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RESEARCH ARTICLE

CERASOMES AS NANO DELIVERY SYSTEM IN COMBATING VARIOUS DISEASES

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ABSTRACT

The conventional liposomal and inorganic nanoparticles suffer from their deficient morphological stability or biocompatibility issues in the physiological environment as theranostic nanoplatforms for the preclinical and clinical applications against various diseases. To overcome the obstacles concerned with bioavailability, biocompatibility, toxicity, insolubility, biological barriers, and other therapeutic adverse effects, nanohybride liposomal cerasomes as nano delivery systems (partially ceramic or silica -coated liposomes) have attracted attention to combat several diseases such as cancer, metabolic and other related disorders. The existence of polyorganosiloxane networks on the surfaces and the incorporation of liposomal bilayer structures into cerasomes boost their morphological stability as well as biocompatibility with similar liposomal or silica nanosizes. These highly stable nanosystems may integrate / encapsulate different cargos with / without ligands and / or polymeric coating as easy surface functionalization to get higher therapeutic efficiencies with controlled cargo-liberation to the targeted site/s and minimal side effects against diseases. This review elucidates chiefly the preparation, functionalization, and biomedical applications of cerasomes as nano delivery system against various diseases.

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INTRODUCTION

Many people suffer from various physiological disorders / diseases such as acne, diabetes mellitus, cancer and other related disorders (e.g. hyper amino acidemia, hyper lipidemia, heart attack, infection, myelo-suppression, neutropenia, inflammation and tumor) exposed by toxicants, infectious agents or transplants accompanied with more aggravation of the disease-state globally owing to the growth of drug-resistance and cytotoxicity (Siam *et al*., 2024; Byard, 2023; Chen *et al*., 2025). The conventional chemotherapy exists non-specificity, insolubility, biological barriers, and creates toxic side effects to the treated patients (Schirrmacher, 2018; Was *et al*., 2022). To overcome the obstacles, nanotechnology-grounded theranostic perspectives have attracted enormous attention to treat the pathological disorders (Malik *et al*., 2023; Xue *et al*., 2021; Mandal, 2023). Though liposomal drug delivery vehicles with or without coated polyethylene glycol (PEG) have gained interest for their targeted sustained liberation of drugs and diagnostic contents with favorable biocompatibility, solubility, non-toxicity, very low / non - antigenicity and immunogenicity, and pleasant elimination kinetics, the liposomes still possess instability owing to hydrolysis of ester bonds and / or oxidation of unsaturated acyl chains of lipids, cargo-drainage from vesicles and / or accumulation / amalgamation of vesicles, lysis by lipases in biological system, and skin-toxicity such as skin eruption/ulcer (erythrodysesthesia) known as Hand-Foot syndrome led by PEGylated phospholipids (Chelliah *et al*., 2025; Yadav *et al*., 2011).

To achieve higher easy functionalization, physicochemical stability and half-life in blood circulation, and to load amphiphilic, hydrophilic and hydrophobic cargos, the hybrid organic-inorganic biomaterial systems such as cerasomes have gained attraction as cerasomes developed via sol-gel reactions and self-assemblies of lipid- alkoxy-organo silane to form liposomal bilayer structures coated with atomic layers of inorganic poly-organo-siloxane networks with cargos through silane-coupler chemistry to get higher theranostic efficacy with sustained cargo-release through biochemical degradation of the Si-C bonds / lipids via pore formation in the siloxane networks (Pathak *et al*., 2024). The present review denotes mainly the preparation, functionalization, characterization and biomedical applications of cerasomes to judge them as theranostic nano drug delivery systems against diseases.

Synthesis of cerasome-forming lipids:

The common cerasome-forming lipids (CFLs) possessing both organic and inorganic parts conjugated to each other in the molecules are synthesized in various ways:

- Synthesis via the simple condensation reactions by utilizing three molecular units such as succinic anhydride, dihexadecylamine and 3-aminopropyltriethoxylsilane (Katagiri *et al*., 2007).
- Synthesis via one-step condensation of dihexadecylamine and 3-triethoxysilyl-propylisocyanate to obtain a simple molecular structure with one urea group (Li *et al*., 2017).

- Synthesis of one amide group in connector unit through hydrosilylation of triethoxysilane and N,N-dihexadecyl-3-buten-amide, and condensation of dihexadecylamine and 3-butenoic acid (Li *et al*., 2017).These three synthesized lipids are water-insoluble. Therefore, the triethoxysilyl head groups should be hydrolyzed for forming amphiphilic molecules before further self-assemblies.
- Synthesis of cationic CFLs with analogous structures to the typical peptide-lipids.
- Synthesis of CFL with two triethoxysilyl head groups for regulating the density of siloxane framework on the surface of cerasomes.
- Synthesis of CFL based on phospholipids with extra triethoxysilyl head groups for the preparation of biodegradable cerasomes.

Preparation of cerasomes: Mainly three typical methods such as ultrasonic dispersions, ethanol sol injections, and thin film hydrations are followed to prepare cerasomes (Li *et al*., 2017; Katagiri *et al*., 1999; Katagiri *et al*., 2003; Jin *et al*., 2012; Zhang *et al*., 2014).

Ultrasonic dispersion method: In brief, the CFLs and hydrochloric acid solution with a moderate (appropriate) acidic pH are mixed and vortexed until turbid dispersion is obtained indicating the formation of multi-lamellar vesicles (MLVs). To get smaller nanoparticles (NPs) with clear dispersion from turbid, MLVs are sonicated with a probe-type sonicator. The stable cerasome-suspension is acquired after incubation of the transparent solution at room temperature (RT) overnight, while the pH conditions take a pivotal role to form cerasomes (Katagiri *et al*., 2003). As this method is applicable for hydrophobic CFLs, cerasomes may also be formed from amphiphilic CFLs directly via this dispersion process without hydrolysis (Li *et al*., 2017).

Ethanol sol injection method: Briefly, the CFLs are incubated in acidic ethanol solution for an appropriate time for promoting lipids-hydrolysis. The obtained solution is gently injected into deionized water with an appropriate pH, and followed by ultrasound for a period of time. The prepared cerasomes are stored at RT for further 24 h to form siloxane network. The ethanol sol injection process has the advantage to fabricate cerasomes in a wide pH range, as the hydrolysis and the subsequent self-assembling processes proceed independently (Li *et al*., 2017).

Thin film hydration method: In brief, CFLs are incubated with acidic ethanol solution at pH 3.0 overnight at RT, followed by dissolution in chloroform. A thin lipid film is obtained by the removal of organic solvent in a rotary evaporator. The obtained lipid film is further dried in a vacuum oven for overnight to remove the solvent completely. The dried lipid film is hydrated in deionized water, mixed with vortex for a period of time for forming MLVs. The vesicular dispersion is further ultrasonicated by a probe-type sonicator to form cerasomes with smaller sizes (Jin *et al*., 2012).

Preparation of drug-loaded cerasomes: Liposomal cerasomes are prepared by the modified thin film hydration techniques utilizing two different approaches (Sarychev *et al*., 2017; Zhang, 2017). In brief, for the 1st approach, cerasome-forming lipoamino acids (CFLA) or CFLA and disintegrating dipalmitoyl phosphatidyl choline (DPPC) lipid mixtures are dissolved in chloroform, followed by removal of organic fraction by vaporization. The thin film obtained, is hydrolyzed with acetic acid solution (5% v/v in deionized water) adjusting to pH 3.0 and stirring at 35°C for 1 h followed by sonication (ultrasonic bath) of the cerasome-dispersion. In accordance with the 2nd approach, CFLA or CFLA and DPPC admixtures are dissipated in 3 mL of hydrochloric acid solution (10% v/v of acid in ethyl alcohol). The dispersal is stirred at 35°C for 1 h followed by the addition of chloroform (1.5 mL). The mixture is then vaporized to avail a thin film followed by lyophilization for 6 h. The dried thin film is moisturized with a doxorubicin (DOX) solution (40% w/v) in PBS (pH 7.4). The sonicated cerasomes (45°C, 30 min) are traversed through an extruder (400 nm pore size). The excess drug is discarded by a dialysis, where 2 mL of the cerasome-suspension (2 mg/mL of CFLA) are placed in a dialysis bag (cut off 12 kDa) to transfer to 25 mL of PBS (pH 7.4) at stirring. The release of DOX from the cerasomes is observed utilizing spectrophotometer at 470 nm. The encapsulation efficiency of drug is calculated as follows: [(Total drug amount added to the cerasomes) – (Total drug amount in the supernatant after dialysis)] / (Total drug amount added to the cerasomes) x 100%.

Preparation of drug-loaded high intensity focused ultrasound (HIFU) and thermosensitive cerasomes (HTSCs): HTSCs are prepared utilizing the Bangham method combined with a sol-gel method and self-assembly procedure (Cao *et al*., 2010; Kawataki *et al*., 2011; Ma *et al*., 2011; Jin *et al*., 2012; Cao *et al*., 2012; Liang *et al*., 2013; Yue and Dai, 2014) (Figure 1). In brief, the lipid materials (DPPC, CFL, MSPC and DSPE-PEG-2000) at different molar ratios are co-dissolved in chloroform. After the elimination of the organic solvent in a vacuum rotary-evaporator, the thin lipid film is dehydrated overnight in vacuum, hydrated in distilled water at 45°C for 30 min, and vortexed for 20 min. The resultant dispersions of multilamellar vesicles (MLVs) are ultrasonicated with a probe-type sonicator for 3 min in an ice bath. The conventional low temperature sensitive liposomes (LTSLs) composed of DPPC, MSPC and DSPE-PEG-2000 (the molar % ratios are 86.5:9.7:3.8) are prepared utilizing the same procedure. Calcein-loaded HTSCs, NR-loaded HTSCs, hydrophilic DOX-loaded HTSCs and LTSLs, and lipophilic DOX-loaded HTSCs are also prepared utilizing the same procedure. For DOX-loading, the utilized molar ratios of drug to total lipids are 1:30 for LDOX, or 1:10 for HDOX (Jin *et al*., 2012; Cao *et al*., 2012; Liang *et al*., 2013). The untrapped LDOX and NR are secluded by spinning at 6000 rpm for 10 min, and the unloaded HDOX and calcein are discarded by passing through the sephadex G-50 column with PBS as the eluent. The samples are stored at 4°C in a locked container for further investigations. The whole method is followed in the dark.

Preparation of paclitaxel (PTX)-loaded magnetic cerasomes (PLMCs): Co-encapsulation of PTX and Fe_3O_4NPs within cerasomes is accomplished utilizing thin film hydration (Hashizume *et al*., 2010). In brief, PTX and CFL are co-dissolved in 5 mL of chloroform. After vaporization of chloroform, the thin film is disseminated in 4 mL diluted water containing sodium citrate-modified Fe_3O_4 at a CFL:PTX ratio of 25:1 (mol:mol), followed by sonication for 5 min with a probe type 60 Sonic Dismembrator for the preparation of magnetic cerasomes (MCs) or PLMCs. Fluorescent magnetic cerasomes (FMCs) are prepared by incorporating 3% NBD-DOPE into cerasomes. The non-encapsulated Fe_3O_4 NPs are removed by gel filtration on sephadex™G-50 columns.

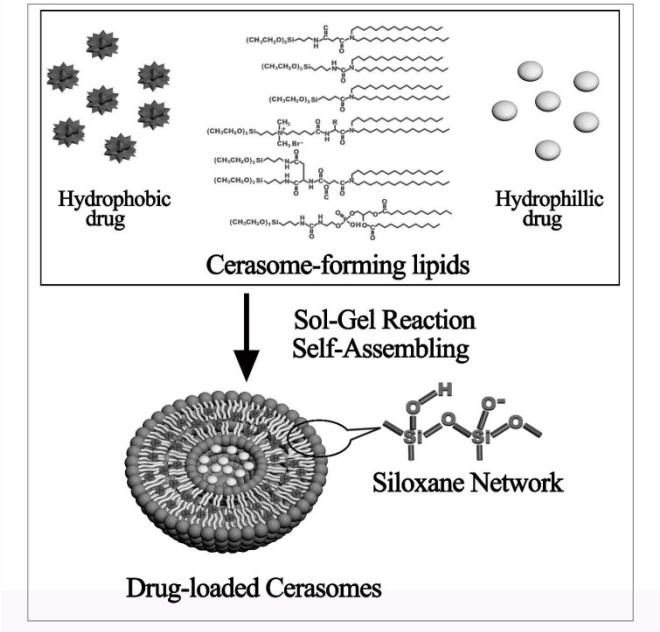

Figure 1. General structures of cerasome-forming lipids and the schematic preparation of drug-loaded cerasomes

Surface functionalization: Owing to the existence of siloxane oligomers, the surfaces of cerasomes may be reformed with silane chemistry i.e. through physical adsorptions or covalent bindings (Hashizume *et al*., 2010). The inclusion of 3-aminopropyltriethoxysilane (APS) to polyanionic cerasomes may result in polycationic cerasomes. Likewise, small molecules, peptides, proteins, and antibodies may also be attached to the surfaces of cerasomes as targeted therapies (Sperling and Parak, 2010). Cerasomes can anchore to the specific cell surface receptors with the support of targeting ligands and are captured through receptor-mediated endocytosis. For efficient targeted delivery, cerasomes functionalized with antibodies (possessing two epitope anchoring sites in a single molecule for higher selectivity and avidity as targeting agent) can anchore to the cell surface target receptors. The fluorescent-tagged-antibodies immobilized on the surfaces of cerasomes are capable to augment the targeted delivery of cerasomes through receptor-mediated endocytosis with higher selectivity owing to the existence of silanol networks on the cerasome-surfaces (Stamn *et al*., 2011). The highly stable triphosphonium (TPP)-surface functionalized cerasomes combined with anti-cancer doxorubicin (DOX) are capable to deliver therapeutic moieties into the targeted mitochondrial matrix through penetration across the mitochondrial membrane owing to the electrostatic attraction between mitochondrial membrane and TPP (Wang *et al*., 2015) [30]. The modified surfaces of immune-cerasomes by chemically anchored anti-epidermal growth factor receptor monoclonal antibody (anti-EGFR mAb) are capable to transport cargos and imaging agents selectively to the targeted tumor cells (Leung *et al*., 2014). The anti-PD-L1 antibody-anchored cerasomes are also capable to provide a better anti-tumor molecular target to minimize the adverse side effects as well as off-targeting of nanoparticles (NPs) to normal cells (Du *et al*., 2018).

Characterizations of cerasomal moieties: The morphology and structure of cerasome-moieties are analyzed by scanning electron microscopy (SEM), transmission electron microscopy (TEM), and atomic force microscopy (AFM). The polydispersity index (PDI), particle size (hydrodynamic diameter), and zeta potential of cerasomes are determined by dynamic light scattering (DLS) at 25°C. Fourier transform infrared spectroscopy (FTIR) is utilized to prove the formation of siloxane bonds on the surfaces of cerasomes and also to observe stretching bands to Si-O-Si and Si-OH groups, hydrolysis of triethoxysilyl groups and the subsequent formation of polysiloxane networks. Cerasome-stability is studied by spectrophotometry at different wavelengths based on cerasomes and cargos. Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectroscopy is utilized to measure mass of cerasome-moieties. The magnetization of Fe_3O_4-conjugated cerasomes is measured in their solid states at room temperature utilizing a vibrating-sample magnetometer (VSM).

Stability of cerasomes: Generally, conventional liposomes as cargo-vehicles are liable to accumulation and fusion for forming larger particles resulting in broken premature leakages as well as rapid elimination of the vesicles from circulation through the vesicular destruction by lipases and lysozymes, while the polyorganosiloxane surface-networks endow cerasomes incredibly higher stability towards surfactant solubilization and lengthy storage in alkaline or acidic conditions compared to liposomes (Zhang *et al*., 2014; Jin *et al*., 2012; Cao *et al*., 2012; Cao *et al*., 2014).

Biocompatibility of cerasomes: Cerasomes show better biocompatibility compared to silica nanoparticles due to the existence of liposomal bilayer membranes having good affinity to cells. As cerasomes have less than 80% biocompatibility in comparison to conventional liposomes experimented with the cell viability for human umbilical vein endothelial cells, the composite cerasomes developed by the combination of cerasome-forming lipids and conventional biocompatible natural lipids through self-assembly method, and also the cerasomes having cholesteryl succinyl silane exhibit better biocompatibility for the treatment diseased cells (Ma *et al*., 2011; Cao *et al*., 2012; Ma et al., 2011a).

Biomedical applications of cerasomes as cargo delivery systems: Cerasomes as cargo-delivery carriers are capable for transporting therapeutic components specifically to the diseased site/s for an optimized effect. The intrinsic features of cerasomal nanoparticles (NPs) such as biodegradability, biocompatibility, high blood stability and sustained cargo-liberation, make them capable for therapeutic drug and gene delivery applications through passive or active targeting to the specific site/s of interest.

General cerasomes as delivery systems: General cerasomes are prepared from conventional organic-inorganic hybrid lipids deficit with any other phospholipid contents or surface modifications. General cerasomes containing hydrophilic doxorubicin (DOX) and hydrophobic paclitaxel (PTX) by thin film hydration exhibit higher chemical and storage stability with controlled drug release to kill diseased cells effectively compared to conventional liposomes (Cao *et al*., 2014). DOX-loaded cerasomal nanocapsules with high stability and uniform size display a pH stimuli-dependent controlled DOX-liberation profile *in vitro* to inhibit the proliferation of cancer cells (Zhang *et al*., 2014). Redox responsive DOX-loaded general cerasomes (lipid containing a cleavable disulfide bond) prepared through ethanol injection technique liberate cargo-

payload to kill diseased cells in a redox responsive way by the destruction of lipid structure after the breakage of disulfide bond in the presence of glutathione (GSH) in tumor cells (Zhou *et al*., 2016). Fe3O4 and PTX-loaded general cerasomes as high stable and controlled drug release nano carrier system integrating diagnostic treatment approach have been utilized to deliver anticancer drug into cancer cells for their killing through the application of simultaneous external magnetic targeted cargo-delivery and magnetic resonance imaging (Cao *et al*., 2014).

Composite cerasomes as delivery systems: In general, composite cerasomes are fabricated through incorporating natural phospholipids into cerasomes to strengthen their characteristics such as stability, biocompatibility and drug liberation. Composite cerasomes fabricated from cerasome-forming lipids and soybean lipids at various molar ratios to load 10-hydroxy-camptothecin (HPCT) have shown higher structural stability, encapsulation efficiency and pharmacokinetic release profile against cancer *in vivo* (Wang *et al*., 2016). Insulin-loaded composite cerasomes (incorporated the phospholipid of DPPC into cerasomes) have exhibited a significant and prolonged hypoglycaemic effect through sustained release of insulin in comparison to liposomes and free insulin (Jin *et al*., 2014). A new method of cancer treatment applied by high intensity focused ultrasound (HIFU) with thermosensitive composite cerasomes (inclusion of low-temperature sensitive liposomes such as DPPC, DSPE-PEG-2000 and MSPC) has shown the inhibitory growth of tumor bearing mice with higher anti-cancer therapeutic efficacy through controlled drug release (Liang *et al*., 2015).

Functionalized cerasomes as delivery system: Generally, drug loaded liposomes take long time to be accumulated in diseased tissues via the enhanced permeability and retention (EPR) effect causing harm to normal tissues owing to their morphological instability, whereas the existence of silanol groups on the surfaces enables cerasomes to be functionalized with specific biomolecules for diseased cells for selective cargo-delivery to diseased cells with an enhanced targeting efficiency. Triphosphonium (TPP) surface-modified cerasomes loaded with DOX may penetrate easily the mitochondrial membranes and assemble within the mitochondrial matrix due to the opposite charges between TPP and mitochondrial membranes resulting in pronounced mitochondrial targeting anti-disease effects (Wang *et al*., 2015). The chemically conjugated anti- selectively target EGFR receptors expressed on tumor cell-surfaces as their anti-cancer activity (Leung *et al*., 2014). The magnetic cerasomes functionalized with magnetic metal alloy by utilizing electroless plating have been used as effective drug carriers for selective targeting and release of drug to the tumor site/s utilizing external magnetic fields as anti-cancer efficiency (Minamida *et al*., 2008). PEGylated cationic cerasomes (PCCs) have been used to deliver siRNAs to specific tumor cells to restrict the generation of disease, causing genes and proteins as gene silencing activity (Jin *et al*., 2014). The highly stable DOX-loaded cerasomes synthesized from cholesteryl succinyl silane (CSS) via ethanol injection method have been utilized to inhibit the production of leukemia cells as anti-cancer therapeutic efficacy with minimal side effects (Ma et al., 2011a). The multifunctional cerasomes synthesized from cholesterol succinyl silane and DSPE-PEG-2000-DOTA by sol-gel reactions and self-assembly processes, labeled with ^{177}Lu and encapsulated with indocyanine green (ICG) for providing dual mode NIR fluorescence (NIRF) and nuclear image-guided-photothermal therapy, have been utilized to ablate cancer cells (Jing *et al*., 2015). The PD-L1 targeted nanohybrid cerasomes labeled with IRDye800CW and Gd-DOTA, and loaded with PTX to expedite dual mode NIRF and MR image-guided chemotherapy have been used against xenografted 4T1 breast cancer and CT26 colon tumor bearing mice to get higher anti-cancer therapeutic efficacy (Du *et al*., 2018).

Pharmacokinetics, biodistribution and elimination of cerasomes-moieties: The pharmacokinetics (PKs) in systemic blood of lipophilic doxorubicin-high intensity focused ultrasound (HIFU) and thermo-sensitive cerasomes-3 (LDOX-HTSCs-3) and hydrophilic DOX-HTSCs-3 (HDOX-HTSCs-3) have been noticed in the tumor free mice (Liang *et al*., 2015). The blood samples have been collected at different time intervals (0.2, 0.5, 1, 2, 4, 8, 12 and 24 h) after intravenous (i.v.) administration of the drug-loaded HTSCs-3 followed by the evaluation of the plasma levels of silane (Si) and DOX. The PKs Si component in LDOX-HTSCs-3 and HDOX-HTSCs-3 have exhibited a more persistent blood circulation time and higher blood concentrations, respectively in comparison with PKs of DOX in LDOX-HTSCs-3 and HDOX-HTSCs-3. HDOX-HTSCs-3 have shown sluggish blood clearance compared to LDOX-HTSCs-3 owing to the lesser negative charges of HDOX-HTSCs-3, while LDOX-HTSCs-3, possessing higher charge density, have displayed relatively shorter half-life through more easily taken up clearance by reticuloendothelial system (RES) (Juliano and Stamp, 1975; Sheng *et al*., 2009; He *et al*., 2010). Despite a few premature drug-liberation of HTSCs-3, the HDOX and LDOX in DOX-loaded HTSCs-3 have exhibited higher half-life compared to conventional LTSL (Park *et al*., 2013), while the plasma concentration for 0-24 h have shown the order of Si in HDOX-HTSCs-3 > Si in LDOX-HTSCs-3 > DOX in LDOX-HTSCs-3 > DOX in HDOX-HTSCs-3. The half-life time ($t_{1/2}$) has been determined to be 12.3±0.95 h for Si in HDOX-HTSCs-3, 10.9±1.12 h for Si in LDOX-HTSCs-3, 8.50±1.49 h for DOX in LDOX-HTSCs-3, and 8.87±1.79 h for DOX in HDOX-HTSCs-3. All the data demonstrate that HTSCs-3 have elevated blood stability, and significantly longer blood circulation time for DOX-loaded HTSCs-3. The systemic biodistribution of the HDOX-HTSCs-3 and LDOX-HTSCs-3 (5 mg DOX/Kg) treated with HIFU after i.v. administration has been investigated in BALB/c mice bearing two tumors (untreated control and treated with HIFU) at both lower legs (Liang *et al*., 2015). The detection of both DOX and Si component in tissue with HIFU treatment has shown the enhanced tumor uptake of HDOX-HTSCs-3 and LDOX-HTSCs-3 in comparison with untreated tumor, while the DOX amount is higher compared to Si amount at the treated tumor site owing to the triggering of DOX release. It is also noted that the uptake of HDOX-HTSCs-3 is a little higher compared to LDOX-HTSCs-3 in most of the organs such as untreated tumor, spleen, heart and kidney, while LDOX-HTSCs-3 have exhibited higher accumulation in the liver compared to HDOX-HTSCs-3 owing to the difference in surface charges between HDOX-HTSCs-3 and LDOX-HTSCs-3, and also active phagocytosis by macrophages in the liver (He *et al*., 2010; Roser *et al*., 1998; Hu *et al*., 2012; Xiao *et al*., 2011). It has been also exhibited that the amount of DOX in most organs is lower compared to the amount of Si except for the treated tumor and kidney. Cerasomes may be primarily excreted through the hepato-pancreatic biliary system and the small

intestine as fecal clearances by mononuclear phagocyte system, followed by the metabolism and recycling of their broken organic lipid contents to fundamental components by the natural enzymes in the biological system, while the cerasomes' stable inorganic polyorganosiloxane network undergoes a natural long-term biodegradation process in the body. The breakdown processed products of silica (>6 nm) may be sequestered in the spleen and liver for several months, or eliminated through the renal excretion (<5 nm) (Mandal, 2025).

CONCLUSIONS AND FUTURE PERSPECTIVES

Nanohybrid cerasomes have higher stability and biocompatibility compared to conventional liposomes and silica NPs, respectively, and capability of easy covalent and non-covalent surface functionalization with hydrophilic polymers, targeted ligands and theranostic moieties. These characteristics enable cerasomes more effective cargo-delivery to diseased site/s owing to their longer circulation residence time as well as sustained cargo release with or without internal or external stimuli for obtaining higher theranostic efficacy against diseases. However, more investigations are required to coordinate the optimization of incorporating multiple cargos, imaging components, ligands, and polymers within the nanohybrid cerasomes to scale up and maintain uniformity on batch to batch from laboratory research to clinical applications. Other detailed studies centered on various parameters such as mechanisms of cellular uptake and interactions, toxicological evaluations or safety profiles, pharmacokinetics, biodistribution, degradation and elimination of nanohybrid cerasomes with different administration-routes such as intravenous, oral, intraperitoneal, and subcutaneous, are needed to fulfill the standard clinical protocols.

Conflict of interest: None declared.

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