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Biocompatible Mesoporous and Soft Nanoarchitectures

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Abstract Soft nanoarchitectures created by biomimetic self-assembly offer unexploited potential for therapeutic drug delivery applications, tissue engineering, and diagnostics. The lipid bilayer building blocks impart biocompatible properties and low toxicity of the resulting nanoassemblies. Our work provides a survey of the recent advances in design and structural studies of functional bicontinuous soft porous nanoarchitectures created from amphiphilic bilayer membrane building blocks. Depending on the packing symmetries and the densities of the curved lipid bilayers, organized in membrane-type nanoparticles, a class of multicompartment nanoobjects involving cubosomes, spongosomes, onion-like liposomes, or vesicles arranged in hierarchical supramolecular architectures, can be obtained. High resolution structural investigations by cryo-transmission electron microscopy microscopy and time-resolved small-angle X-ray scattering (SAXS) have demonstrated that binding and complexation of rigid protein molecules to flexible membrane–vesicle building blocks may generate significant changes in the curvature of the membrane interfaces and may induce formation of bicontinuous cubic nanoarchitectures. Enzyme-mediated cubic nanoarchitecture generation represents another low-energy fabrication method of nanoporous liquid crystalline assemblies. The kinetic pathway of packing ready-to-assemble membrane building blocks (vesicles, nanocubosomes) into nanoarchitectonic vehicles has been revealed by rapid-mixing stopped-flow SAXS experiments.

Keywords Soft nanoarchitectures · Lipid bilayer building block · Self-assembled nanochannel networks · Bicontinuous cubic mesoporous materials · Membrane curvature · Time-resolved SAXS

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1 Introduction

Soft porous nanoarchitectures are abundant in nature and inspire the fabrication of functional mesoporous assemblies by biomimetism [1–16]. A remarkable stability of hierarchically organized porous structures has been demonstrated for the wing scales of certain butterfly species (e.g. *Callophrys rubi*) [1]. Scanning electron micrographs of wing scales have revealed that their polymerized chitin material is structured in three-dimensional (3D) networks with complex topologies involving gyroid cubic and face-centred cubic structures at different organization levels [1]. Crystalline arrangements, associated with sophisticated hierarchical porous architectures, including cubic lattice formation, have been observed also in cell membranes under stress or disease conditions [2–6]. Cubic lipid membrane organizations, with space groups specified by Luzzati et al. [8, 9], have been found in several cell types (skin cells, animal and plant cells, etc.) both under physiological or pathological conditions [3]. In this context, current compartmentalization research aims to mimic and reproduce the spatial organization of cellular membranes maintaining life functions, localization mechanisms, scaffolding and transport of substances [16, 17].

Mesoporous materials have constituted vast research interest since the pioneering work of Kresge in 1992 [18–37]. Their studies have significantly contributed to the development of the materials nanoarchitectonics field through the creation of nanoarchitectures with confined spaces, modulable interfaces, multifunctional and multicompartment mesoassemblies [38–69]. Transmission electron microscopy (TEM), X-ray diffraction (XRD) and small-angle X-ray scattering (SAXS) have been the principal experimental methods for establishing the mesoscale periodicity and nanoporous organization of these new materials [18, 25]. CryoTEM and SAXS have been particularly required for soft matter nanoarchitectures characterization [1–10, 15, 52, 70].

Both self-assembly of soft-matter building blocks and layer-by-layer (LbL) deposition strategies have been advantageous for preparation of soft nanostructures [40, 42, 70–77]. Self-assembly is the driving force behind the formation of amphihilic architectures with different spatial organizations. It is triggered by week noncovalent interactions, hydrophobic forces, hydrogen bonding, dipole–dipole and electrostatic colloidal forces, metal–ligand interactions, aromatic π–π stacking, steric forces, steric exclusion effects, and entropy. Functional supramolecular assemblies have been created through spontaneous packing and ordering of designed small molecule building blocks, amphiphilic polymers, bioactive components, and hybrid structures including hollow nanoparticles [65–68]. At the molecular and nanoscale levels, directed self-assembly has been governed by stimuli such as light irradiation, temperature, solvent polarity, pH, metal ions gradient, electrochemical redox potential, magnetic field, as well as by templating scaffolds [70, 71, 74]. Organized soft materials obtained by self-assembly of nanoscopic components and building blocks are referred to as self-assembled nanomaterials.

Liquid crystalline architectures of spontaneously ordered biomolecular soft matter building blocks are of particular interest [78–95]. The morphologies and the structural complexity of such self-assembled mesostructures can be controlled by different external stimuli [78–89]. Their building blocks comprise a variety of amphiphilic, lipid, peptide, DNA, organic molecule and diblock or triblock copolymer derivatives [69, 78–144]. The tuneable mesoporous structure, well-defined surface properties and large surface areas have favoured new strategies for design of hybrid and stimuli-responsive materials [145–154]. Soft templates have demonstrated considerable potential for creation of novel mesoporous structures [40, 42, 69]. The possibility for engineering of the nanometer-scale pores and interfacial patterns has been exploited for the fabrication of novel hierarchically organized self-assembled materials and colloidal delivery systems [145–171].

The rich lipid polymorphism and the formation of liquid crystalline lipid phases by self-assembly upon contact with water have inspired the generation of biocompatible mesoporous media of both ordered and random channel architectures [172–233]. Such structures can mimic some naturally occurring complex fluid systems (Fig. 1).

Amphiphilic bilayers and lipid membrane leaflets are basic building blocks of liquid crystalline biomimetic cubic

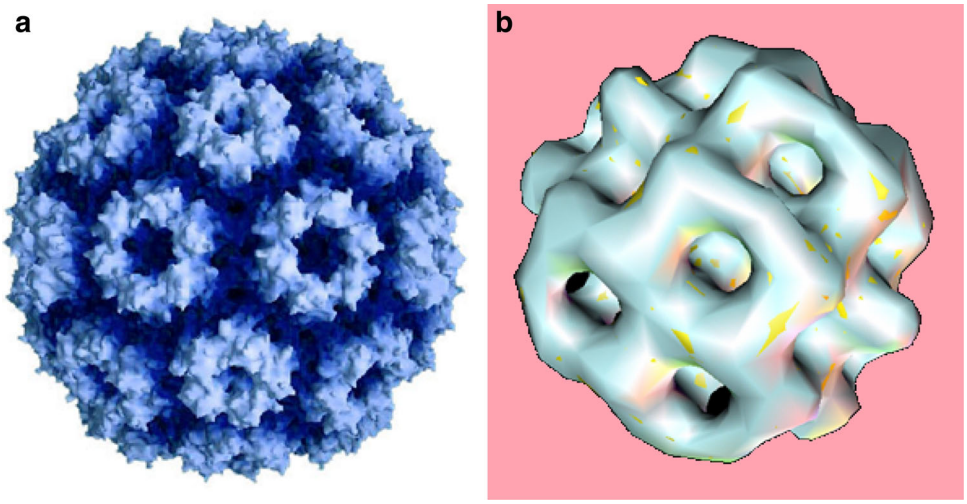

Fig. 1 Structural similarity between the nanoporous organization of the *Cowpea chlorotic mottle virus* (*CCMV*) particle (icosahedral symmetry, PDB code: *1cwp*) (**a**) and the nanochannel organization of a cubosome nanoparticle of a diamond-type structure (*Pn3m* space group of symmetry) (**b**). The protein cages in (**a**) enclose channels of low interfacial elasticity and weak responsiveness to environmental effects. The cubosome membranes in (**b**) are hydration-stimulus responsive and allow noteworthy variations of the channel diameters [55]

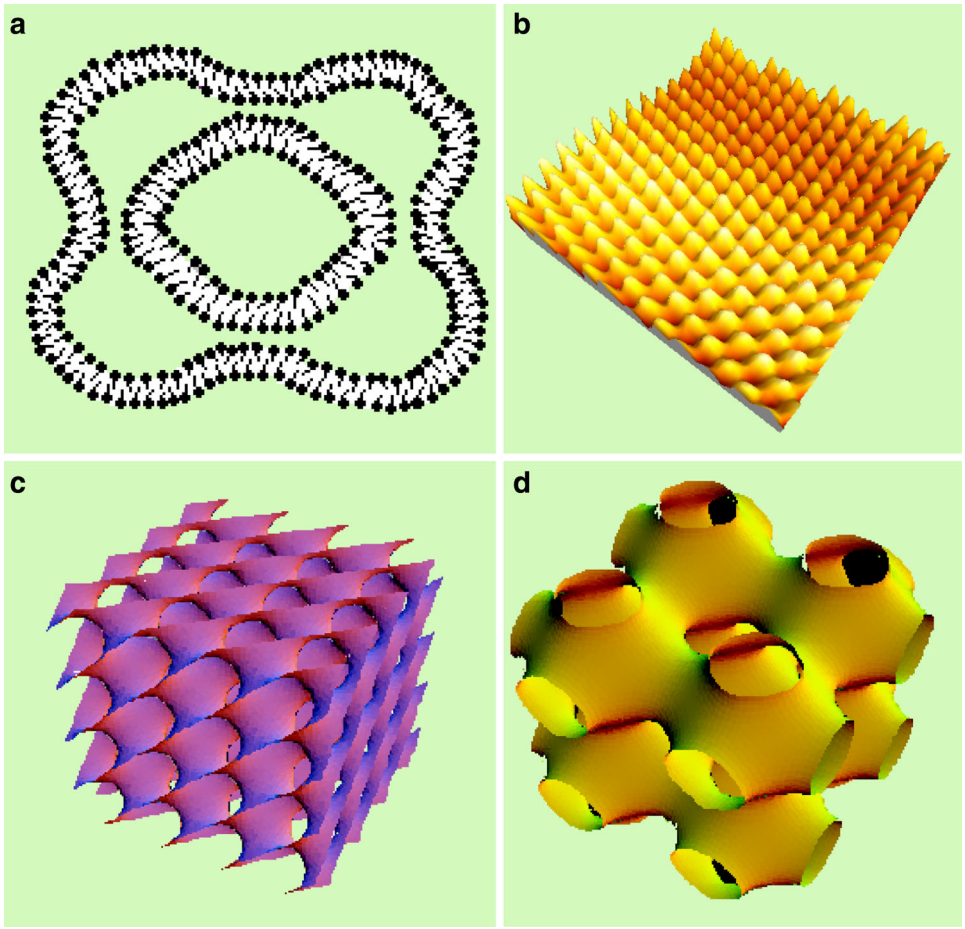

Fig. 2 Lipid bilayer membrane building blocks (**a**), which may generate nanostructured folded membrane leaflets (**b**) and three-dimensional (3D) inverted cubic membranous structures of bicontinuous *double diamond* (*Pn3m*) (**c**) or primitive (*Im3m*) (**d**) symmetries (see refs. [8, 9] for the cubic lattice space groups)

structures (Fig. 2). Bilayer membrane building blocks can be organized either into highly ordered crystalline structures (Fig. 2c, d) or into random bicontinuous 3D sponges (Fig. 3a). Lipid tubules can also pack into periodic (Fig. 3b) and hierarchically organized nanoarchitectures [234–237].

The periodic 3D organization of lipid membranes into a cubic array of unit cells yields bicontinuous cubic lattice architectures of various symmetries [8, 9, 145, 172, 173]. In these structures, the lipid bilayer separates intertwined networks of aqueous channels forming a complex multi-compartment architecture. The thickness and rigidity of the lipid bilayer membrane and the water channel dimensions are important parameters determining the stability of the 3D bicontinuous cubic architecture and its capacity for upload of active molecules. Molecular hydration in the confined spaces of the aqueous channels and the hydrogen bonding at the lipid/water interfaces govern the diffusion in the self-assembled amphiphilic networks. Both the aqueous (hydrophilic) channel compartments and the lipid bilayers (hydrophobic compartments) may embed guest molecules.

2 Engineering of Soft Membranous Nanoarchitectures

The membrane thickness and flexibility are crucial factors in the design of soft nanoarchitectures with sophisticated structures and morphologies. Figure 4 presents a broad-sense membrane nanoarchitectonics design involving the confinement of flexible amphiphilic membranes in diverse shapes.

Nanoscale engineering of cubic membrane architectures has been performed by varying the lipid type, the choice of the grafted functional groups, as well as by compositional tuning of lipid–amphiphile mixtures. Self-assembled mixtures of phytantriol (PHY) or monoolein (MO) with other lipids and amphiphiles have permitted the successful realization of bicontinuous membrane architectures with tunable nanometer-scale pore sizes [175–181]. Engineering of the water channel networks has produced either swelling or shrinking of the aqueous compartments in these nanostructures that demonstrate remarkable membrane elasticity [20, 55, 95, 145, 148, 158, 175, 176, 180, 203, 215]. Such elasticity of the interfaces is not inherent for solid porous materials (e.g. mesoporous silica MCM 41-48,

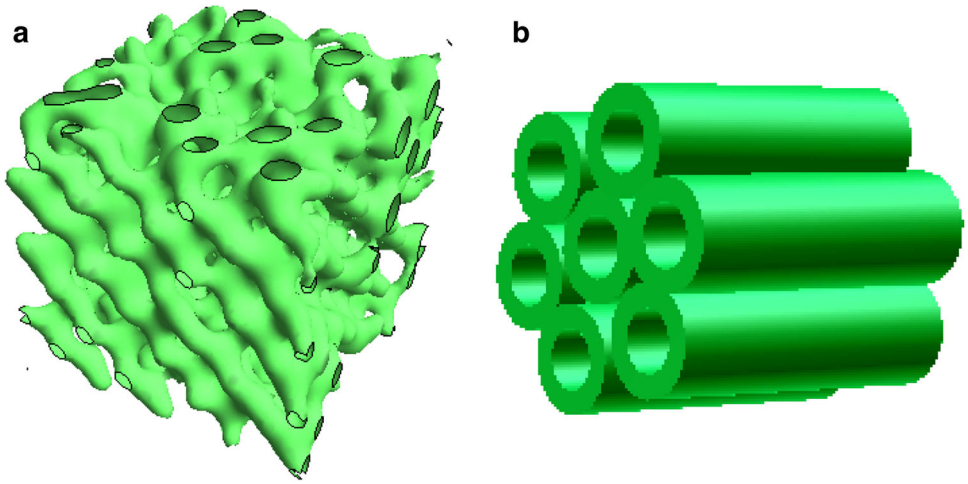

Fig. 3 Sponge type liquid crystalline assembly involving a randomly organized bicontinuous lipid membrane (**a**) and an inverted hexagonal structure of packed lipid tubes (**b**)

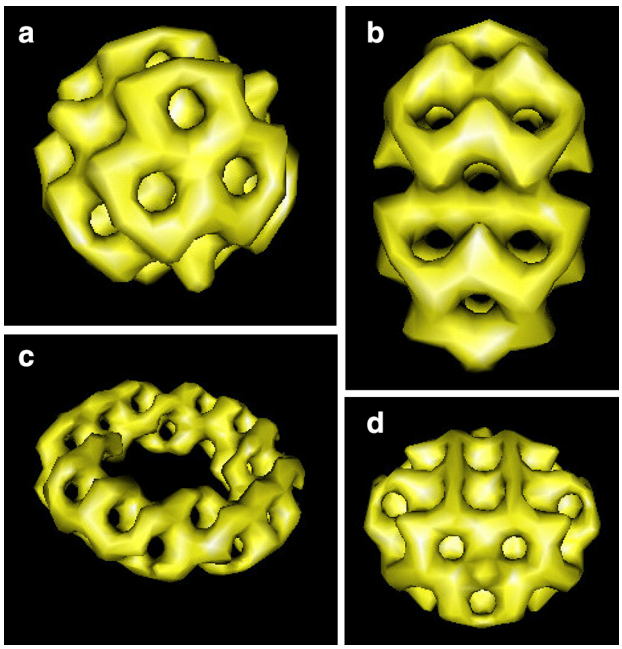

Fig. 4 Examples of nanoarchitectonic device building-up from amphiphilic bilayer building blocks. **a** Nanochannelled spherical drug delivery carrier, **b** artificial mitochondrion skeleton, **c** perforated torus, and **d** nanocurled element

SBA-15, etc.), which limits their loading capacity for guest molecules.

Large aqueous channels have been suggested to be important for both the encapsulation efficiency of hydrophilic guest macromolecules in host lipid mesostructures as well as for the solubilisation and ordering of membrane proteins with big extramembrane domains [55, 58, 95, 157, 158, 181, 193, 201–205, 214]. The engineered amphiphilic mesophases have enabled guest molecules crystallization into nano- and micro-crystals upon addition of crystallization screens to the bicontinuous cubic membrane templates [101, 157, 158, 212].

Functionalization of the membrane interfaces has been realized by means of anchoring of ionizable and molecular recognition groups [14, 43, 54, 189, 203, 216]. Either stimulus-responsiveness of the nanoarchitectures or control of the sizes of the aqueous channel compartments have been achieved by engineering of the lipid/water interfaces through functionalization [52, 174–178, 180, 181]. Further to the engineering of the fluid membrane interfaces [21, 54, 154, 158, 163, 196, 238–243], the engineering of soft nanoarchitectures on solid supports has attracted significant interest [40, 42, 56, 95, 163–166]. Experiments on adsorption of liquid crystalline lipid nanoparticles with nanochannelled organization on supporting templates of varying hydrophobicities (hydrophobic surfaces, hydrophilic silica surfaces, cationic silanized silica surfaces) (Fig. 5) have revealed the importance of the intermolecular interactions and lipid composition for the deposited nanoporous layer structures [165].

In the above approach, a layer with multicompartment organization adheres to the underlying substrate in a single step. At variance, the layer-by-layer (LbL) deposition strategy [40, 42, 75–77] utilizes a sequence of repetitive steps, involving alternating building blocks, for fabrication of soft nanoarchitectures.

3 Mechanism of Generation and Growth of Cubosome Nanoarchitectures from Membrane Building Blocks

Biocompatible mesoporous architectures can be built-up from membrane bilayers in a "bottom–up" approach [227, 228]. The structural mechanism involves curved bilayers packing and fusion into growing ordered membrane structures, for instance of a cubic symmetry [227]. Packing of curved membranes makes possible the nanochannel

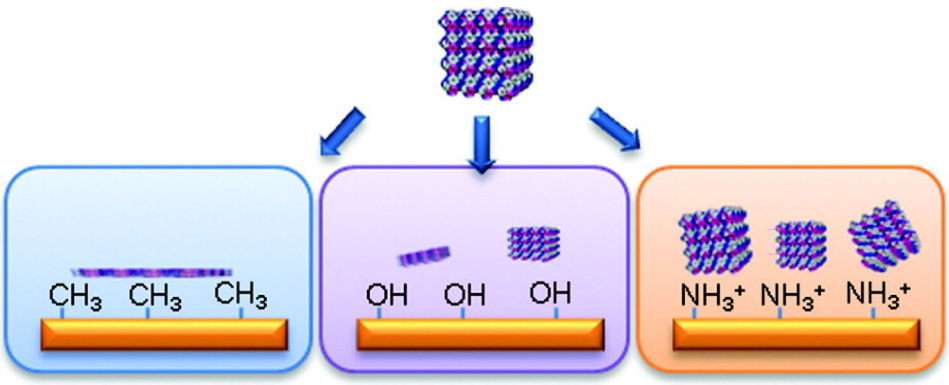

Fig. 5 Nanostructured interfaces obtained by deposition of nanoporous building blocks on supports. Reprinted with permission from [165]. Copyright (2012) American Chemical Society

network formation [228]. Modelisation studies, based on the nodal surfaces approach, have demonstrated that the growth of small cubosome nanoparticles from nanovesicles occurs through discrete stages determined by the packing symmetry (Fig. 6). Figure 6 shows that configurations with open nanochannels can be geometrically stable for particles with diameters that are divisible by a minimal size (ca. 54 nm for monoolein assemblies in excess water) dependent on the cubic lattice dimension.

Experiments performed with cryo-TEM and freeze-fracture electron microscopy have confirmed that the nanocubosome units, with sizes smaller than 60 nm, are indeed the cubic-membrane building blocks of larger cubosomal structures [15, 21, 204, 227, 228]. Nanocubosomes involve a few cubic unit cells only and do not display intensive sharp Bragg diffraction peaks in their X-ray patterns at variance to bulk lipid cubic phases and large cubosomal aggregates [150, 171, 176, 196, 200–203]. Figure 7 shows experimental and theoretical SAXS curves of small nanocubosome building blocks.

A characteristic feature of the soft cubosomal assemblies is the fluctuating nature of their interfaces, which are often functionalized by PEGylated lipid derivatives or amphiphilic copolymer stabilizers [21, 204, 207, 227]. It should be stressed that biomacromolecular loading in such cubosomic architectures often provokes membrane undulations [58] and certain defects in the periodic nanochannel organization. The latter could not preserve a single crystal cubic lattice template (Fig. 8). Despite of the local structural perturbations due to the uploaded guest molecules, the SAXS patterns have confirmed the overall bicontinuous cubic architecture [58, 201].

4 Approaches for Preparation of Soft Nanoarchitectures of Bicontinuous Cubic Organization

4.1 Molecular Self-assembly from "Bottom–up"

Amphiphilic liquid crystalline nanoarchitectures may form spontaneously upon hydration of lyotropic lipids in excess aqueous phase. A variety of lipids and amphiphiles with nonlamellar propensities assemble into curved membranes forming mesostructures with stimuli-responsive aqueous channels [95–99, 101, 129, 145, 146, 149, 172, 184, 196, 215]. Bicontinuous cubic, and in some cases micellar cubic, phases have been reported as a function of the compositional phase diagrams of selected amphiphilic mixtures [142, 146, 151, 171, 174, 176, 177, 187–192, 200, 211].

4.2 "Top–Down" Fragmentation of Bulk Liquid Crystalline Phases

The "top–down" approach consists in dispersion of bulk lyotropic lipid cubic phases in excess aqueous medium into nanoparticles using surfactant agents and mechanical agitation power [217–224]. In this approach, the cubic unit cell size appears to be crucial for the fragmentation of the bulk amphiphilic cubic lattice as it is linked up with the liquid crystal domain size. Various kinds of amphiphilic block co-polymers [190, 210, 217–224], PEGylated lipids and surfactants [58, 132, 134, 178, 204, 205] as well as interfacially active proteins, such as casein [229], may provide surface shells for stabilization of the dispersed liquid crystalline cubic nanoparticles. Sonication of melted monoglyceride lipids in aqueous Poloxamer 407/F127 surfactant solutions has been the simplest method for cubosome preparation [217].

The lipid thin-film-hydration method has been frequently employed for preparation of mixed amphiphilic and functionalized lipid nanoarchitectures [54, 55, 144, 202–205, 227, 228]. The amphiphilic components of interest are dissolved in chloroform solvent to allow for homogeneous mixing. The organic solution is subjected to continuous flow of nitrogen gas towards solvent evaporation and removal. Subsequently, the lyophilized lipid film is hydrated in aqueous buffer yielding the formation of multicomponent liquid crystalline assembly after vortexing and agitation. Depending on the studied mixed lipid composition, the dispersed system may involve cubosomes,

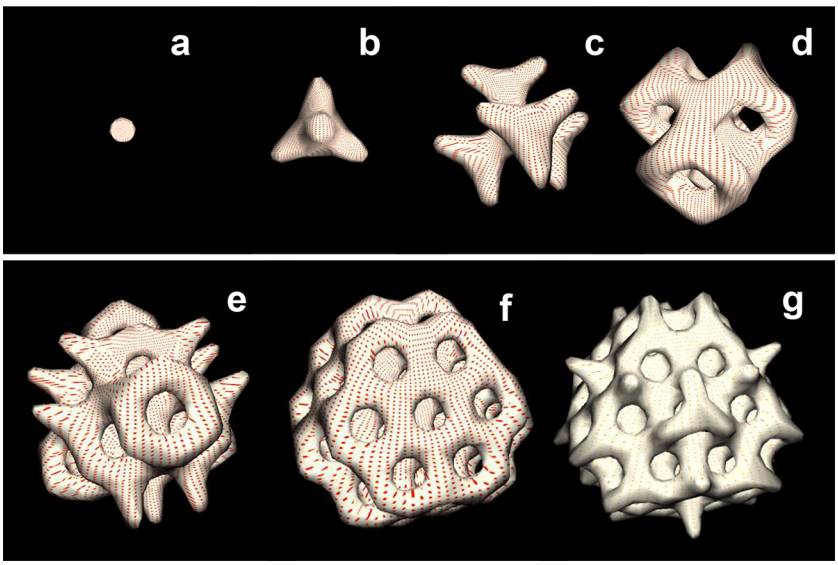

Fig. 6 Pathway of tetrahedral-channel-network building-up in diamond-type cubosomal nanoarchitectures starting from a single nanovesicle membrane shaped in a small unilamellar vesicle. Reprinted with permission from [227]. Copyright (2006) American Chemical Society

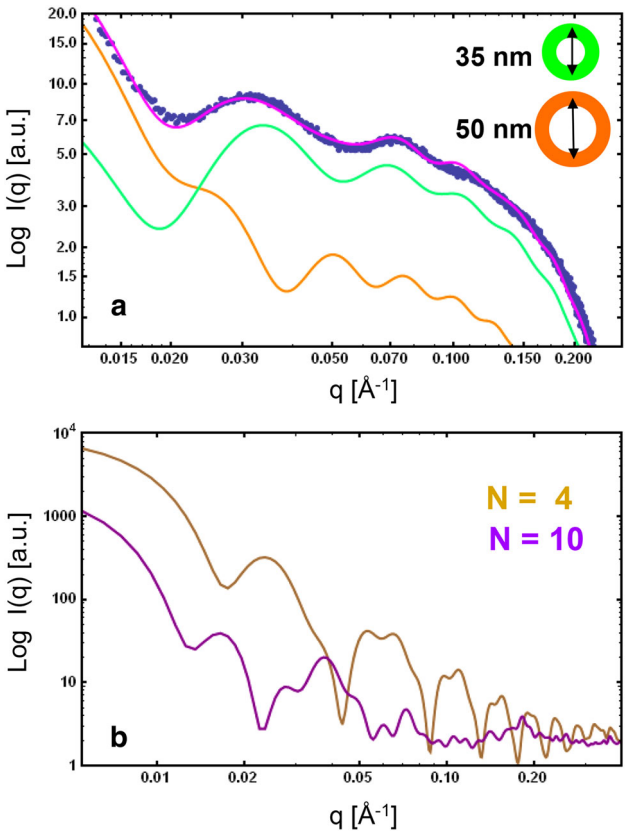

Fig. 7 SAXS patterns of nanocubosome building blocks. **a** Experimental SAXS curves fitted with coexisting populations of lipid particles: 35 nm nanoparticle diameters (*green*) and 50 nm nanoparticle diameters (*orange*). **b** Calculated model scattering patterns for monodispersed cubosomes with N = 4 (*brown curve*) and N = 10 (*violet curve*), where N indicates the number of nodes (repeat volumes) in the cubic particles. Reprinted with permission from [228]. Copyright (2012) American Chemical Society (Color figure online)

spongosomes, vesicles, or intermediate kinds of internally self-organized membranous nanoparticles (Fig. 9).

Cubosome particles have been obtained also from liquid precursor formulations formed by bulk mixtures of nonlamellar lipids (monoglyceride, phytantriol), hydrotropic chemical agents (ethanol, propyleneglycol) and water [224–226]. The dispersion into nanostructures has been performed through the dilution-line method using a Poloxamer stabilizer (e.g. F127 copolymer) dissolved in the aqueous phase and mechanical vortexing.

Agitation and treatment methods of the initially obtained coarse dispersions of cubic aggregates have been employed towards emulsification and fragmentation of the liquid crystalline lipid phases in emulsifier solutions [95, 174, 199, 223, 224]. Combinations of magnetic stirring, vortexing, sonication bath, pulsed sonication, high pressure/high shear microfluidic homogeneization, heating in autoclave, and other high energy input devices have been utilized. These treatments have allowed generating more uniform and fine dispersions of liquid crystalline nanoparticles.

4.3 Enzymatic-Assisted Cubosome Formation

A conceptual advance in the production of nanostructured lipid particles has been marked by enzymatic processing of lipid emulsions with specific compositions [230–233]. A mixture of a nondigestible lipid (phytantriol) and a digestible short-chained triglyceride has been subjected to enzymatic lipolysis [230]. Particles of internal cubic structures have crystallized in the dispersion medium after the release of the soluble lipolytic products away from the nondigestible lipid aggregates. The kinetics of the phase transition from an unstructured emulsion to soft mesoporous particles of inner cubic symmetry has been monitored by time-resolved small-angle X-ray scattering. The

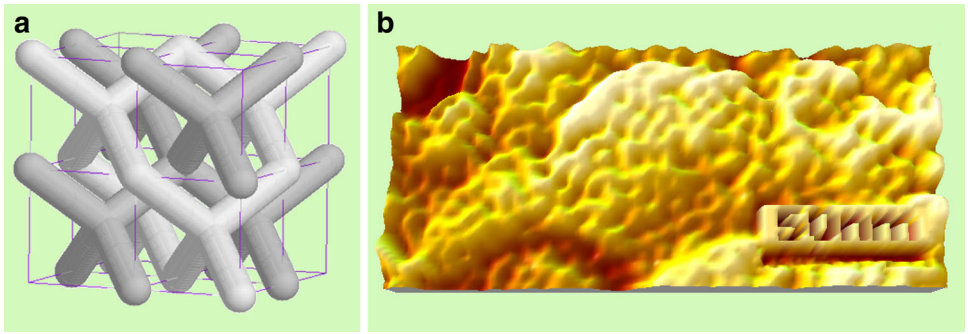

Fig. 8 **a** Idealized single crystal cubic lattice of a double diamond type (space group *Pn3m*) and (**b**) reconstructed freeze-fracture electron microscopy image section of an experimental cubosomal assembly displaying fluctuating membrane interfaces after biomacromolecular upload

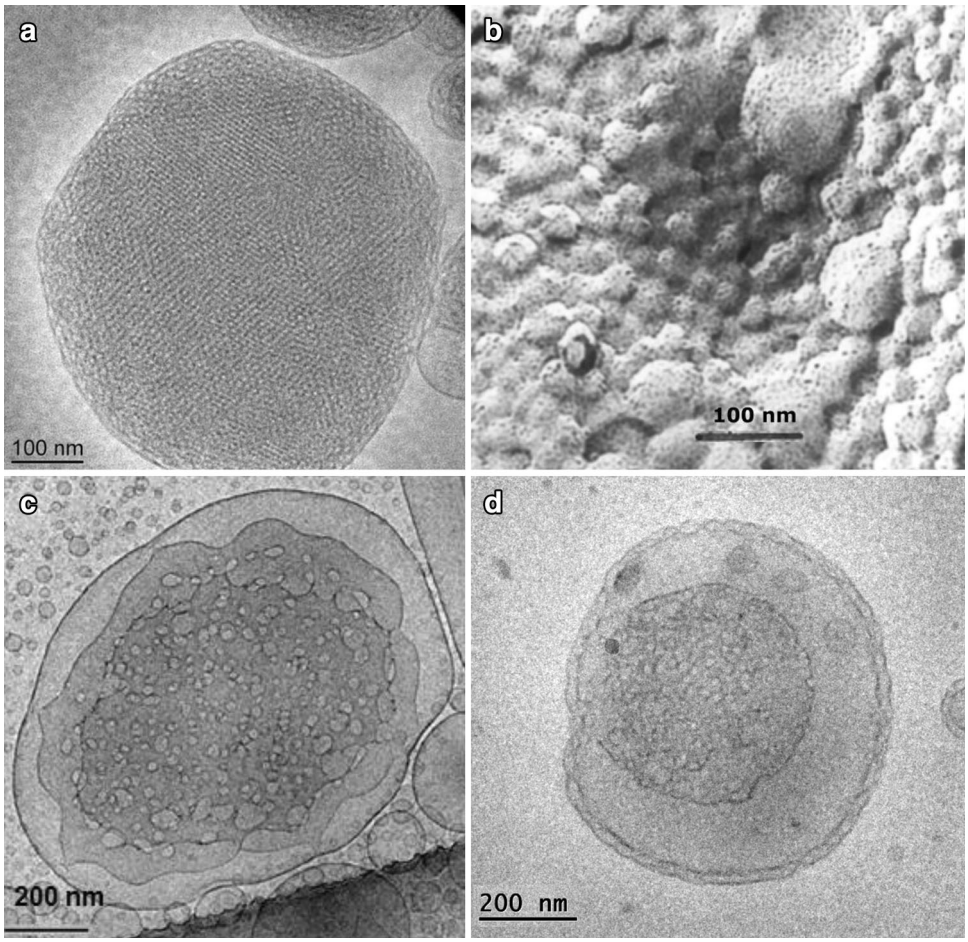

Fig. 9 Cyo-TEM (**a**, **c**, **d**) and freeze-fracture electron microscopy (**b**) images of liquid crystalline lipid particles prepared by the lipid thin-film hydration method. **a**, **b** Cubosomes, (**c**) spongosome accompanied by small vesicles, and (**d**) a mixed type nanoobject consisting of a dense membrane core and a vesicular membrane shell

enzymatically-assisted generation of liquid crystalline nanoparticles of inner cubic order has been evidenced also by cryo-transmission electron microscopy [230].

4.4 Nanoarchitectonics Employing Ready-to-Assemble Membrane Building Blocks and Interfacial Curvature Modulators

A "bottom–up" approach in nanoarchitectonics involves assembling of ready-to-use nanobuilding blocks into supramolecular mesoporous structures. It has been emphasized that lipid bilayer building blocks and vesicular membranes are required for the formation of cubic-membrane type nanoobjects [15, 228]. Moreover, uptake of guest entities with curvature-modulating properties in lipid nanoparticles may transform the membrane building blocks into nanochannel-type assemblies displaying structural order (Fig. 10). Examples of such transformations have been observed upon assembly of vesicular or bicontinuous lipid membranes of flexible interfaces with relatively stiff biomolecules such as proteins of β-sheet conformation and plasmid DNA (pDNA) [15, 144].

Interestingly, neurotrophic protein BDNF (brain-derived neurotrophic factor) loading into lipid membrane nanoassemblies has yielded multicompartment nanoparticles with a dense core and a porous periphery of aqueous channels [15]. Exceptional temporal (Fig. 11a) and spatial (Fig. 11b) resolutions of the lipid-protein nanoarchitecture formation have been achieved through a rapid-mixing stopped-flow set-up coupled to in situ structural SAXS measurements at a highly-brilliant synchrotron radiation source and cryo-TEM imaging (Fig. 11). The upload of the stiff BDNF protein molecules in the lipid nanoparticles has induced a lower curvature—to a higher membrane curvature phase transition. The protein–lipid complexation and ordering has driven the vesicular membranes to organize into nanoparticles containing nanoperiodic domains of diamond cubic (D) and gyroid cubic (G) symmetries (Fig. 11b).

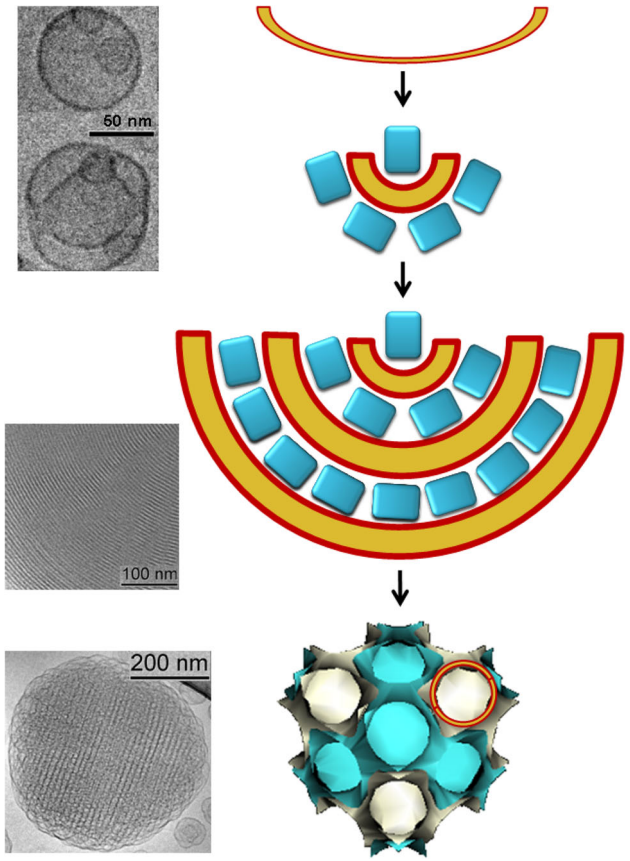

Fig. 10 Protein-driven hierarchical-architecture design in cubosome nanoparticle shapes as revealed by cryo-TEM images (*left column*). Flexible lipid membranes (*top*) undergo stepwise curvature changes upon dynamic assembly and ordering of the bound protein BDNF (brain-derived neurotrophic factor). The discrete jumps of curvature, leading to nanochannelled architecture formation of cubic packing (*bottom*), are governed by the nonflexible neurotrophic BDNF-protein molecules with β-sheet structure (represented as stiff cylinders). Reprinted with permission from [15]. Copyright (2014) American Chemical Society

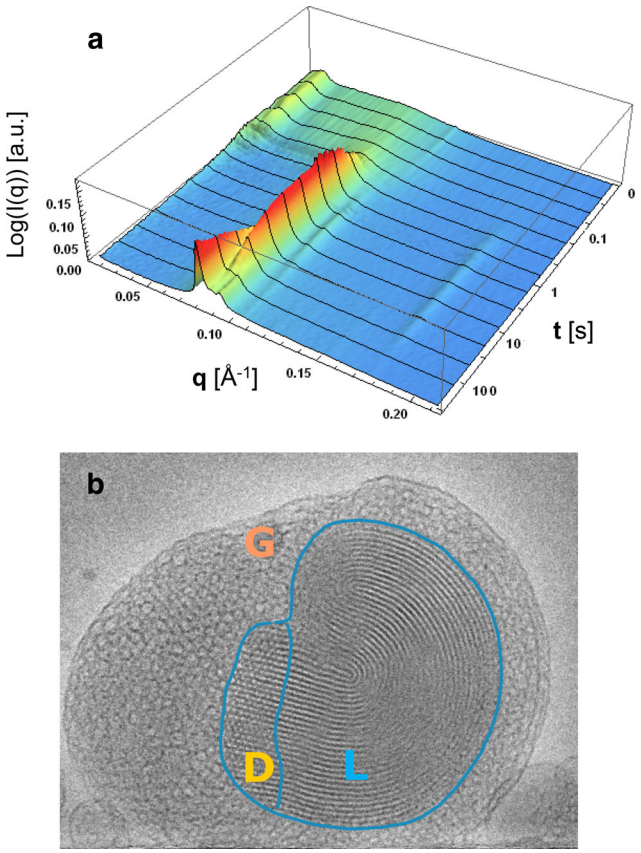

Fig. 11 **a** Millisecond time-resolved small-angle X-ray scattering (SAXS) patterns revealing the structural pathway of formation of liquid crystalline lipid–protein nanoparticles with multicompartment channel-network topology, and (**b**) a cryo-TEM image of a three-phase nanostructure stably formed throughout the BDNF-protein upload in lipid membrane-type particles. The *blue line* in **b** indicates the domain boundaries between the inner *L*, *D*, and *G* mesophase structures: *L*—lamellar L_{α}, *D*—bicontinuous cubic double diamond *Pn3m*, and *G*—bicontinuous cubic gyroid *Ia3d* structures. Reprinted with permission from [15]. Copyright (2014) American Chemical Society (Color figure online)

The kinetics pathway of the bilayer vesicle-to-cubic membrane transition upon neurotrophic protein binding has been quantified by SAXS analysis [15]. Membrane architectures of varying curvatures have been resolved with time depending on the percentage of protein loading in the lipid phase (vesicular mixture→onions→cubic/lamellar/cubic three-phase nanoparticles) (Fig. 12). The performed structural study has established that 82 % of the protein molecules were entrapped in lipid membranous nanostructures and at membrane interfaces within the first second from their administration (Fig. 12). It has been concluded that porous membranes, organized in cubic lattice architecture can be obtained from lipid vesicles. Towards that aim one should subject low-curvature vesicular membrane building blocks to hierarchical assembly using suitable non-flexible

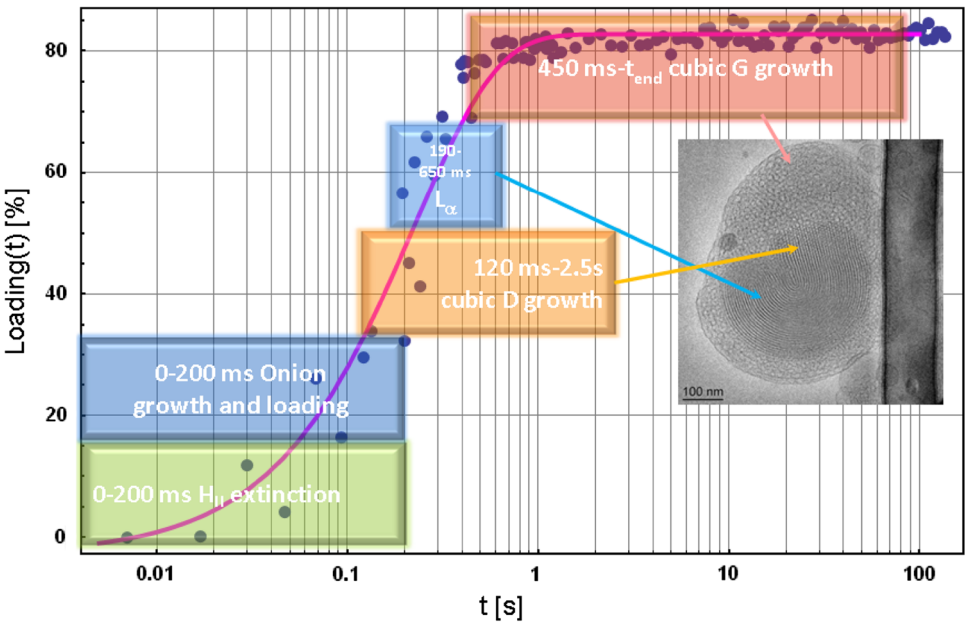

Fig. 12 Kinetic pathway of quantitative protein uptake by lipid membranous nanoassemblies established from analysis of millisecond time-resolved SAXS sequences. Reprinted with permission from [15]. Copyright (2014) American Chemical Society

bridging units like charged protein molecules of β-sheet conformation [15].

Cubic membranes have been efficient also for uptake of DNA building blocks [130, 142, 144]. Self-assembled lipid-DNA complexes have been characterized by rich topologies [130–144]. The kinetic pathway of self-association of plasmid DNA (pDNA) to cationic cubosomes has been investigated by millisecond time-resolved SAXS coupled to a rapid-mixing stopped flow device [144]. Binding of pDNA to the cationic lipid nanocarriers has considerably modified the curvature of the lipid/water interfaces and has led to formation of onion-type lipoplex complexes (Fig. 13). The performed structural analysis has revealed the intermediate states associated with lipid-membrane-curvature changes induced upon pDNA entrapment in the lipid phase (Fig. 13c). The investigated dynamic self-assembly process has been suggested to involve at least three stages: (1) fast electrostatic binding of the negatively-charged pDNA molecules to the positively-charged membrane interfaces accompanied by charge neutralization (rate constant k_1), (2) dynamic formation of onion lamellar entities (lipoplexes) with modified membrane curvatures (rate constant k_2), and (3) relatively slow remodeling of the kinetically trapped shapes toward equilibrium structures of more ordered or aggregated states (rate constant k_3). The rate constant k_2 of the rapid complexation processes has been estimated from the recorded sequence of dynamic roentgenograms [144]. Fully condensed pDNA has been obtained over the sub-second time scales (Fig. 13b,c).

Time-resolved SAXS coupled to a rapid-mixing stopped-flow technique has been successfully employed also to monitor the association of membrane building blocks under the influence of multivalent ions and pH-induced curvature variations [244–249]. Electrostatic interactions, determining the ionic equilibria and complexation reactions at the membrane interfaces have been shown to govern the mechanism of the lamellar liquid-crystalline to inverse bicontinuous-cubic phase transition through changes in the membrane curvature [248].

5 Recent Structural Studies and Characterization Techniques

The advances in amphiphile and membrane nanoarchitectonics require the employment of modern structural methods for characterization of the studied nanoarchitectures, macromolecular folding, packing of building blocks, and confinement of guest molecules in the nanochannel-type mesophases [250–272]. The nanoscale organization of self-assembled mesoporous systems and the kinetics of nanoarchitecture generation have been principally studied by static and time-resolved small-angle X-ray scattering (SAXS) [20, 132, 144, 150, 160, 177–181, 187, 195, 200, 211, 213, 214, 216, 221, 222, 228]. The phase behavior and stimulus responsiveness of the assemblies has been assessed using synchrotron radiation sources [55, 101, 151, 171, 176, 196, 197, 200–206, 230, 250–258]. Morphological features have been visualized by means of cryo-TEM imaging [15, 132, 165, 186, 199, 217–220, 228], cryo-FESEM imaging [207, 235], and freeze-fracture electron microscopy [21, 54, 58, 204]. High throughput methodologies have been proposed for preparation and structural

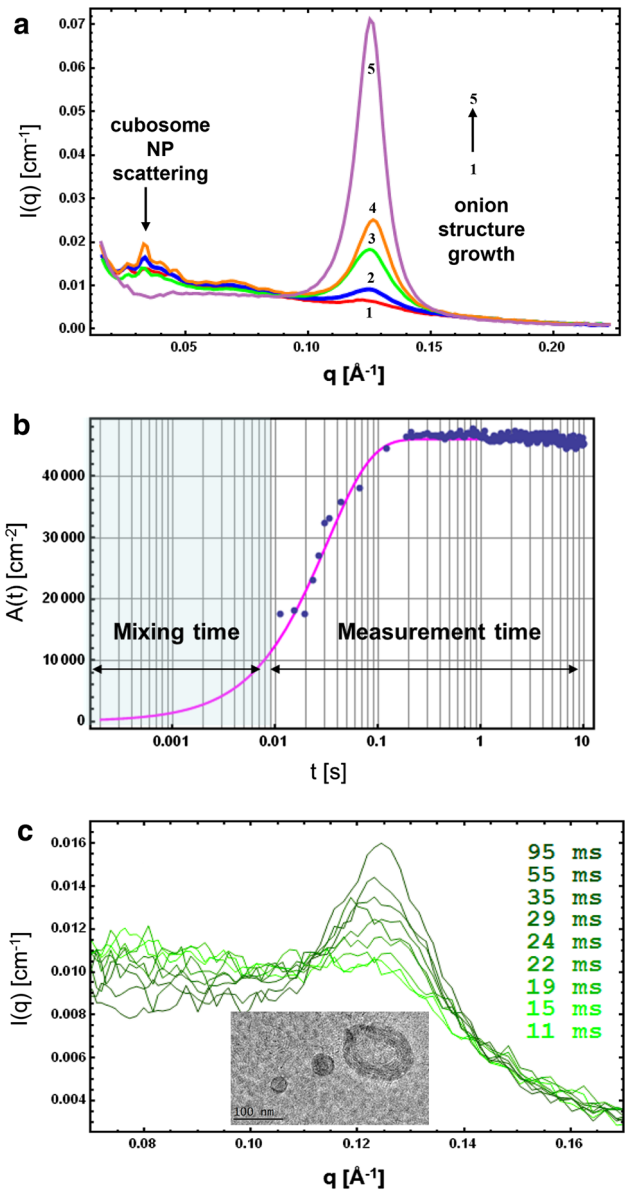

Fig. 13 Plasmid DNA-driven transformation of nanochannel-type lipid carriers into tightly packed layered architectures involving compacted DNA macromolecules. **a** SAXS patterns showing that the curved lipid membranes in the cubosome nanoparticles are transformed, with the increase in the pDNA upload, into lower-curvature onion-membrane complexes encapsulating pDNA. **b** Kinetic dependence of the Bragg peaks intensity characterizing the pathway of the lipoplex formation. **c** Millisecond time-resolved SAXS patterns upon in situ monitoring of the lipoplex formation with a rapid-mixing stopped-flow device. Reprinted with permission from [144]. Copyright (2013) American Chemical Society

analysis of soft matter nanoporous systems [105, 188, 190, 210, 212].

Dynamic nonequilibrium processes occurring with soft nanoarchitectures have been investigated in great detail using time-resolved structural measurements [200, 250, 254–257]. Various external stimuli (temperature, UV light, pressure jump, stop-flow rapid mixing, rapid immersion, shear stress, magnetic field, pH, and ions injection) have been applied for generation of nanostructures discernible with time resolution [244, 250, 251]. For example, the dynamic organization of drug-loaded lipid formulations has been in situ characterized by synchrotron SAXS coupled to a remote-controlled system for buffer addition with simultaneous temperature control [197]. Fast structural transitions have been observed upon exposure of precursor lipid nanoassemblies to body fluid environmental conditions. The enhanced hydration (rapid water-uptake) has resulted, within a few 100 s, in significant structural changes of the initial L_2-phase formulation of the local anaesthetic bupivacaine into non-lamellar phases of nanochannelled type (cubic *Pn3 m* and H_2 structures) [197]. In another work, the nonequilibrium cylinder-to-sphere morphological transition kinetics in block copolymer systems has been investigated on the millisecond time scale by combination of time-resolved small-angle neutron (TR-SANS) or X-ray scattering (TR-SAXS) and stopped-flow mixing technique [255]. The kinetic pathway, determined in situ, has elucidated the mechanism of the self-assembly process (fast fragmentation of cylinders *versus* gradual decrease in cylinder length) and the intermediates occurring throughout the instability regime in relatively diluted systems of polymer nanoparticles [255].

The lamellar-to-cubic lipid membrane phase transition has received considerable attention (Fig. 14) given that it is important in the context of cellular membrane functions [2, 3] and for the development of layered and nanochannelled delivery systems [15, 174, 177, 178]. The liquid crystalline architecture of delivery devices has been indicated to be crucial for the regulation of the controlled release properties of the self-assembled lipid nanoarchitectures [175, 182, 184, 189].

6 Current Applications

6.1 Protein Crystallization Matrices

Bicontinuous lipid cubic membrane architectures provide friendly geometry for reconstitution of membrane proteins in biomimetic medium [201, 273–288]. Membrane proteins are spontaneously solubilised in the lipid membranes without denaturing and aggregation. Moreover, they possess freedom to move along the lipid bilayers and to oligomerize into nuclei that precede the crystal growth of ordered structures suitable for X-ray crystallography analysis. In meso crystallization of membrane proteins in lipid cubic phases has allowed the discovery of the X-ray structures of several functional membrane proteins [273, 281–287]. A chief advance in transmembrane proteins

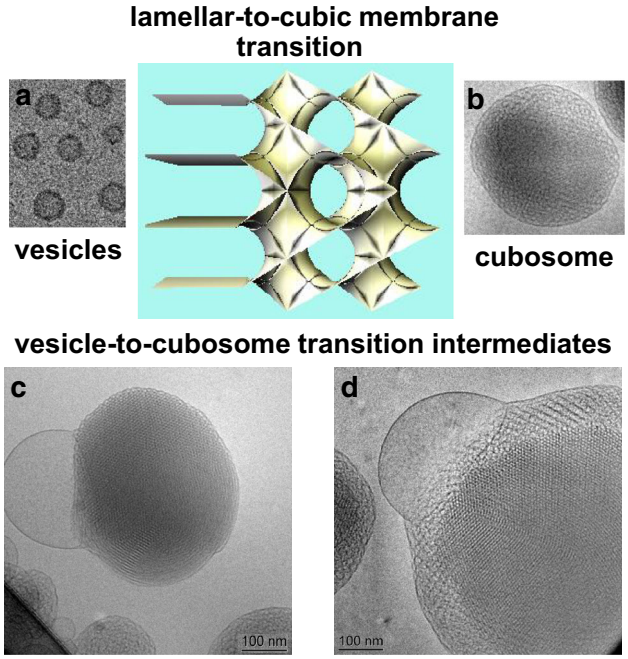

Fig. 14 Lamellar-to-cubic lipid membrane transition (*top panel* **a**, **b**) and vesicle-to-cubosome transition intermediates (*bottom panel* **c**, **d**) as revealed by modelisation [178] and cryo-TEM imaging [15, 228]

crystallography exploiting the in meso crystallization method has been the structural characterization of the G-protein coupled receptor (GPCR) proteins [282, 284, 287].

6.2 Theranostic Applications

Anti-cancer treatment with minimal side effects has stimulated the development of modern theranostics approaches using nanotechnologies [289–299]. For the purposes of SPECT/CT imaging (single photon emission computed tomography (SPECT) combined with computed tomography (CT), a method for radiolabeling of nanochannel-type phytantriol-based liquid crystalline particles has been proposed [289]. Nanoparticle labelling by technetium (^{99m}Tc) has been performed using an appropriate polyamine–triazododecane chelating agent for in vivo imaging applications. Interestingly, the radiolabeling efficiency has been dependent on inner liquid crystalline architecture of the investigated lipid particles (hexosomes or cubosomes). The established biodistribution of the nanoparticle-administered imaging agent at several hours post-injection has given promising outcome for early disease detection (Fig. 15).

Stimuli-responsive theranostic systems have been produced by incorporation of gold nanoparticles and nanorods (GNR) (Fig. 16) in liquid crystalline lipid phases, amphiphilic and mesoporous copolymer particles [23, 293–295]. The purpose has been to achieve on-demand release of drugs from nanocarriers activated by near-infrared (NIR) light (650–900 nm). Plasmonic heating of the liquid crystalline carriers has been induced by laser pulse illumination taking into account that gold nanoparticles can be tuned to absorb light in the NIR wavelength range. The photothermal effect has been dependent on the concentration of the GNR [294].

6.3 Drug Delivery by Soft Porous Matter

The biocompatibility of the lipid and amphiphilic nanochannelled architectures has been favourable for a number of drug delivery applications [134, 300–335]. Loading of peptides, therapeutic proteins, drugs, diagnostic agents, nucleic acids, vitamins, cosmetic ingredients, etc. has been realized with a variety of soft matter nanocarriers [129–144, 201, 300, 301]. The safety of these nanosystems has been guaranteed by the low toxicity of the lipid and the

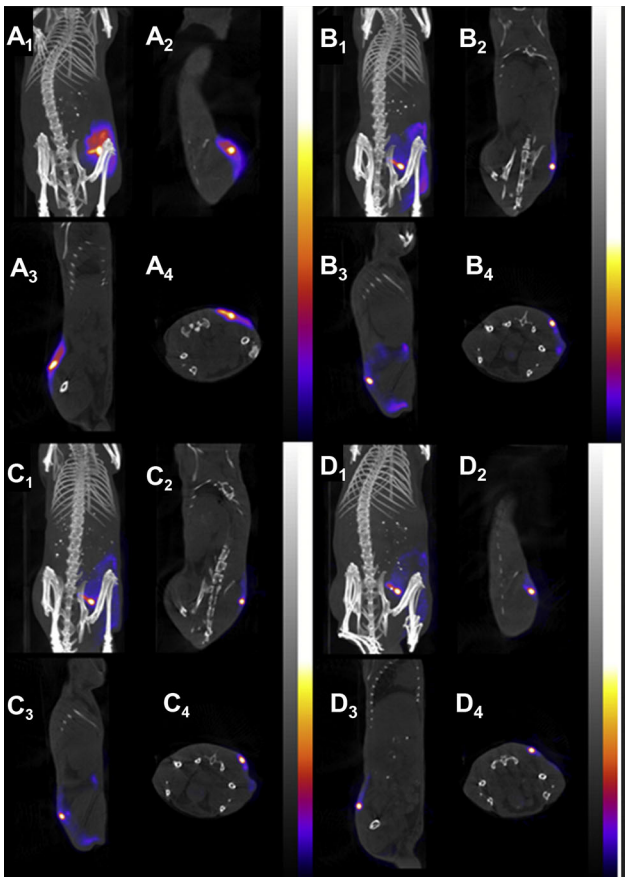

Fig. 15 NanoSPECT/CT-imaging with ^{99m}Tc-SpmTrien-hexosomes indicating radiolabeled hexosomal depot in the subcutaneous adipose tissue after subcutaneous injection into the flank of healthy mice. The post-injection time is 5 min (*A*), 3 h (*B*), 6 h (*C*), and 24 h (*D*). Reprinted from Ref. [289] with permission from Elsevier. Copyright (2013) Elsevier Ltd

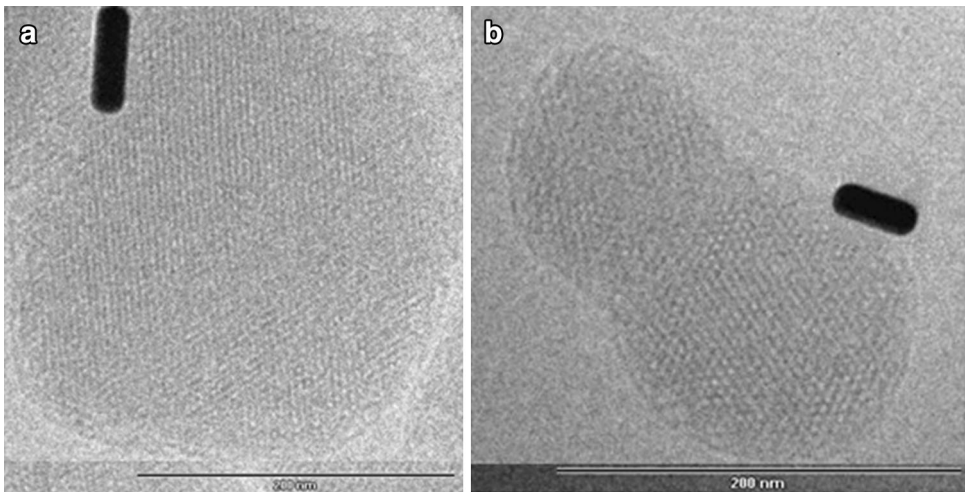

Fig. 16 Cryo-TEM images of liquid crystalline lipid particles involving gold nanorods (GNR) with different sizes/aspect ratios. **a** 0.3 nM 810 nm GNR and **b** 0.3 nM 660 nm GNR in phytantriol-based cubosomes. Reprinted with permission from [294]. Copyright (2012) American Chemical Society

biocompatible block-copolymer constituents. Lipid and amphiphile nanoarchitectures have been valuable in reducing the toxicity of drug substances and augmenting their capacity for crossing the cellular barriers [307–309, 313, 318, 320, 321]. Functionalizaion of cubic nanoarchitectures [21, 54, 189, 201, 203, 208, 216, 291, 324] has been useful in applications aiming at enhanced specificity and targeting. Advancements have been reported in stimuli-triggered nanochannelled devices for controlled drug delivery, multimodal diagnostics, and personalized medical care [16, 34, 62, 93, 128, 160, 166, 175, 180, 181, 304, 327, 331–333]. A problem which requires further studies is how to achieve control of the drug release time and the spatial targeting through engineering of the liquid crystalline nanoparticles [161].

Protein and peptide nanoencapsulation presents strong ongoing interest as well [15, 55, 58, 193, 201–205, 208, 226, 328–331]. The entrapment of protein molecules in cubosomic nanocarriers, sterically stabilized by amphiphilic poly(ethylene glycol) (PEG) or other amphiphilic polymer shells, has been investigated in recent works [58, 201–205, 214]. Attention has been paid to protein containers and nanoparticulate stimuli-responsive liquid crystalline systems and bio-nano interfaces [327–335]. PEGylation has been established to influence the pharmacokinetics of the administered nanoparticles, peptides and proteins, and their interaction with biological fluids and cells [111, 134, 220, 326]. Inhibition of blood protein adsorption (anti-opsonization) has been favoured by linear PEG chains anchored at a relatively low surface coverage and by higher PEG lengths. Whereas linear PEG chains have helped reducing the nonspecific protein adsorption, excessive PEGylation has hindered the nanoparticles binding to target sites. This has been due to decreased receptor-mediated nanoparticle cellular uptake and capacity for crossing the biological barriers. The analysis of the counter effects of PEGylation on anti-opsonization and active targeting has permitted to optimize the nanoparticles interaction with biological interfaces and cell receptors by creation of multicomponent lipidic nanoarchitectures built-up from both neutral and charged lipids and PEGylated derivatives [134].

7 Scaling Soft Porosity at the Mesoscale

Accumulating evidence has indicated the remarkable analogy between the membrane topology of inverse bicontinuous cubic mesophases, either bulk gels or dispersed liquid crystalline particles, and that of cellular organelle (mitochondria, endoplasmic reticulum) membranes [2–6]. The lattice periodicity in cubic membranes of living cells has been established to be an order of magnitude bigger as compared to that in self-assembled amphiphilic cubosomes [3]. Recently, the cubic lattice periodicity in synthetic particulate systems has been scaled to a larger dimension through self-assembly of dendritic–linear block copolymers [216]. The solvent-precipitated polymer cubosomes with inner bicontinuous cubic structure have been much greater in size (Fig. 17a) in comparison to the usually reported lipidic cubosomes [217–223]. The lattice parameter, determined by SAXS analysis (Fig. 17b), has been considerably larger as well [216]. Studies of dendritic block copolymer self-assembly at different length scales have proposed also the chemical functionalization of the bilayer membranes in the polymeric particles of *Im3m*, *Pn3m* or *Ia3d* cubic symmetries [216]. Whereas microphase-separated block copolymers have usually self-assembled into regular structures on the length scale between 10 and 100 nm, polyphilic star-branched polymers have self-assembled into liquid crystalline morphologies with a unit cell size in the range of a few nanometers

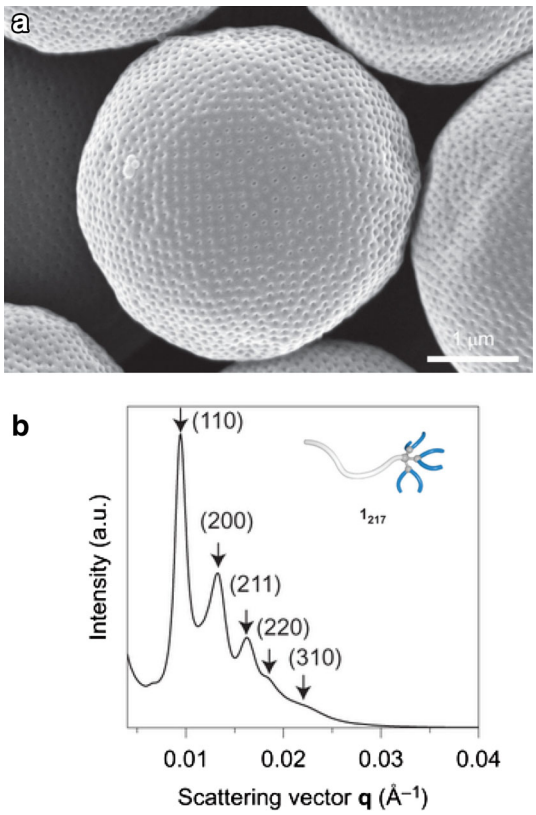

Fig. 17 **a** SEM image of a polymer cubosome obtained from a dendritic–linear block copolymer $\mathbf{1_{217}}$ (peripheral PEG chains with average molecular weight (M_n) of 350 g mol^{-1}, degree of polymerization (DP_n) of seven repeat units) displaying a spherical morphology and a perforated shell enclosing an internal bicontinuous structure. **b** SAXS pattern obtained from dried polymer cubosomes of $\mathbf{1_{217}}$ showing a primitive cubic (*Im*3*m*) lattice organization (cubic lattice parameter, $a = 93.4$ nm). Reprinted with permission from Macmillan Publishers Ltd.: Ref. [216] [Nature Chemistry]. Copyright (2014) Nature Publishing Group

(3–15 nm scale) [80]. Such mesoporous materials with tunable properties have been suggested to offer new platforms as storage vehicles, sensors, nanotemplates and bioreactors.

8 Conclusion and Perspectives

The presented here "bottom–up" nanoarchitectonics design involves assembling of membrane nano-building blocks into ordered cubosomal or other types of 3D membranous architectures forming nanochannelled templates. The flexible amphiphilic membranes and functionalized lipid/water interfaces favour valuable stimulus-responsiveness of the created nanoassemblies. Structural studies have revealed that vesicular membranes are required as lipid bilayer building blocks for stable formation of dispersed cubic lipid membrane nanoparticles. Despite that the morphological features of the bicontinuous cubic liquid crystalline lipid structures are analogous to those of some solid mesoporous materials, their mechanical properties essentially differ. The channels diameters in solid mesoporous scaffolds are fixed and cannot be influenced through hydration modulation or biomolecular loading. At variance, the softness and the flexibility of the amphiphilic polymer and lipid/water interfaces are favourable for immobilization of large protein molecules and offer diverse biomedical applications including tissue engineering, diagnostics and therapy towards personalized health care.

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