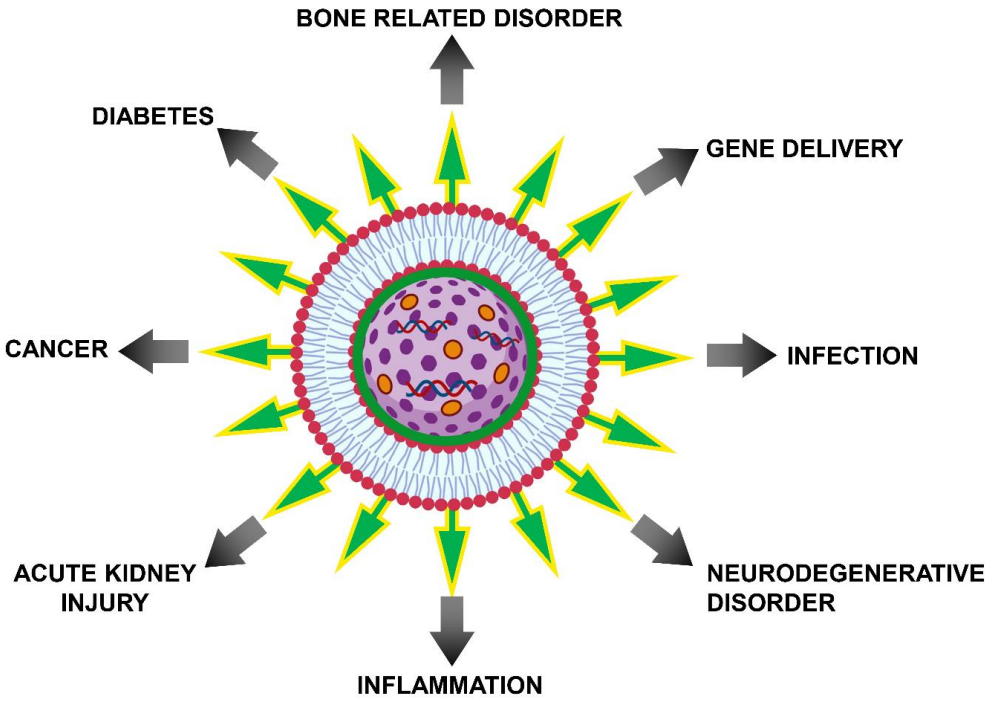

Fig. 1. Lipid Bilayer coated mesoporous silica nanoparticles have been used to treat a variety of biological problems.

and MSN considered to be ideal candidates for drug delivery applications [16]. Protocell nanocarrier could be helpful for delivery of therapeutics in alleviate life-threatening diseases like cancer, neurological disorders, etc. In life threatening diseases like cancer, therapeutic agent has less specificity and protocell based nanocarrier can effectively delivers at the specified site. Protocell effectively delivers a highly toxic drug to a selected target site without affecting normal cells. The hybrid system was able to enhance aqueous solubility along with permeability across the membrane. While strongest cellular barriers can be easily permeated to deliver the therapeutic agent [5]. For the fabrication of protocells natural or synthetic lipids are used as encapsulating polymer over MSN surface. The precursors like soya lecithin or cholesterol promotes flexibility in protocell nanocarrier and was required in very small quantities. Natural phospholipids have certain limitations which prone to oxidation and reduced stability. The use of surfactant components may improve the stability characteristics of natural phospholipids. Semisynthetic or synthetic phospholipids have modulated features and are potentially protected from environmental effects. The crucial part in designing protocell is processing temperature and method adopted for processing. The appropriate mean temperature can augment crystalline characteristics to lipid molecules and acquire desirable spherical shape associated with MSN. Fig. 1 represents the composition of protocell consisting of MSN core and lipid bilayer structure.

FUNCTIONAL CHARACTERISTICS OF PROTOCELL

The Protocell flexible design and synergistic qualities confer a unique set of properties that can be separately created or tweaked for specific uses. The protocell is nothing but the fusion between bilayer liposome and MSN which protects the drug release into a non-targeted environment. The synergistic combination of material with the interaction between bilayer lipid and mesoporous structure results to provide lateral bilayer fluidity [17]. Synergistic combination purports biophysical features for effective release and targeting. The bilayer coating minimizes nonspecific binding and enhances endosomal escape which retains the formulation in circulation. The protocell can be combined with imaging components that promote theranostic carrier properties. The protocells are multifunctional and can able to load therapeutic agents and imaging agents along with targeting moieties like peptides, proteins, antibodies,

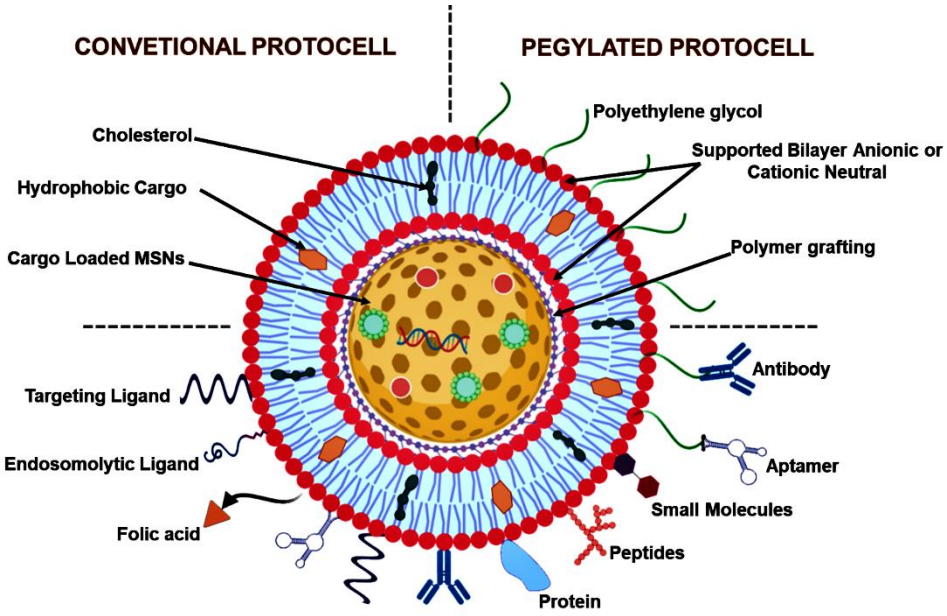

Fig. 2. The multifaceted function of protocell.

etc. as represented in Fig. 2. The mesoporous structure controls the release of drugs from the inner compartment with advancement in the release supported by a bilayer lipid structure.

SYNTHESIS OF MSNS (AN INNER CORE – STEP 1)

Mesoporous Silica (MSN) is a basic component of protocells and is considered the heart of protocells. Understanding the synthesis of core components like MSN is important as navigating the important function of the protocell. For the synthesis of MSN, templating agent, surfactant, the concentration of silica precursor, reaction temperature, pH and polycondensation time, etc. needs to understand and verify specifically to get the desirable properties of MSN [18]. Based on the type of precursor selected, the method and mechanism of the formation of MSN may vary. Previously for the synthesis of MSN, the Stober method was the most frequent and preferred method of choice used for the synthesis which involves hydrolysis and subsequent condensation of silane precursor [19]. Many advanced techniques are available in the laboratory as well as on commercial scale provides a uniform synthesis of MSN which including sol-gel, hydrothermal, green method, co-precipitation, vapor deposition, etc. The generalized mechanism of the formation of mesoporous structure is highlighted in Fig. 3.

Loading of Cargo (Step 2 for protocell design)

Loading cargo is the most difficult step in designing a drug delivery carrier. Factors like surface area, pore size, pore diameter, the molecular structure of cargo, interaction at the interface, presence of moisture, etc. can affect the drug loading characteristics. The presence of surface graft could load additional drugs via surface chemistry. The nano entity permeates across the cellular barrier depending on diameter as well as surface characteristics. Possibly two or more therapeutic agents can be loaded on MSN one inside the pore and the second on the surface-grafted MSN. The grafting techniques utilize, coupling agents, polymers, lipids, crosslinkers, etc. for loading of multiple drugs. The interaction between the surface group of MSN and the drug may be non-covalent. The drug possibly adsorbs on the surface of MSN via the osmotic gradient method or passive diffusion in a saturated solution. The mesoporous structure has limited loading volume around 8 – 24% of the chemotherapeutic drug can be loaded. The loading volume can be increased by chemical surface modification techniques. Post sorption

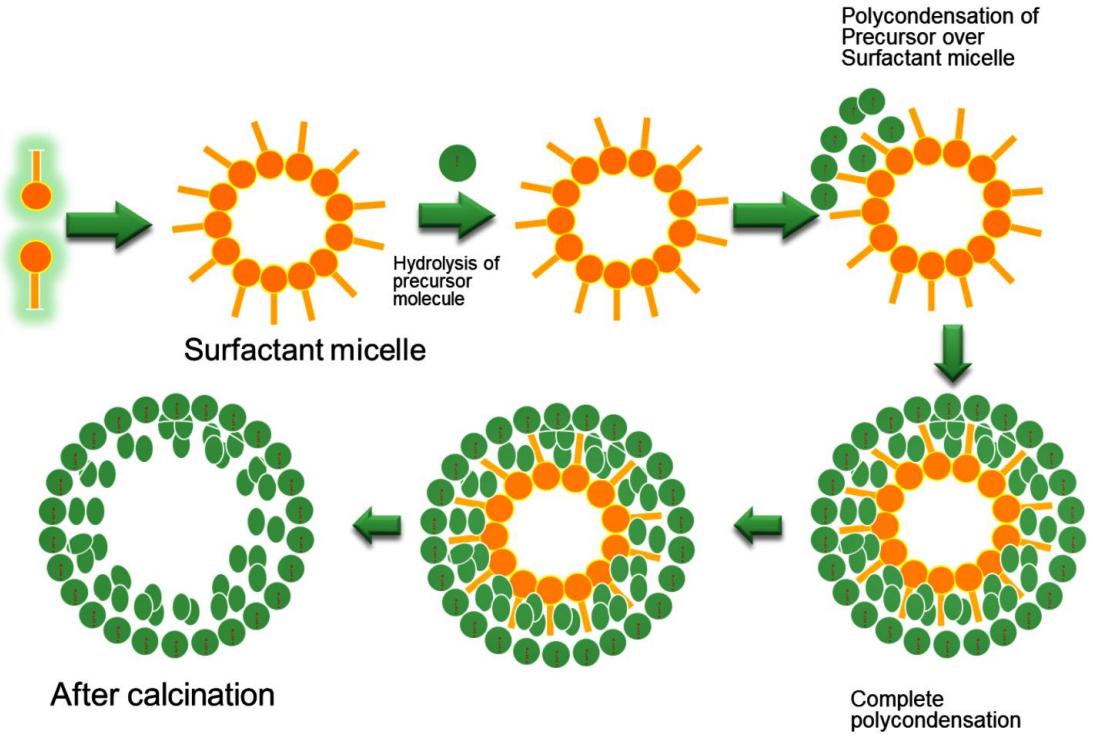

Fig. 3. Mechanism of mesoporous structure formation.

method build hydrophilic or ionic interaction with the loading substrate. The post-sorption allows the adsorption of molecules on the surface of the carrier particle. The loading conditions can be accelerated by the use of ultrasonication, pulse mode sonication, microwave, heating, stirring, etc. with further drying or recovery of the product via high-speed centrifugation or filtration [20].

LIPID ENCAPSULATION AND SURFACE MODIFICATION STRATEGIES

Lipid Bilayer Encapsulation/Coating (LBE)

Lipid bilayer encapsulates (LBE) form bilayer structures on solid supports like silicon, silica, alumina, or mica has strong interaction between phospholipids and solid supports. The fusing mechanisms build a strong structure between MSN and LBE. The interaction between LBE and solid substrate can be estimated using adsorption theories like Langmuir – Blodgett or Langmuir Schaeffer approaches. The solids substrate allows dispersing in the lipids for the creation of a Langmuir monolayer. The lipids act as subphases and start depositing on the solid substrate in the monolayer form. The formation of the Langmuir monolayer structure suggests the subphase can be formed on the surface of a water/buffer medium and simulated with a biological interface. A few factors influence the interaction between solids substrate and LBE, compositions, temperature, subphase, surface charge, etc. [21].

Association between LBE and solid support

The lipids specifically selected to desirably form colloidal aggregates like liposomes and resembles to spherical structure having solid core act as support. Outer shell of protocell resembles the structural integrity similar to the liposomal structure. The liposome consists of two or more combination of phospholipid structures that forms a spherical aggregate [8, 21].

The fusion method forms a spherical encapsulation on the surface of the mesoporous structure after being exposed to hydrated conditions. The sizes of protocells can be segregated to get the desired effect via the extrusion process [22]. The exchange between the organic solvent and buffer media perpetrates the transition of surface interaction and the formation of hydrogen bonds in presence of water. The presence of buffer converts them to lipids bilayer structure and forms a protocell [23].

The tuning with the use of two or more phospholipids provides the grafting of a wide range of biomolecules on the surfaces. In the most cases, zwitterionic lipids are preferably used which promotes stability and interaction with solids substrate [24, 25]. The selection of the appropriate type of lipids for designing LBE is considered to be the most crucial part of the preparation of protocells. Mostly, the selection criteria of lipids were based on melting transition temperature. The selection of the appropriate type of lipids may be decided based on transportation, permeation, distribution, fluidity, stability, diffusivity, etc, and factors required for the permeation across the biological membrane [13]. The melting temperature of saturated (DSPC) and unsaturated lipids (DOPC) are far more located at two extreme points like 55 °C and -17 °C respectively. The combination of two extreme temperature points may be considered as good combination in selecting lipids for bilayer coating. Lipids at some extent provide good stability and strength to the bilayer lipids structure. High-temperature lipids provide strength and stability which reduces leakage of the encapsulated component. The limitations associated with high-temperature lipids are difficulty to conjugate with external ligands and reduced multivalent interaction. While low-temperature lipids promote interaction at cell surfaces and promote binding with the targeted cell component. The second parameter considered for LBE was a surface charge. The surface interaction influences the binding or fusing ability with inorganic surfaces. Additionally, the surface charge of lipids plays a major role during an interaction at the site of activity or cell/tissue surfaces [22]. Additionally, combination containing lipids and other components unveil characteristics like fluidity, membrane flexibility, stability during circulation, etc. While specialized surface groups like carboxyl, amine, hydroxyl, etc. provides unique features to the designed bilayer component. Ethanolamine lipids are more specifically designed for targeting purposes [16, 26].

Surface Modification of Protocell

Surface modification or surface tuning converts ordinary protocells into functional or interactive protocell structures. The presence of extended surface groups of LBE is responsible for surface interaction with external ligands. The ligand was selected based on the type of delivery system available. The first prompt change observed was the interconversion of a hydrophilic to a hydrophobic surface or vice versa. Based on the type of targeting site the interchange can be promoted to get the desired therapeutic effect. The modification provides alteration in surface charge or possibly converted to a layer-by-layer structure. Surface alteration contributes to improving biocompatibility, bio interaction, and cell adhesion characteristics. Various ligands can be loaded on the surface like magnetic nanoparticles, fluorescent dyes, quantum dots, etc. to enhance the targetability along with image-guided drug delivery [27]. Conjugation with suitable polymers like natural (e.g., dextran, alginate, and chitosan) or synthetic (e.g., poly (ethylene glycol) (PEG), poly (vinyl alcohol) (PVA), and poly (vinyl pyrrolidone) (PVP)), etc. were considered promptly

CONCLUSION AND FUTURE SCOPE

In recent years, nanotechnology-based advancements have provided the most advanced form of medication delivery systems. The protocell is a cutting-edge nanotech invention for the treatment of a variety of ailments. The necessity of encapsulating aids in improving the flexibility of synthesized MSN for multi-component distribution. The customizable properties of protocells allow for a variety of disease-targeting strategies. Protocell-based nanoparticles can successfully treat life-threatening disorders such as cancer, Parkinson's disease, and Alzheimer's disease. The protocell not just to transports the chemotherapeutic agent to the target location, but also transports nucleic acid, DNA, or a biological element. In the future, surface features may be used to investigate protocell utilization in theranostics applications. It may be conceivable to use the stimuli-responsive release in conjunction with self-invasion to kill viruses or cancer cells. In the future, multimodal therapeutic approaches may be improved with additional support in vaccine preparation. The protocell could be considered as more effective for gene transfection, delivery of nucleic acid, biological materials as well as targeted drug delivery applications.

CONFLICTS OF INTEREST

The authors do not have any conflicts of interest.

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